CLINICAL REVIEW

Application Type	NDA supplement
Application Number(s)	022496 S-035
Priority or Standard	Standard
Submit Date(s)	May 22, 2020
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Division/Office	Division of Anesthesiology, Addiction Medicine, and Pain Medicine/Office of New Drugs
Reviewer Name(s)	Erin L. Zenilman, M.D.
Review Completion Date	February 16, 2021
Established/Proper Name	Bupivacaine liposome injectable suspension
(Proposed) Trade Name	EXPAREL
Applicant	Pacira Pharmaceuticals, Inc.
Dosage Form(s)	Injectable suspension
Applicant Proposed Dosing Regimen(s)	Single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg)
Applicant Proposed Indication(s)/Population(s)	EXPAREL is indicated for single-dose infiltration in patients aged 6 years and older to produce postsurgical local analgesia and in adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	EXPAREL is indicated for single-dose infiltration in patients aged 6 years and older to produce postsurgical local analgesia and in adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
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
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
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

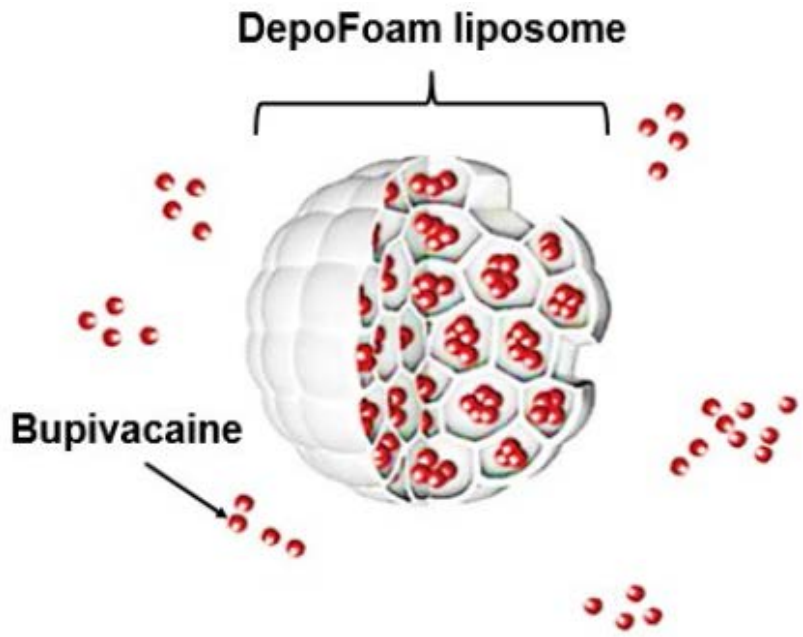
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
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
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

EXPAREL was developed to prolong the local analgesic effects of bupivacaine. EXPAREL consists of microscopic spherical liposomes that are multivesicular and composed of a honeycomb-like structure of numerous non-concentric internal aqueous chambers containing bupivacaine. Each chamber is separated from adjacent chambers by lipid membranes. The lipids, which include phospholipids, cholesterol, and triglycerides, are either naturally occurring substances or close analogs of endogenous lipids. The liposomes are part of an extended-release DepoFoam® drug delivery system.

Figure 1. EXPAREL Multivesicular Liposome



Source: Applicant's Clinical Overview, submitted May 22, 2020, page 8

The active ingredient of the formulation is bupivacaine, which is released from the liposomes by a mechanism that involves reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time. Bupivacaine hydrochloride (HCl) is the active ingredient in a currently marketed product Marcaine (NDA 016964, approved October 3, 1972), which is the reference listed drug for this supplemental NDA (sNDA).

EXPAREL was originally approved in the United States in 2011. The current indication for EXPAREL is for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266

mg (20 mL), and the recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL). Upon original approval, several pediatric postmarketing requirements (PMRs) were issued. The following PMR is applicable to this submission:

> PMR 1834-5: A multicenter, randomized, open-label, IR bupivacaine-controlled (for subjects 12 to less than 17 years old) and single arm (for subjects 6 to less than 12 years old) study to evaluate the safety and pharmacokinetic profile of a single intraoperative administration of EXPAREL via infiltration for postoperative analgesia in a variety of surgical procedures in adolescent subjects 6 to less than 17 years old.

The Applicant conducted Study 402-C-319 (Study 319) to fulfill PMR 1834-5. The Applicant submitted data from Study 319 and a pilot study, Study 402-C-120 (Study 120) to support the approval of EXPAREL for use in single-dose infiltration in children 6 years of age and older to produce postsurgical local analgesia. The Applicant proposed a dose of 4 mg/kg in pediatric patients, up to a maximum of 266 mg, based on actual body weight.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of EXPAREL via local infiltration for children aged 6 to less than 17 years was extrapolated from the efficacy of EXPAREL in adults for the same indication. Bupivacaine HCl is approved for use in children 12 years and older. However, bupivacaine and other local anesthetics, such as lidocaine and ropivacaine, are routinely used for local infiltration and regional anesthetic techniques in children of all age groups, down to neonates. For a drug class with a well-established mechanism of action, such as local anesthetics, it is reasonable to believe that any drug within the drug class would be as effective in children over the age of two as in adults.[1] Therefore, the efficacy assessments included in this submission were exploratory only and Study 319 was not powered to demonstrate efficacy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Bupivacaine HCl was first approved in the United States in 1972 (NDA 016964) and has been widely used in the management of postsurgical pain in adults and in children since its approval. Bupivacaine has been demonstrated to be safe and effective for use via wound infiltration, peripheral nerve blockade, and neuraxial anesthesia in a variety of clinical settings and for a wide range of surgical procedures. Based on the well-known safety profile and effectiveness of bupivacaine, in combination with the ongoing opioid epidemic, there is considerable interest in developing bupivacaine products with extended-release profiles in an effort to prolong the analgesic effect. EXPAREL, a formulation of bupivacaine in a DepoFoam® liposome, has the potential to extend the duration of action of bupivacaine and to reduce the need for opioid analgesic drugs.

EXPAREL was first approved in the United States in 2011 (NDA 022496). The current indication for EXPAREL is for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266 mg (20 mL), and the recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL).

The Applicant is proposing to add a pediatric indication for EXPAREL as a single-dose infiltration in subjects 6 to less than 17 years old. The proposed pediatric dose is 4 mg/kg, not to exceed 266 mg, the approved maximum dose in adults for local infiltration. The safety issue of greatest concern with administration of any local anesthetic, including EXPAREL, is local anesthetic systemic toxicity (LAST), which typically presents as central nervous system excitation and/or depression, as well as, cardiotoxicity. Due to the extended-release properties of EXPAREL, there is also increased concern for delayed manifestations of local anesthetic systemic toxicity. However, the potential for extended pain relief at the surgical incision (i.e. approximately 72 hours) may be beneficial over other shorter-acting local anesthetics (i.e., approximately 3 to 8 hours), and the potential for another product labeled for pediatric use may be beneficial in the treatment of pediatric postsurgical pain.

After review of all of the available safety data from Studies 120 and 319, these data appear to support the safety of surgical infiltration of EXPAREL 4 mg/kg, up to a maximum of 266 mg, in children greater than 6 years of age, who are undergoing spine or cardiac procedures. The most frequently observed adverse reactions following EXPAREL administration were nausea, vomiting, constipation, hypotension, anemia, muscle twitching, vision blurred, and tachycardia. There were no deaths, discontinuations due to an adverse event, or suspected cases of LAST or delayed LAST in the pediatric population evaluated. In addition, the safety profile of EXPAREL in Studies 120 and 319 was similar to the general safety profile of EXPAREL in adults.

Furthermore, the pharmacokinetic data collected in Studies 120 and 319 were similar to the pharmacokinetic data collected in adults in matching surgical procedures (Studies 117 and 118). Based on the totality of safety and pharmacokinetic data, it is reasonable to conclude that the safety profile of EXPAREL for wound infiltration would also be similar in less vascular surgical sites in children aged 6 to less than 17 years.

Therefore, the totality of the submitted safety and pharmacokinetic data support the proposed indication and the proposed dose of EXPAREL in pediatric patients greater than 6 years of age. The efficacy of EXPAREL for local infiltration in pediatric subjects aged 6 to less than 17 years of age was extrapolated from the efficacy of EXPAREL for local infiltration in adult subjects. It is reasonable to extrapolate efficacy from adults to children because children over the age of two are likely to respond similarly to EXPAREL as adults based on similar pathophysiology, mechanism of action, and pharmacodynamic responses to local anesthetics.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Children experience postoperative pain similar to adults.[2] • Untreated postsurgical pain can result in anxiety and poor healing.[3]	Postoperative pain in pediatric subjects should be treated with a multimodal pain regimen, including local anesthetics, when appropriate.
Current Treatment Options	• Bupivacaine HCl (long acting immediate-release local anesthetic – up to 8 hours of postsurgical pain relief), widely used for surgical wound infiltration; recommended dose for children over the age of 12 years is 2-2.5 mg/kg, up to a maximum of 175 mg • Ropivacaine HCl (long acting local immediate-release anesthetic—up to 8 hours of postsurgical pain relief), widely used for surgical wound infiltration, less cardiotoxic than bupivacaine; not approved for pediatric use • Lidocaine HCl (intermediate acting immediate-release local anesthetic – up to 3 hours of postsurgical pain relief), widely used for surgical wound infiltration; recommended dose for children over the age of 3 years is 4.5 mg/kg • Chloroprocaine HCl (short acting immediate-release local anesthetic –	There are many options of local anesthetics for local infiltration to treat postsurgical pain in children. The selection of a local anesthetic depends on the subject, the procedure, provider preference, or availability. Bupivacaine, ropivacaine, lidocaine, and chloroprocaine are all immediate-release local anesthetics. In comparison, EXPAREL and Posimir are extended-release bupivacaine products, which release small amounts of drug product (i.e., bupivacaine) into the surgical site over an extended period of time (i.e., approximately 72 hours). Bupivacaine,

	up to 1 hour of postsurgical pain relief), rapid onset of action, typically used to provide neuraxial anesthesia; recommended dose for children over the age of 3 years is 11 mg/kg • Posimir (extended-release bupivacaine solution – up to 72 hours of postsurgical relief), narrow indication (for administration into the subacromial space under direct arthroscopic visualization to produce post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression in adults); not approved for pediatric use	lidocaine, and chloroprocaine are approved for pediatric use in limited age groups; whereas, ropivacaine and Posimir are not approved for pediatric use. However, local anesthetics, particularly bupivacaine and ropivacaine, are routinely used for local infiltration and regional anesthetic techniques in children of all age groups, down to neonates. [4]
Benefit	• EXPAREL is a liposomal form of bupivacaine HCl with a potential duration of 72 hours, which is longer than Bupivacaine HCl and Ropivacaine HCl. • EXPAREL initially peaks at 0 to 2 hours after administration and then gradually rises to a second peak 24 to 48 hours after administration; whereas, Bupivacaine HCl peaks at 0 to 2 hours after administration and then quickly decreases during the 8 hours after administration. During the bupivacaine peak, the plasma bupivacaine level is typically higher than the plasma bupivacaine levels observed during either of the EXPAREL peaks. Based on systemic exposure curves of EXPAREL versus bupivacaine, it is possible that EXPAREL may have a lower risk of local anesthetic systemic toxicity than bupivacaine in the immediate postoperative period. • With extended-release properties, EXPAREL has the potential to reduce the need for opioid analgesic drugs; however the Applicant did not conduct clinical studies to demonstrate opioid-sparring effect of EXPAREL. • The efficacy of EXPAREL in children can be extrapolated from the efficacy of EXPAREL in adults, because children over the age of two have similar pathophysiology, mechanism of action, and pharmacodynamic response to local anesthetics as adults.	EXPAREL can be used, as a component of a multimodal regimen to treat postoperative incisional pain in children undergoing surgery. The efficacy of EXAREL in children was extrapolated from the efficacy of EXPAREL in adults. The potential for 72 hours of postsurgical pain relief at the surgical incision may be beneficial over other shorter-acting local anesthetics. Study 319 was not powered to detect a difference in efficacy in children ages 12 to less than 17 years who were randomized to receive either EXPAREL or bupivacaine HCl. Therefore, no efficacy conclusions regarding Study 319 data can be made. However, our assessment of the exploratory efficacy findings in Study 319 did not dispute the extrapolation of efficacy from adults to children.

Risk and Risk Management	• Infiltration with local anesthetics can result in local anesthetic systemic toxicity (LAST), which if not treated, can result in serious morbidity or mortality. • Signs and symptoms of toxicity have been reported at a wide range of maximum plasma concentrations (Cmax) due to high variability in plasma concentrations for inducing systemic toxicity.[5] Although some studies have reported the CNS toxicity threshold at total bupivacaine levels of 2–3 mcg/mL (2000 -3000 ng/mL),[5] others have demonstrated CNS toxicity at total bupivacaine plasma levels as low as 0.8 mcg/mL (800 ng/mL).[6] Of all the pediatric subjects who received EXPAREL, only one subject had a Cmax over 1 mcg/mL (1000 ng/mL). The remaining subjects had a Cmax less than 0.8 mcg/mL (800 ng/mL). • Safety data, including treatment-emergent adverse events and pharmacokinetic data, were assessed to determine the risk of LAST in children aged 6 to less than 17 years undergoing spine or cardiac surgery who were administered 4 mg/kg (up to 266mg) of EXPAREL via local infiltration for postoperative pain. The Applicant chose spine and cardiac surgeries, two highly vascular procedures, to evaluate the safety of EXPAREL in anatomical areas with the potential for the highest bupivacaine absorption, and therefore, the potential for the highest systemic plasma levels of bupivacaine and likely highest risk of LAST. • By demonstrating the safety of EXPAREL in these highly vascular anatomical compartments, the Applicant intended to justify the safety of EXPAREL 4 mg/kg, up to 266 mg, in other less vascular anatomical compartments (e.g., inguinal hernia incision).	The safety of EXPAREL was assessed in 65 subjects aged 6 to less than 17 years undergoing spine or cardiac surgery in Study 319, and 15 subjects aged 12 to 17 years undergoing spine surgery in Study 120. In these studies, the most frequently reported adverse events following EXPAREL administration were nausea, vomiting, constipation, hypotension, anemia, muscle twitching, vision blurred, and tachycardia. The gastrointestinal adverse events (i.e., nausea, vomiting, constipation) are consistent with the most frequently reported adverse events in the adult studies. Significant surgical blood loss frequently occurs in highly invasive procedures, such as spine and cardiac surgery, leading to fluid shifts, anemia, hypotension, and reflex tachycardia. Transient muscle twitching often occurs following spine surgery due to spinal muscle manipulation and is unlikely associated with systemic toxicity of EXPAREL. The adverse event of blurred vision was more frequently reported in pediatric subjects than in the adult general surgery pool of subjects; however, this finding is likely due to prone positioning for spine surgery rather than local anesthetic toxicity. There were no deaths, reported cases of LAST, or delayed LAST in the pediatric development program. In general, the adverse event profile of pediatric

		subjects was similar to that in adult subjects. The pharmacokinetic data from spine and cardiac surgery in Study 319 were compared to the pharmacokinetic data from spine and cardiac surgery in adults in Study 402-C-117 (Study 117) and 402-C-118 (Study 118), respectively. The mean Cmax for pediatric spine surgery subjects was 353 ng/mL, and the mean Cmax for pediatric cardiac surgery subjects was 447 ng/mL. In comparison, the mean Cmax was for adult spine surgery subjects was 513 ng/mL, and the mean Cmax for adult cardiac surgery subjects was 445 ng/mL. The systemic exposure levels in children were consistent with systemic exposure levels in adults undergoing similar surgeries. In addition, all the mean Cmax values were below plasma levels typically associated with LAST. Based our assessment of the safety and pharmacokinetic data in children undergoing spine or cardiac surgeries, including a comparison to the safety and pharmacokinetic data from adults, it is reasonable to conclude that the safety profile of EXPAREL 4 mg/kg, up to 266 mg, for wound infiltration would also be similar in other, less vascular surgical sites, in children aged 6 to less than 17 years.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Supplement 035 was submitted by the Applicant to extend the use of EXPAREL via surgical wound infiltration to pediatric subjects aged 6 years and older for production of postsurgical local analgesia. It was once believed that infants and children did not experience pain similar to adults. However, it is now understood that peripheral, spinal, and supraspinal afferent pain pathways are mature in neonates and therefore, pediatric postsurgical pain must be treated similarly to adult postsurgical pain even in the youngest children and infants. Untreated postsurgical pain in children can result in increased anxiety, poor healing, and chronic pain conditions. Therefore, pediatric pain specialists recommend a multimodal pain regimen for treatment of postsurgical pain in children. [1,2,3]

A multimodal approach to post-surgical pain management typically involves the combination of local anesthetics, non-opioid analgesics, and opioid analgesics. Prior to the opioid crisis in the US, opioid analgesics were the mainstay for the management of post-operative pain. However, current strategies are focused on alternative pain management techniques, including local anesthetic wound infiltration, peripheral nerve blockade, and neuraxial anesthesia. This paradigm shift has resulted in increasing interest in developing products that prolong the duration of efficacy of immediate release local anesthetics, such as EXPAREL.

EXAREL is indicated for single-dose infiltration to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia for adults aged 18 years and older. However, the Applicant currently seeks approval to extend the indication in children aged 6 years and older to single-dose infiltration to produce postsurgical local analgesia only. Of note, the Applicant is working on a pediatric development program for the use of EXPAREL for interscalene brachial plexus nerve block to fulfill PMR 3372-1.

2.2. Analysis of Current Treatment Options

The following table summarizes the local anesthetics most commonly used in the perioperative period for production of postsurgical analgesia.

Table 1. Summary of FDA-Approved Local Anesthetics for Postsurgical Analgesia

Product Name NDA #	Year of Approval	Relevant Indication	Route of Administration	Pediatric Dosing for Infiltration
Xylocaine (Lidocaine HCl) NDA 006488	1948	Production of local or regional anesthesia by infiltration techniques and intravenous regional anesthesia, by peripheral nerve block techniques, and by central neural techniques, when the accepted procedures for the techniques as described in standard textbooks are observed	Local infiltration, intravenous administration, peripherical nerve block or epidural administration	For children over 3 years of age, the dose should not exceed 4.5 mg/kg.
Nesacaine (Chloroprocaine HCl) NDA 009435	1955	1% and 2% Injections: Production of local anesthesia by infiltration and peripheral nerve block 2% and 3% Injections: Production of local anesthesia by infiltration, peripheral and central nerve block, including lumbar and caudal epidural blocks	Local infiltration, peripheral nerve block or epidural administration	For children over 3 years of age, the dose should not exceed 11 mg/kg.
Marcaine (Bupivacaine HCl) NDA 016964	1972	Production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures	Local infiltration, peripheral nerve block, retrobulbar block, sympathetic block or epidural administration	For children over 12 years of age, the recommended dose is 2-2.5 mg/kg, up to a maximum of 175 mg.
Naropin (Ropivacaine HCl) NDA 020533	1996	Production of local or regional anesthesia for surgery and for acute pain management Surgical Anesthesia: epidural block for surgery including cesarean section; major nerve block; local infiltration Acute Pain Management: epidural continuous infusion or intermittent bolus, e.g., postoperative or labor; local infiltration	Local infiltration, epidural administration, or peripheral nerve block	The safety and efficacy in pediatric patients have not been established.
EXPAREL (Bupivacaine liposomal injectable solution) NDA 022496	2011	For single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia	Local infiltration or interscalene nerve block	The safety and efficacy in pediatric patients have not been established.
Posimir (Bupivacaine solution) NDA 204803	2021	For administration into the subacromial space under direct arthroscopic visualization to produce post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression	Local infiltration	The safety and efficacy in pediatric patients have not been established.

The safety issue with all local anesthetics involves systemic and local toxicity. Local anesthetic systemic toxicity (LAST) presents as central nervous system excitation and/or depression and cardiotoxicity. As documented in the Adverse Reactions section of the bupivacaine labeling, but applicable to all local anesthetics, the following LAST reactions are described by system:

Central nervous system: Excitation and/or depression; restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions.

Cardiovascular system: High doses or inadvertent intravascular injection may result in myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, cardiac arrest. Bupivacaine HCl is considered the most cardiotoxic local anesthetic due to its potency in blocking nerve conduction and depressing cardiac contractility.

Local reactions can include persistent anesthesia, paresthesia, weakness, or paralysis.

Cases of delayed LAST, occurring several days after drug administration, have been reported with immediate-release local anesthetics and extended-release local anesthetics. Due to extended-release properties of EXPAREL and Posimir, there is an increased concern for the possibility of delayed manifestations of LAST.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

In 2011, EXPAREL was approved in the United States with an indication for administration into the surgical site to produce postsurgical analgesia. In 2014, the Applicant submitted an sNDA for an additional indication of EXPAREL, postsurgical analgesia via nerve block. This sNDA was not approved during the first review cycle; however, in 2018, during the second review cycle, EXPAREL was approved for use as an interscalene brachial plexus nerve block to produce postsurgical regional anesthesia. The current indication for EXPAREL is for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

PMRs were issued for each indication. In 2011, PMR 1834-1, 1834-2, 1834-3, and 1834-4 were issued for local infiltration for children 12 to less than 17 years, 6 to less than 12 years, 2 to less than 6 years, and birth to less than 2 years, respectively. In 2019, the Division released the Applicant from these four PMRs and reissued PMR 1834-5, 1834-6, and 1834-7 for children 6 to less than 17 years, 2 to less than 6 years, and birth to less than 2 years, respectively. PMR 1834-5 combined 1834-1 and 1834-2 into one age group (6 to less than 17 years).

This sNDA submission serves as the final report submission for PMR 1834-5, required under the Pediatric Research Equity Act (PREA). The Applicant also seeks to expand the use of EXPAREL for

local infiltration to produce postsurgical local analgesia to subjects aged 6 years and older.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following table summarizes the history of communication between the Applicant and the Division regarding local infiltration of EXPAREL for children aged 6 to less than 17 years.

Table 2. Summary of Key Communications Between Pacira and FDA Regarding Study 402-C-319 for Local Infiltration of EXPAREL in Children Aged 6 to less than 17 years

Date	Event
October 28, 2011	Division issued NDA Approval Letter with four PMRs (1834-1: 12 to less than 17 years, 1834-2: 6 to less than 12 years, 1834-3: 2 to less than 6 years, 1834-4: birth to less than 2 years).
January 16, 2012	Applicant submitted Study 319 protocol for review.
November 12, 2012	Division provided comments on Study 319 protocol.
October 31, 2013	Applicant submitted revised Study 319 protocol for review.
February 5, 2014	Division provided comments on revised Study 319 protocol.
October 23, 2015	Applicant requested Type C Meeting to discuss Study 319 protocol.
March 24, 2016	Division and Applicant had a Type C Meeting and discussed appropriate surgical models and study designs for Applicant's protocol.
June 17, 2016	Applicant submitted revised Study 319 protocol for review.
October 14, 2016	Division provided comments on revised Study 402-C-319 protocol.
July 20, 2017	Applicant requested Type C Meeting and provided data from the Cleveland Clinic to inform dosing and to identify surgical procedures.
September 1, 2017	Division provided preliminary comments for Type C Meeting, including a request for additional information on retrospective Cleveland Clinic data.
September 8, 2017	Applicant requested deferral of Type C Meeting.
September 14, 2017	Division granted deferral of Type C Meeting.
March 23, 2018	Applicant submitted Type C Meeting package, including revised Study 319 protocol and additional retrospective Cleveland Clinic data to support the dose of 4 mg/kg.
April 23, 2018	Division and Applicant had Type C Meeting to discuss appropriate surgical procedures, active comparators, and PK sampling schemes. Division agreed that Applicant can extrapolate efficacy from adults for pediatric subjects older than 2 years and that Study 319 does not need to be powered for efficacy.
September 14, 2018	Applicant submitted revised Study 319 protocol for review.
November 9, 2018	Division agreed that the proposed Study 319 protocol, entitled "A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 Years," may proceed.
April 4, 2019	Applicant requested Type B Meeting to discuss the sNDA to expand EXPAREL's indication to single dose infiltration in subjects aged 6 to less than 17 years

Date	Event
May 30, 2019	Division released Applicant from four original PMRs and reissued three PMRs (1834-5: 6 to less than 17 years, 1834-6: 2 to less than 6 years, 1834-7: 0 to less than 2 years).
August 28, 2019	Division and Applicant had Type B Meeting to discuss the presentation of safety and efficacy data from Study 319 in the Applicant's sNDA submission.
May 22, 2020	Applicant submitted sNDA (Supplement 35) to fulfill PMR 1834-5.
July 30, 2020	Division sent Information Request regarding differences observed between the spine surgery group and cardiac surgery group in Study 319.
August 14, 2020	Applicant responded to Information Request providing a rationale for differences observed between the spine and cardiac groups in Study 319.
October 13, 2020	Division sent Information Request regarding Section 6.1 of the label.
October 21, 2020	Applicant responded to Information Request adding adverse reactions observed in Studies 120 and 319 to Section 6.1 of the label.
January 8, 2021	Division sent Information Request for a summary and assessment of the protocol deviations in Study 319.
January 18. 2021	Applicant responded to Information Request providing a summary and assessment of the protocol deviations in Study 319.
January 27, 2021	Division sent Information Request to Applicant regarding dosing for obese children (BMI > 95th percentile) .
February 2, 2021	Applicant responded to Information Request providing a rationale for dosing obese children based on total body weight.

The Applicant and the Division had many interactions regarding the study design for Study 319. These discussions focused on appropriate surgical procedures and dosing regimens for children aged 6 to less than 17 years. The Division agreed that the Applicant could extrapolate efficacy for this age group from efficacy in adult studies and advised the Applicant to study the safety and pharmacokinetics of EXPAREL in this age group. The Applicant originally proposed to study a variety of surgical procedures performed in children. However, the Applicant did not have safety and efficacy data in adult patients undergoing similar procedures to support all the proposed surgical procedures. The Applicant proposed a starting dose of 4 mg/kg based on retrospective data from the Cleveland Clinic database. The Division expressed concerns during multiple communications that these retrospective data were not adequate to support the dose of 4 mg/kg. After additional consideration, the Applicant selected two surgical procedures, spine surgery and cardiac surgery, in highly vascular anatomical areas with the potential for the highest and fastest drug absorption, and therefore, likely highest systemic exposure and risk of systemic toxicity. The Applicant also conducted a pilot study, Study 120, assessing the safety of EXPAREL 4 mg/kg in children aged 12 to less than 17 years undergoing spine surgery. The data from Study 120 was submitted, along with PK modeling, to provide support for the proposed dose and the proposed surgical procedures. The Applicant also proposed matching the PK data from pediatric spine and cardiac surgical procedures to PK data in adults who also underwent spine and cardiac procedures, respectively. After reviewing all the data, including PK modeling, the Division agreed that Study 319 may proceed with a dose of 4 mg/kg in pediatric patients

undergoing spine or cardiac surgery. The Applicant and the Division further discussed that the safety data generated from Study 319, where EXPAREL is administered in highly vascular anatomical compartments, may support the safety of EXPAREL administration in other less vascular anatomical compartments. The Division agreed that if the Applicant is able to demonstrate safety in pediatric cardiac and spine patients, as well as able to demonstrate matching PK to adults undergoing similar procedures, the data generated in Study 319 may be utilized to support a generalized indication for wound infiltration for children over the age of 6 years.

3.3. Foreign Regulatory Actions and Marketing History

On November 16, 2020, EXPAREL was approved by the European Medicines Agency (EMA) for use as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small-to-medium-sized surgical wounds in adults.

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

4.1. Office of Scientific Investigations (OSI)

At the time of this clinical review, the facilities inspections were not completed and the OSI review was pending.

4.2. Product Quality

There were no new product quality data submitted for this NDA supplement.

4.3. Clinical Microbiology

EXPAREL is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

4.4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology data submitted for this NDA supplement.

4.5. Clinical Pharmacology

Study 120

The PK data from Study 120 was not analyzed for this sNDA, because the PK data from Study 319 was more complete than the data from Study 120. However, the mean Cmax for the 15 subjects in Study 120 was 410 ng/mL (min 78.8 ng/mL, max 559 ng/mL).

Study 319

The Applicant submitted pharmacokinetic (PK) data from Study 319 to support the use of EXPAREL in children aged 6 to less than 17 years. A total of 17 spine surgery subjects who received EXPAREL and 21 cardiac surgery subjects who received EXPAREL underwent PK sampling. All of these subjects received a single dose of 4 mg/kg of EXPAREL, up to a maximum of 266 mg. Since only five subjects underwent spine surgery in Group 2 (6 to less than 12 years), the pharmacokinetic data from these subjects were evaluated with the pharmacokinetic data from the subjects who received EXPAREL in Group 1 (12 to less than 17 years). It is reasonable to evaluate the younger subjects with the older age group because many of the spine surgery subjects in Group 2 were 11 years of age. The mean Cmax for the spine surgery subjects was 353 ng/mL (min 187 ng/mL, max 595 ng/mL), and the mean Cmax for cardiac surgery subjects was 447 ng/mL (min 194 ng/mL, max 1290 ng/mL). The cardiac surgery subject with a Cmax of 1290 ng/mL did not experience any treatment-emergent adverse events; this subject only had baseline tachycardia prior to surgery and EXPAREL administration. This subject was the only subject who received EXPAREL with a Cmax over 800 ng/mL. Therefore, this outlier contributed to the higher mean Cmax observed in the cardiac surgery group as compared to the spine surgery group.

The Applicant also submitted PK data from Study 402-C-117 (Study 117), which was an open-label study evaluating the safety and PK of EXPAREL administered via local infiltration in adults undergoing spine surgery, and from Study 402-C-118 (Study 118), which was an open-label study evaluating the safety and PK of EXPAREL administered via local infiltration in adults undergoing cardiac surgery. All of the adult subjects in Studies 117 and 118 received a single dose of 266 mg of EXPAREL. Among the 11 subjects who had PK sampling in Study 117, the mean Cmax was 513 ng/mL (min 228 ng/mL, max 1150 ng/mL), and among the five subjects who had PK sampling in Study 118, the mean Cmax was 445 ng/mL (min 291 ng/mL, max 621 ng/mL). The mean Cmax in adult spine surgery subjects was higher than the mean Cmax in adult cardiac surgery subjects; whereas, the mean Cmax in pediatric spine surgery subjects was lower than the mean Cmax in pediatric cardiac surgery subjects. However, all of the mean Cmax values were below plasma levels typically associated with local anesthetic systemic toxicity, and the observed differences in all the Cmax values (adults and children) were reasonably close to one another such that there does not appear to be any clinically meaningful differences in exposure between all of the groups.

In summary, the systemic exposure levels in pediatric subjects undergoing spine or cardiac surgeries were consistent with the systemic exposure levels in adult subjects undergoing the same procedures. Additionally, the mean Cmax values in both pediatric and adult subjects were below the plasma levels typically associated with local anesthetic systemic toxicity.

The following is verbatim from the clinical pharmacology review by Dr. Suresh Naraharisetti, dated February 12, 2021:

> The pediatric subjects underwent matching surgical procedures in spine and cardiac as that of adults. In spine procedure, compared to the adults dosed at EXPAREL 266 mg, the pediatric subjects' (6 to <17 y) dosed at 4 mg/kg showed ~ 30% lower Cmax and 30% lower partial AUCs up to AUC0-40h. In cardiac procedures, compared to the adults, the pediatric subjects (6 to <12 y) showed similar Cmax and ~18% increase in AUC0-last (AUC0-72h). Owing to a cross-study comparison and multiple factors that may affect absorption of peri-operative product like EXPAREL, the observed PK differences between pediatrics dosed at 4 mg/kg and adults dosed at 266 mg cannot be considered drastically different. Hence, it is reasonable to say that the exposure in pediatrics in matching surgical procedures of cardiac and spine surgeries can be considered reasonably similar to the adults.

The clinical team agrees with the assessment by Dr. Naraharisetti and the clinical pharmacology team. Refer to Dr. Naraharisetti's review for a detailed analysis of the pharmacokinetic data.

4.6. Devices and Companion Diagnostic Issues

This section is not relevant to this sNDA.

4.7. Consumer Study Reviews

This section is not relevant to this sNDA.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The following is an overview of Study 319, the pivotal study, and Study 120, the pilot study, for PMR 1834-5 and Supplement 35.

Table 3. Summary of Study 402-C-319 (NCT 03682302) and Study 402-C-120 (NCT0348501)

Study	Study Design (# of Centers)	Regimen/Route	Study Endpoints	No. of subjects enrolled	Study Population
402-C-319 (pivotal study)	Phase 3, open-label, active-controlled, randomized, multicenter (US: 15)	EXPAREL 4 mg/kg (max 266 mg) Bupivacaine HCl 2 mg/kg (max 175 mg) Infiltration into the surgical site	PK endpoints: • Area under the curve (AUC) • Maximum plasma concentration (Cmax) • Apparent terminal elimination half-life (t1/2el) • Apparent clearance (CL/F) • Apparent volume of distribution (Vd/F) Safety endpoints: • Change from baseline in vital signs • Summary of neurological assessments • Change from baseline in clinical laboratory data • ECG tracings (normal versus abnormal) • Incidence of treatment-emergent AEs (TEAEs) and SAEs until Day 30 Efficacy endpoints: (exploratory only): • Pain intensity scores • AUC of pain intensity scores • Total opioid consumption • Time to first postsurgical opioid medication	EXPAREL 4 mg/kg (12 to <17): 31 Bupi HCl 2 mg/kg (12 to <17): 30 EXPAREL 4 mg/kg (6 to <12): 34	Subjects 12 to <17 years of age; spine surgery Subjects 6 to <12 years of age; spine or cardiac surgery
402-C-120 (pilot study)	Phase 1, open-Label, single-arm, single-center (US: 1)	EXPAREL 4 mg/kg (maximum 266 mg) Infiltration into the surgical site	PK endpoints: • Area under the curve (AUC) • Maximum plasma concentration (Cmax) • Time of maximum plasma concentration (Tmax) • Apparent terminal elimination half-life • Apparent clearance (CL/F) • Apparent volume of distribution Safety Endpoints: • Change from baseline in vital signs • Summary of neurological assessments • Change from baseline in clinical laboratory data • Incidence of treatment-emergent AEs (TEAEs) and SAEs through Day 30	15	Subjects 12 to <17 years of age; spine surgery

5.2. Review Strategy

The Applicant conducted one Phase 3 study, Study 319, to fulfill PMR 1834-5. Since the Division agreed that the efficacy data on surgical wound infiltration could be extrapolated from adults to children greater than two years old, this review will focus on the safety data provided in Study 319 and the pilot study, Study 120.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 Years (Study 319)

The majority of the data to support this sNDA is from Study 319, entitled "A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 Years." The Division and the Applicant agreed that the Applicant may extrapolate efficacy from adults to pediatric subjects down to two years of age, and therefore, this study did not need to be powered to demonstrate efficacy.

Study 319 assessed the pharmacokinetics and safety of EXPAREL in two surgical procedures, spine surgery and cardiac surgery. Additional exploratory efficacy endpoints were also evaluated. The Applicant selected cardiac and spine surgical procedures, which are in highly vascular anatomical compartments, to evaluate the pharmacokinetics and safety of EXPAREL in areas with the highest potential for drug absorption, likely to result in the highest total systemic levels of EXPAREL. Although systemic levels of local anesthetics do not correlate to local efficacy, higher systemic levels of local anesthetics are more likely to result in signs and symptoms of local anesthetic systemic toxicity (LAST).

The primary objective of Study 319 was to evaluate the PK of EXPAREL in pediatric subjects aged 6 to less than 17 years undergoing spine or cardiac surgeries. The secondary objective of Study 319 was to evaluate the safety of EXPAREL in pediatric subjects aged 6 to less than 17 years undergoing spine or cardiac surgeries. Study 319 was not powered to demonstrate efficacy. Efficacy data were collected for exploratory purposes only, and therefore, clinically meaningful conclusions from these exploratory data cannot be made. The efficacy of EXPAREL for single-dose infiltration to produce postsurgical local analgesia in adults may be extrapolated to pediatric subjects on the basis of similar pathophysiology, mechanism of action, and pharmacodynamic responses to local anesthetics between pediatric and adult subjects.

The subsequent subsections in Section 6 will focus on general study information, including study design and conduct, and the exploratory efficacy data.

6.1.1. Study Design

Study 319 was a two-part study evaluating the PK and safety of EXPAREL in pediatric subjects aged 6 to less than 17 years. The following table summarizes the study groups.

Table 4. Study Groups for Study 402-C-319

	Surgery Type, Dose, and Number of Subjects [n]	
	Part 1 (PK and Safety)	Part 2 (Safety)
Group 1 (subjects aged 12 to <17 years)	Spine Surgery EXPAREL 4 mg/kg [15] bupivacaine HCl 2 mg/kg [15]	Spine Surgery EXPAREL 4 mg/kg [15] bupivacaine HCl 2 mg/kg [15]
Group 2 (subjects aged 6 to <12 years)	Spine or Cardiac Surgery EXPAREL 4 mg/kg [15]	Spine or Cardiac Surgery EXPAREL 4 mg/kg [15]

Source: Applicant's Protocol 402-C-319, May 22, 2020, page 3

Part 1 of the study assessed both the PK and safety in subjects, and Part 2 assessed safety only. Both Part 1 and Part 2 included two study groups. Group 1 included subjects aged 12 to less than 17 years undergoing spine surgery, and Group 2 included subjects aged 6 to less than 12 years undergoing spine surgery or cardiac surgery.

In Group 1, the subjects were randomized to receive either EXPAREL or bupivacaine, an active comparator, via local infiltration. In Group 2, subjects received EXPAREL via local infiltration only. Subjects in Group 2 were not randomized to an active comparator group because per the bupivacaine package insert, bupivacaine is not recommended in children less than 12 years old. In both groups, the dose of EXPAREL administered was 4 mg/kg, based on actual body weight, up to a maximum dose of 266 mg, and in Group 1, the dose of bupivacaine was 2 mg/kg, based on actual body weight, up to a maximum dose of 175 mg.

The Applicant intended to enroll a minimum of 15 subjects into each subgroup of both Group 1 and Group 2 for a total of 60 subjects in Group 1 (30 EXPAREL, 30 bupivacaine) and 30 subjects in Group 2, and an overall total of 90 subjects in the study.

The Applicant exceeded the minimum proposed sample size and enrolled a total of 95 subjects, 61 subjects in Group 1 and 34 subjects in Group 2. Of the 61 subjects in Group 1, 31 subjects received EXPAREL and 30 subjects received bupivacaine. All 34 subjects in Group 2 received EXPAREL. The sample size is adequate to support the safety of EXPAREL because there was a relatively even distribution of subjects who received EXPAREL in each age group, and there were no unexpected safety events in either age group warranting additional enrollment. Refer to Section 8 for discussion of all pertinent safety data.

Eligibility Criteria:

Inclusion Criteria

1. Subjects whose parent(s) or guardian(s) has/have signed and dated the ICF for the subject to participate in the study, and subjects who have provided written assent to participate in the study (if capable).
2. American Society of Anesthesiologists (ASA) Class 1-3.
3. Male or female subjects 6 to less than 17 years of age on the day of surgery.
4. Body mass index (BMI) at screening within the 5th to 95th percentile for age and sex
5. A negative pregnancy test for female subjects of childbearing potential must be available prior to the start of surgery. The pregnancy test must be conducted in the preoperative holding area according to the study site's standard of care.
6. Subjects and their parent(s)/guardian(s) must be able to speak, read, and understand the language of the ICF and any instruments used for collecting subject-reported outcomes to enable accurate and appropriate responses to study assessments, and provide informed consent/assent.
7. Subjects must be able to adhere to the study visit schedule and complete all study assessments.

Exclusion Criteria

1. Currently pregnant, breastfeeding, or planning to become pregnant during the study or within 1 month after study drug administration.
2. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics or to opioid medication.
3. Contraindication to bupivacaine HCl or other amide-type local anesthetics or to opioid medication.
4. Administration of EXPAREL or bupivacaine HCl within 30 days prior to study drug administration.
5. Subjects with coagulopathies or immunodeficiency disorders.
6. History of, suspected, or known addiction to or abuse of drugs or alcohol within the past two years.
7. Clinically significant medical or psychiatric disease that, in the opinion of the investigator, indicates an increased vulnerability to study drugs and/or procedures.
8. Administration of an investigational drug within 30 days or five elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
9. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postsurgical course.

Procedures

The following table summarizes the schedule of assessments for Study 319.

Table 5. Time and Events Schedule of Study Procedures

Time Window	Screen Visit Within 30 d	D1 Preop	OR	15 min ±5 min	30 min ±5 min	1 h ±15 min	2 h ±15 min	4 h ±15 min	8 h ±30 min	12 h ±1 h	24 h ±1 h	36 h ±2 h	48 h ±2 h	60 h ±2 h	72 h ±2 h	96 h ±4 h	Hosp Dis	D7 Call ±1 d	D30 Visit[1] ±3 d
Obtain signed informed consent/assent	X																		
Assess/confirm eligibility	X	X	X																
Record medical history and surgical history	X	X																	
Record demographics and baseline characteristics	X																		
Urine pregnancy test (for females of childbearing potential	X	X																	
Urine drug screen and alcohol breath test at the investigator's discretion	X	X																	
Physical examination	X																		X
12-lead ECG[2]	X[3]																		
Clinical laboratory tests (hematology, chemistry, urinalysis)[4]	X	X														X			
Perform neurological assessment	X						X	X	X	X	X	X	X	X	X	X	X		X
Measure and record vital signs[5]	X	X					X	X	X	X	X	X	X	X	X	X	X		X
Record age-specific pain intensity score[6]	X							X	X	X	X	X	X	X	X	X	X		
Collect PK blood samples per time windows in Table 3				←	-	-	-	-	-	-	-	-	-	-	-	→			
Prepare study medication			X																
Administer study medication; record dosage, volume, size of incision, and administration start and stop times			X																
Record intraoperative opioids administered and doses			X																
Record surgery start and stop times			X																
Record times and doses of all pain management medication administered			←	-	-	-	-	-	-	-	-	-	-	-	-	→			
Record date and time of discharge																	X		

Source: Applicant's Study Body Report, submitted May 22, 2020, page 41

The Applicant Study Body Report states (verbatim):

> Subjects were screened within 30 days prior to study drug administration. The screening visit, subjects were assessed for past or present neurologic, cardiac, and general medical conditions that, in the opinion of the investigator, precluded them from study participation. After the informed consent form (ICF) was signed by the subject's legal guardian and written assent was provided by the subject, if capable, medical and surgical histories were taken and the following assessments were performed: physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, neurological assessment, clinical laboratory tests (i.e., hematology, chemistry, and urinalysis), pain intensity score, urine pregnancy test for females of childbearing potential, urine drug screen, and alcohol breath test.
>
> On Day 1, eligible subjects received the study drug before closure of the surgical site via local infiltration. Use of intraoperative opioids, acetaminophen, ketorolac, or other NSAIDs, was permitted in accordance with each study site's standard of care. Additional use of local anesthetics within 96 hours following the administration of EXPAREL was prohibited.

There was no required length of stay in the hospital. Subjects were discharged based on the medical judgment of the treating physician. For subjects discharged from the hospital before the 96 hours assessments were completed, a nurse performed all required assessments, including obtaining additional PK samples, at the subject's home.

A follow-up phone call was scheduled on Day 7 and a follow-up visit was scheduled on Day 30.

Postsurgical Pain Management

Use of postsurgical pain medication in cases of insufficient analgesia was permitted according to each study site's standard of care. The investigator recorded all postsurgical pain medications administered to the subjects until hospital discharge. Additional use of local anesthetics within 96 hours following the administration of EXPAREL was prohibited.

Postsurgical Assessments

Postsurgical assessments were conducted until 96 hours and included pain intensity, neurological assessment, clinical laboratory tests, and vital signs. Pain intensity assessments were performed utilizing using the 11-point Numeric Rating Scale at Rest (NRS-R) for subjects aged 12 to less than 17 years and the Color Analog Scale (CAS) for subjects aged 6 to less than 12 years.

Adverse events (AEs) were recorded from the time the ICF was signed until Day 30.

Study Endpoints

PK endpoints:

- Area under the plasma concentration-versus-time curve (AUC)
- Maximum plasma concentration (Cmax)
- The apparent terminal elimination half-life (t1/2el)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vd/F)

Safety endpoints:

- Change from baseline in vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure)
- Summary of neurological assessments (subjects who were oriented, disoriented, not assessable), numbness (of lips, tongue, or around mouth), metallic taste, hearing problems, vision problems, and muscle twitching
- Change from baseline in clinical laboratory data
- ECG tracings were classified as 'normal, 'abnormal not clinically significant' or

'abnormal clinically significant'
• Incidence of treatment-emergent AEs (TEAEs) and SAEs until Day 30

Efficacy endpoints (for exploratory purposes only):

• Pain intensity scores
• The AUC of pain intensity scores for the specified time intervals
• Total opioid consumption in oral morphine equivalents
• Time to first postsurgical use of opioid medication

Statistical Analysis Plan

The Applicant Study Body Report states (verbatim):

> A comprehensive statistical analysis plan was developed for this study. Descriptive statistics were provided for continuous data. Tabulations by category were provided for categorical data. This study was not powered for efficacy.
>
> A prospective population PK analysis plan was developed. Nonlinear mixed-effect modeling was used to analyze the sparse concentration-versus-time data.
>
> Population and individual PK parameters were estimated. Individual PK parameters estimated for each subject were used to compute PK exposures (AUC and Cmax). All PK parameters were presented in listings and descriptive summary statistics, including the arithmetic mean, median, range, standard deviation, and coefficient of variation. Details and results of this mixed-effect modeling analysis were reported separately.
>
> The sample size was based on the number of subjects necessary to characterize the PK profile of EXPAREL in pediatric subjects.

Protocol Amendments

There were no protocol amendments for this sNDA.

6.1.2. Study Results

Compliance with Good Clinical Practices

On the first page of the Clinical Study Report for Study 319, the Applicant states, "This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents."

Financial Disclosure

Donald C. Manning, MD, PhD, Chief Medical Officer, signed FDA form 3453 on May 19, 2020,

certifying that he had not entered into any financial arrangements with any of the listed clinical investigators where the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, he certified that each listed investigator confirmed they had no proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b). He further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

Patient Disposition

The following is a summary of the study subject disposition for Study 319.

Table 6. Summary of Subject Disposition

	Group 1 (12 to <17 years)			Group 2 (6 to <12 years)		
	EXPAREL 4 mg/kg	Bupivacaine HCl 2 mg/kg	Total	Spine surgery	Cardiac surgery	Total[1]
Screened[2], n	31	30	61	6	30	37[1]
Randomized, n	31	30	61	6	30	37[1]
Not Treated, n	0	0	0	1	1	3[1]
Treated, n	31	30	61	5	29	34
Completed Study[3], n (%)	30 (96.8)	28 (93.3)	58 (95.1)	5 (83.3)	28 (93.3)	33 (89.2)
Discontinued from Study[3], n (%)	1 (3.2)	2 (6.7)	3 (4.9)	1 (16.7)	2 (6.7)	4 (10.8)
Reasons for Discontinuation[3], n (%)						
Death, n (%)	0	0	0	0	0	0
Adverse Event, n (%)	0	0	0	1 (16.7)	0	1 (2.7)
Lack of Efficacy, n (%)	0	0	0	0	0	0
Lost to Follow-up, n (%)	1 (3.2)	2 (6.7)	3 (4.9)	0	1 (3.3)	1 (2.7)
Withdrawal by Subject, n (%)	0	0	0	0	0	0
Other, n (%)	0	0	0	0	1 (3.3)	2 (5.4)

Abbreviations: HCl=hydrochloride
1 Subject (b) (6) was not treated and the surgery type was unavailable.
2 Signed the informed consent form.
3 As randomized.
Source: Applicant's Study Report Body, submitted May 22, 2020, page 53

Fifty-eight subjects in Group 1 (12 to less than 17 years) and 33 subjects in Group 2 (6 to less than 12 years) completed the study. However, of the subjects who received EXPAREL, 30 subjects in Group 1 and 33 subjects in Group 2 completed the study. Twenty-eight of the 58 subjects in Group 1 were in the bupivacaine HCl group. In general, the subjects who received EXPAREL were evenly distributed between age groups.

Three subjects were lost to follow up in Group 1 – one subject who received EXPAREL and two subjects who received bupivacaine. The subject who received EXPAREL did not complete the 7-day follow up phone call or the 30-day follow up visit. The subjects who received bupivacaine

both did not complete the 30-day follow up visit.

In Group 2, two subjects were not treated, and one subject was lost to follow up. One subject who was not treated underwent cardiac surgery. This subject's chest was left open, and the investigational drug was not administered around the incision. The other subject who was not treated underwent spine surgery and experienced an adverse event during the procedure. This subject lost motor signals in the lower extremities prior to administration of the study drug. The surgery was discontinued, a wound vacuum-assisted closure device was applied, and a second surgery was performed at a later date. The subject who was lost to follow up underwent cardiac surgery and did not completed the 30-day follow up visit.

In Group 1, all of the subjects underwent spine surgery. In Group 2, only six subjects underwent spine surgery and 30 subjects underwent cardiac surgery. The uneven distribution of spine surgery subjects in Groups 1 and 2 is expected because children typically have spine surgery within three years of a growth spurt (i.e., 14 to 16 years old) and before skeletal maturity.[7] The distribution of the cardiac surgery subjects is also expected because children typically have congenital cardiac lesions that are identified early and the repair cannot wait until adolescence.

Protocol Violations/Deviations

The following two tables summarize the protocol deviations in Study 319.

Table 7. Protocol Deviations in Study 319 in Group 1 (12 to less than 17 Years)

Protocol Deviation Category	EXPAREL Study Arm N = 31 n (%)	Bupivacaine HCl Study Arm N = 30 n (%)	Total N = 61 n (%)
Subjects with any PD	20 (64.5)	19 (63.3)	39 (63.9)
Missing Vital Sign(s)	12 (38.7)	11 (36.7)	23 (37.7)
Missing NRS Pain Score	11 (35.5)	9 (30.0)	20 (32.8)
Missing Neurologic Assessment	9 (29.0)	8 (26.7)	17 (27.9)
Missing Laboratory Test	3 (9.7)	4 (13.3)	7 (11.5)
Eligibility Criteria Not Met (Inclusion #4 - Body Mass Index)	0 (0.0)	2 (6.7)	2 (3.3)
Missing ECG	1 (3.2)	1 (3.3)	2 (3.3)
Missing PK Sample	2 (6.5)	0 (0.0)	2 (3.3)
Missed Day 7 Phone Call or Day 30 Visit	0 (0.0)	1 (3.3)	1 (1.6)
Missing Color Analog Scale	1 (3.2)	0 (0.0)	1 (1.6)
Missing Unscheduled PK, ECG, and Labs for an AESI or SAE	0 (0.0)	1 (3.3)	1 (1.6)
Physical Exam Missing at Day 30 Visit	1 (3.2)	0 (0.0)	1 (1.6)
Study Drug Error (used commercial EXPAREL)	1 (3.2)	0 (0.0)	1 (1.6)

Source: Applicant's response to information request, submitted January 18, 2021, page 3

Table 8. Protocol Deviations in Study 319 in Group 2 (6 to less than 12 years)

Protocol Deviation Category	Spine Surgery N = 30 n (%)	Cardiac Surgery N = 6 n (%)	Total N = 37 n (%)
Subjects with any PD	21 (70.0)	4 (66.7)	25 (67.6)
Missing Vital Sign(s)	10 (33.3)	1 (16.7)	11 (29.7)
Eligibility Criteria Not Met (Inclusion #4 - Body Mass Index)	7 (23.3)	2 (33.3)	9 (24.3)
Missing Color Analog Scale	7 (23.3)	1 (16.7)	8 (21.6)
Missing Neurologic Assessment	5 (16.7)	1 (16.7)	6 (16.2)
Missing Laboratory Test	5 (16.7)	0 (0.0)	5 (13.5)
Missing ECG	4 (13.3)	0 (0.0)	4 (10.8)
Missing PK Sample	3 (10.0)	0 (0.0)	3 (8.1)
Non-compliance - Procedure Not Performed Per Protocol	2 (6.7)	1 (16.7)	3 (8.1)
Missed Day 7 Phone Call or Day 30 Visit	0 (0.0)	1 (16.7)	1 (2.7)

Source: Applicant's response to information request, submitted January 18, 2021, page 3

In Study 319, there were 11 significant protocol deviations identified. All the deviations were for subjects entered into the study with a BMI outside the criteria range, 5th to 95th percentile for age and sex. Refer to additional discussion on pediatric subjects with BMIs greater than 95th percentile in Section 8.5.

The primary objective of Study 319 was to evaluate the PK of EXPAREL in pediatric subjects aged 6 to less than 17 years undergoing spine or cardiac surgeries. The only PK-related protocol deviations were missing PK samples. Additional subjects were enrolled into the PK portion of the study to ensure completeness of the PK data.

The secondary objective of Study 319 was to evaluate the safety of EXPAREL in study subjects. The protocol deviations related to safety assessments were primarily related to missed assessments (e.g., individual vital signs assessments and neurological assessments). These missed assessments most likely did not impact the reliability or interpretability of the study results because the majority of assessment were obtained and the results were consistent across all study groups.

Efficacy measurements, pain scores using Numerical Rating Scale (NRS) or Color Analog Scale(CAS), were performed for exploratory purposes only. A total of 334 protocol deviations were associated with these exploratory endpoints. The majority of the missing pain intensity scale values were from assessments conducted prior to administration of analgesic rescue medication.

Overall, the significant protocol deviations and other minor protocol deviations during this study did not have a meaningful impact on the quality or integrity of the clinical data.

Demographic Characteristics

The following table describes the demographics in Group 1 (12 to less than 17 years).

Table 9. Summary of Demographics in Group 1 (12 to less than 17 years)

Characteristic	Group 1 (12 to <17 years)		
	EXPAREL 4 mg/kg n (%)	Bupivacaine HCl 2 mg/kg n (%)	Total
Age (years)			
n	31	30	61
Mean	13.8	13.9	13.8
SD	1.33	1.33	1.32
Median	14.0	14.0	14.0
Minimum, Maximum	12, 16	12, 16	12, 16
Sex, n (%)			
Female	28 (90.3)	22 (73.3)	50 (82.0)
Male	3 (9.7)	8 (26.7)	11 (18.0)
Ethnicity, n (%)			
Hispanic or Latino	10 (32.3)	7 (23.3)	17 (27.9)
Not Hispanic or Latino	19 (61.3)	23 (76.7)	42 (68.9)
Not reported	2 (6.5)	0	2 (3.3)
Race, n (%)			
Asian	2 (6.5)	0	2 (3.3)
Black/African American	5 (16.1)	3 (10.0)	8 (13.1)
White	21 (67.7)	26 (86.7)	47 (77.0)
Other	1 (3.2)	1 (3.3)	2 (3.3)
Native Hawaiian/ Pacific Islander	--	--	--
Not reported	2 (6.5)	0	2 (3.3)

Abbreviations: HCl=hydrochloride; SD=standard deviation
Source: Applicant's Study Body Report, submitted May 22, 2020, page 60

In Group 1, the study population was predominantly white (> 67%), non-Hispanic or Latino (> 61%), and female (> 73%). In each treatment group, the mean age of subjects was approximately 14 years (age range 12 to 16 years). This distribution is acceptable because there are no known differences in the pharmacokinetics or safety of EXPAREL according to race or gender.

The following table describes the demographics in Group 2 (6 to less than 12 years).

Table 10. Summary of Demographics in Group 2 (6 to less than 12 years)

Characteristic	Group 2 (6 to <12 years)		
	Spine Surgery	Cardiac Surgery	Total
Age (years), n			
n	5	29	34
Mean	10.0	8.7	8.9
SD	1.73	1.77	1.80
Median	11.0	8.0	9.0
Minimum, Maximum	7, 11	6, 12	6, 12
Sex, n (%)			
Female	2 (40.0)	14 (48.3)	16 (47.1)
Male	3 (60.0)	15 (51.7)	18 (52.9)
Ethnicity, n (%)			
Hispanic or Latino	0	9 (31.0)	9 (26.5)
Not Hispanic or Latino	5 (100.0)	20 (69.0)	25 (73.5)
Race, n (%)			
Asian	0	0	0
Black/African American	1 (20.0)	2 (6.9)	3 (8.8)
White	4 (80.0)	26 (89.7)	30 (88.2)
Other	0	0	0
Native Hawaiian/ Pacific Islander	0	1 (3.4)	1 (2.9)

Abbreviations: HCl=hydrochloride; SD=standard deviation
Source: Applicant's Study Body Report, submitted May 22, 2020, page 61

In Group 2, the study population was predominantly white (> 80%), non-Hispanic or Latino (> 69%), and was approximately balanced between males and females. The mean age for all subjects was approximately nine years (age range, six to 12 years), and half of the subjects (n=17) were between the ages of six years and eight years. This ratio is reassuring given the increased concern for systemic toxicity in the youngest subjects. As expected, the spine surgery subjects had a higher mean age (10 years) in comparison to the cardiac surgery subjects (8.7 years) because spine surgery typically occurs within 3 years of a growth spurt (i.e., 14 to 16 years) and cardiac surgery for congenital cardiac lesions typically occurs before adolescence.

Other Relevant Baseline Characteristics (e.g., disease characteristics)

In Group 1, most subjects had an American Society of Anesthesiologists (ASA) classification of 1 or 2. In Group 2, most subjects underwent cardiac surgery and had an ASA classification of 3.

The ASA Physical Status Classification System is used to assess and communicate pre-anesthetic medical co-morbidities and can be helpful in predicting perioperative risks. The system has six classifications ranging from an ASA 1 (a normal healthy subject) to an ASA 6 (a declared brain-dead subject whose organs are being removed for donor purposes).

Pediatric subjects with uncorrected congenital cardiac abnormalities are classified as ASA 3

physical status. Subjects undergoing cardiac surgery had, on average, more cardiovascular co-morbidities (e.g., valvular dysfunction and systolic and diastolic cardiac dysfunction) and greater risks of cardiorespiratory complications than the spine surgery subjects. Therefore, the evaluation of the pharmacokinetics and safety of EXPAREL in this population was particularly informative for this review.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study drug was administered intraoperatively by study staff.

The investigator or designee maintained accurate records demonstrating dates and units of drug received, lot numbers, subjects to whom drug was administered, and accounts of any drug destroyed accidentally or deliberately. Drug accountability data were confirmed by a study monitor. Inventory records were readily available for inspection by the study monitor and appropriate regulatory authorities at any time.

Intraoperatively, the use of opioids, acetaminophen, ketorolac, or other NSAIDs was permitted according to each respective site's standard of care. Mixing drugs with EXPAREL (e.g., epinephrine, dexamethasone, clonidine) was prohibited.

Postoperatively, rescue pain management was administered according to each study site's respective standard of care. The use of additional local anesthetics within 96 hours following administration of EXPAREL was prohibited.

Efficacy Results – Primary Endpoint

This study was not powered for efficacy and did not include a primary efficacy endpoint.

Data Quality and Integrity

The Applicant Study Body Report states (verbatim):

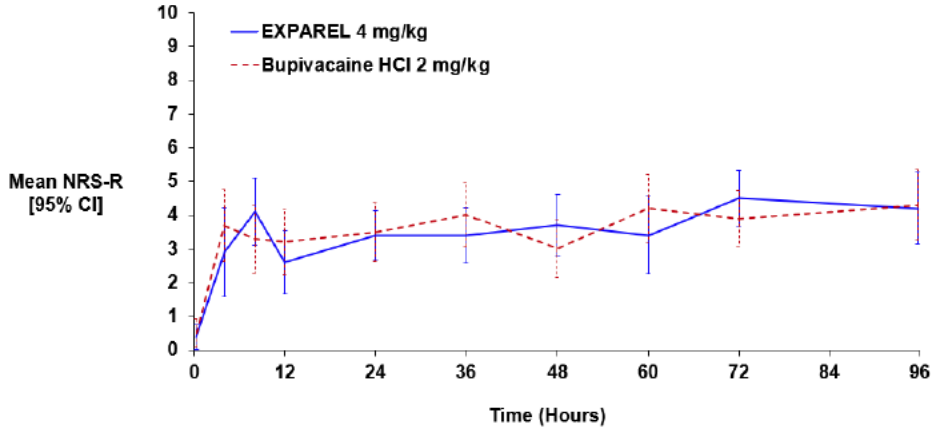
> Data for this study were recorded via an electronic data capture system using case report forms (CRFs) and were source-document verified. Each CRF was reviewed and approved by the investigator. A comprehensive validation check program was used to verify the data. Discrepancies were generated accordingly and transferred electronically to the CRF at the study center for resolution by the investigator or study coordinator.

Efficacy Results – exploratory endpoints

<u>Group 1 (12 to less than 17 years)</u>

The following figure compares NRS-R pain intensity scores in subjects in Group 1 who received EXPAREL versus the bupivacaine.

Figure 2. Mean NRS-R Pain Intensity Scores through 96 Hours in Study 319 (Group 1)



Note: NRS-R pain intensity scores are observed means and are not adjusted for rescue medication.
CI: confidence interval; CSR: clinical study report; HCl: hydrochloride; NRS-R: numeric rating scale at rest
Source: Applicant's Clinical Summary of Efficacy, submitted May 22, 2020, page 25

Figure 2 demonstrates that the mean NRS-R pain intensity scores were similar between the EXPAREL and Bupivacaine HCl groups over the 96 hours following spine surgery.

The following table provides a comparison of the area under the curve (AUC) of the pain intensity scores between the EXPAREL and Bupivacaine HCl groups.

Table 11. AUC of NRS-R Pain Intensity in Study 319 (Group 1)

AUC of NRS-R Pain Intensity, Mean (SD)	EXPAREL 4 mg/kg (N=31)	Bupivacaine HCl 2 mg/kg (N=30)
4-24 hours	51.0 (37.81)	64.7 (41.90)
4-48 hours	139.0 (63.05)	154.6 (83.70)
4-72 hours	232.6 (105.31)	241.4 (126.10)
4-96 hours	306.7 (137.43)	304.2 (162.43)
4 hours-hospital discharge	264.9 (124.79)	262.4 (155.45)

AUC: area under the curve; CSR: clinical study report; HCl: hydrochloride; NRS-R: numeric rating scale at rest; SD: standard deviation
Source: Applicant's Clinical Summary of Efficacy, submitted May 22, 2020, page 25

The mean AUC for NRS-R pain intensity scores were lower in the EXPAREL group through 72 hours and generally similar from 72 hours through hospital discharge. Since there was no standardization in intraoperative or postoperative pain regimen, it is not possible to conclude if these differences are clinically meaningful. Furthermore, this study was not powered to demonstrate significant differences in efficacy between study groups.

The following table provides a comparison of postoperative opioid use between the EXPAREL and Bupivacaine HCl groups.

Table 12. Postsurgical Opioid Pain Management Medication Use in Study 319 (Group 1)

	EXPAREL 4 mg/kg (N=31)	Bupivacaine HCl 2 mg/kg (N=30)
Postsurgical Consumption of Opioid Pain Management Medication (MME)		
0-24 hours		
Geometric Mean (%CV)	46.06 (91.665)	52.66 (70.126)
Median	62.50	90.80
Minimum, Maximum	0, 320.0	0.5, 290.0
0-48 hours		
Geometric Mean (%CV)	100.05 (80.116)	113.17 (64.124)
Median	109.50	132.95
Minimum, Maximum	15.0, 546.5	15.5, 455.5
0-72 hours		
Geometric Mean (%CV)	136.61 (66.942)	155.17 (57.927)
Median	125.00	158.30
Minimum, Maximum	30.0, 546.5	49.2, 532.5
Time to First Use of Postsurgical Opioid Pain Management Medication (hours)		
Subjects Administered, n (%)	31 (100.0)	29 (96.7)
Median (Q1, Q3)	0.82 (0.40, 6.90)	0.60 (0.33, 0.98)
Minimum, Maximum	0.05, 38.10	0.13, 7.43

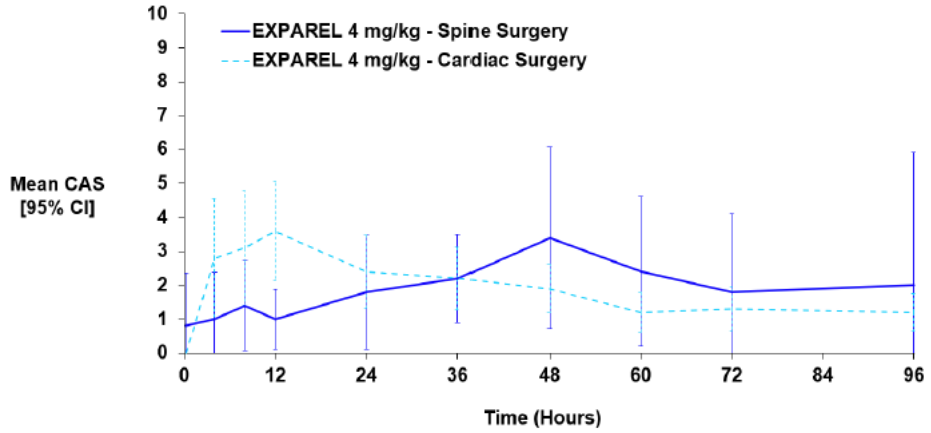
CSR: clinical study report; CV: coefficient of variation; HCl: hydrochloride; MME: morphine milligram equivalents; Q1: first quartile; Q3: third quartile
Source: Applicant's Clinical Summary of Efficacy, submitted May 22, 2020, page 27

In Group 1, all subjects, except for one subject in the bupivacaine HCl group, received opioid medications postoperatively. The geometric mean total opioid consumption over 72 hours was approximately 137 morphine milligram equivalents (MME) in the EXPAREL group and approximately 155 MME in the Bupivacaine HCl group. The median time to first postsurgical opioid medication use was 0.82 hours in the EXPAREL group and 0.60 hours in the Bupivacaine HCl group. Since there was no standardization in intraoperative or postoperative pain regimen, it is not possible to conclude if the differences in MME or in time to first opioid use are clinically meaningful. Furthermore, this study was not powered to demonstrate a difference in this endpoint.

Group 2 (6 to less than 12 years)

The following figure compares CAS pain intensity scores in subjects in Group 2 who received EXPAREL versus the bupivacaine.

Figure 3. Mean CAS Pain Intensity Scores through 96 Hours in Study 319 (Group 2)



Note: CAS pain scores are observed means and are not adjusted for rescue medication.
CAS: color analog scale; CI: confidence interval; CSR: clinical study report
Source: Applicant's Clinical Summary of Efficacy, submitted May 22, 2020, page 26

All subjects in Group 2 received EXPAREL. The mean CAS scores were lower in spine surgery group than cardiac surgery group through 36 hours and were higher in spine surgery group from 36 hours to 96 hours; however, the difference from 72 to 96 hours was minimal. The mean CAS scores were generally low in both surgical procedures at all time points through 96 hours.

The etiology for the lower pain scores in spine surgery subjects in the first 36 hours and higher pain scores from 36 to 96 hours is not apparent. Differences in institutional intraoperative and postoperative pain regimens, as well as, differences in postoperative physical therapy requirements, may have contributed to the differences in mean CAS scores in these groups.

The following table provides a comparison of the AUC of CAS pain intensity scores between the spine surgery group and the cardiac surgery group.

Table 13. AUC of CAS Pain Intensity in Study 319 (Group 2)

AUC of CAS Pain Intensity, Mean (SD)	EXPAREL 4 mg/kg Spine Surgery (N=5)	EXPAREL 4 mg/kg Cardiac Surgery (N=29)
4-24 hours	30.2 (21.99)	46.9 (45.04)
4-48 hours	92.7 (64.53)	101.0 (76.35)
4-72 hours	153.5 (113.87)	134.3 (89.09)
4-96 hours	223.5 (184.73)	158.8 (104.26)
4 hours-hospital discharge	192.3 (141.43)	155.8 (99.07)

AUC: area under the curve; CAS: color analog scale; CSR: clinical study report; SD: standard deviation
Source: Applicant's Clinical Summary of Efficacy, submitted May 22, 2020, page 26

The mean AUC values for CAS pain intensity scores with EXPAREL were lower in the spine surgery group than the cardiac surgery group through 48 hours and were higher in the spine surgery group through 96 hours.

The following table provides a comparison of postoperative opioid use between the spine surgery group and the cardiac surgery group.

Table 14. Postsurgical Opioid Pain Management Medication Use in Study 319 (Group 2)

	EXPAREL 4 mg/kg Spine Surgery (N=5)	EXPAREL 4 mg/kg Cardiac Surgery (N=29)
Postsurgical Consumption of Opioid Pain Management Medication (MME)		
0-24 hours		
Geometric Mean (%CV)	1.84 (120.869)	16.63 (74.389)
Median	3.75	18.00
Minimum, Maximum	0, 16.8	0.5, 70.5
0-48 hours		
Geometric Mean (%CV)	6.48 (82.613)	20.94 (80.100)
Median	15.00	27.00
Minimum, Maximum	0, 34.2	0, 91.0
0-72 hours		
Geometric Mean (%CV)	10.65 (80.991)	23.53 (88.519)
Median	30.45	27.00
Minimum, Maximum	0, 64.2	0, 145.0
Time to First Use of Postsurgical Opioid Pain Management Medication (hours)		
Subjects Administered, n (%)	4 (80.0)	28 (96.6)
Median (Q1, Q3)	15.77 (9.00, 19.68)	2.43 (1.37, 4.25)
Minimum, Maximum	0.68, 72.00*	0.22, 72.00*

* censored observation
CSR: clinical study report; CV: coefficient of variation; MME: morphine milligram equivalents; Q1: first quartile; Q3: third
Source: Applicant's Clinical Summary of Efficacy, submitted May 22, 2020, page 28

In Group 2, all subjects, except one spine surgery subject and one cardiac surgery subject, received opioid medications postoperatively. The geometric mean total opioid consumption over 72 hours was approximately 11 MME in subjects who had spine surgery and approximately 24 MME in subjects who had cardiac surgery. Since there was no standardization in intraoperative or postoperative pain regimen, it is not possible to conclude if the total MME use is clinically meaningful.

The median time to first postsurgical opioid medication use was 15.8 hours following spine surgery and 2.4 hours following cardiac surgery. The Applicant proposed that this difference may be due to the smaller sample size in spine surgery group (n=5) versus the sample size of the cardiac surgery group (n=29). This explanation is reasonable because when assessing the spine surgery subjects in Group 1 and Group 2 together (n=36), the median time to first rescue medication is shorter for all spine surgery subjects who received EXPAREL in Study 319 (i.e., 0.95 hours) compared to all cardiac surgery subjects (i.e., 2.43 hours). It is unclear whether the time to first opioid use is clinically meaningful, as there was no active comparator for this age group.

Dose/Dose Response

A single dose of EXPAREL, 4 mg/kg up to 266 mg, was administered during this study.

Durability of Response

EXPAREL was a given as a single dose and had an expected duration of action up to 72 hours based on previous adult data.

Persistence of Effect

EXPAREL is an extended-release local anesthetic that has a bimodal curve with an initial peak occurring at approximately 0 to 2 hours and a second peak at approximately 24 to 48 hours after single-dose administration. Given that EXPAREL is not intended for long-term or chronic use, long-term efficacy studies were not included in the pediatric clinical development program of EXPAREL. Data on the persistence of efficacy (i.e., beyond 96 hours or hospital discharge) and tolerance effects are not available or applicable.

7. Integrated Review of Effectiveness

This section is not relevant to this sNDA. One study (Study 319) evaluated efficacy endpoints for exploratory purposes only. Therefore, the integration of efficacy data is not necessary.

8. Review of Safety

8.1. Safety Review Approach

This review focused on the evaluation of the safety of EXPAREL via local infiltration in children aged 6 to less than 17 years. The pivotal study, Study 319, included subjects aged 6 to less than 17 years undergoing spine surgery and cardiac surgery; whereas, the pilot study, Study 120, included subjects aged 12 to 17 years undergoing spine surgery only. The most important safety issue related to EXPAREL is LAST, which can present as central nervous system excitation and/or depression and cardiotoxicity. Furthermore, since EXPAREL is an extended-release local anesthetic, the possibility of delayed presentation of LAST was also evaluated.

The objective of Study 120 was to evaluate the pharmacokinetics and safety of EXPAREL in children aged 12 to less than 17 years having spine surgery. This type of surgery was selected as a procedure in a highly vascular anatomical area with the expected highest systemic absorption of EXPAREL. Preliminary data from this study was used to confirm the safety of the dose of EXAPREL 4 mg/kg for Study 319.

The objective of Study 319 was to evaluate the pharmacokinetics and safety of EXPAREL in

children aged 6 to less than 17 years undergoing spine or cardiac surgery. These procedures were chosen because they represent highly vascular anatomical compartments where the expected absorption of EXPAREL would be high in comparison to other less vascularized surgical sites. The administration of EXPAREL at these surgical sites would likely yield the highest systemic plasma concentration of EXPAREL, and therefore, result in the highest risk for local anesthetic systemic toxicity. In addition, pediatric subjects with underlying cardiac conditions who undergo cardiac surgery are considered to be more susceptible to the risks of local anesthetic systemic toxicity than those without such cardiac conditions.[8] Furthermore, patients who undergo cardiac and spine surgical procedures generally require prolonged hospital stays, which allowed for complete characterization of the pharmacokinetic profile in these pediatric subjects.

During Study 319 protocol negotiation phase, the Applicant and the Division discussed that if the Applicant is able to demonstrate the safety of EXPAREL when administered via infiltration into these highly vascular surgical sites, and if the Applicant was able to match the pediatric PK data to adult PK data from similar surgical procedures, then the safety of EXPAREL 4mg/kg, up to 266 mg, may be extrapolated to all surgical sites requiring wound infiltration in children ages 6 to less than 17 years.

The assessment of the safety of EXPAREL via local infiltration in children 6 to less than 17 years was based on the data from Studies 120 and 319. The review of this data focused on adverse events that may be associated with signs and symptoms of LAST (e.g., arrythmias, dizziness, paresthesia) in relation to the timing of the administration of EXPAREL and determination of the probable cause of the adverse events (e.g., EXPAREL, procedure type, subject co-morbidities). The review of adverse events in the younger age group, aged 6 to less than 12, was particularly informative because the cardiac subjects in this group were considered more susceptible to LAST due to their cardiac co-morbidities.[8] In addition, children aged 6 to less than 12 years typically have not started puberty, and therefore, their body compositions differ from adults; whereas, adolescents aged 12 to less than 17 years typically have similar body compositions to adults. These differences may affect systemic exposure and clearance of drugs.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In Studies 120 and 319, there were 80 pediatric subjects, ages 6 to less than 17 years, who received EXPAREL 4 mg/kg via wound infiltration.

A total of 15 subjects participated in Study 120 to evaluate the safety of EXPAREL via local infiltration in children 12 to less than 17 years. All 15 subjects underwent spine surgery and received 4 mg/kg of EXPAREL. The number of subjects was adequate for a pilot study. This study provided additional data to support the safety of the proposed EXPAREL dose of 4 mg/kg.

Ninety-five subjects participated in Study 319 to assess the safety of EXPAREL via local

infiltration in children 6 to less than 17 years. In Group 1 (12 to less than 17 years), 61 subjects underwent spinal surgery – 31 subjects received EXPAREL 4mg/kg and 30 subjects received bupivacaine HCl 2mg/kg as an active comparator. In Group 2 (6 to less than 12 years), five subjects underwent spinal surgery and 29 subjects underwent cardiac surgery. All of the subjects in Group 2 received EXPAREL 4 mg/kg. A total of 65 subjects received EXPAREL.

There was a significantly lower number of subjects in Group 2 who underwent spine surgery versus cardiac surgery. Children often have spine surgery within 3 years of a growth spurt (i.e., 14 to 16 years old) and before skeletal maturity.[7] In comparison, children that have cardiac surgery typically have congenital cardiac lesions that are identified early and the repair cannot wait until adolescence. Therefore, the distribution of subjects in Group 2 of Study 319 is expected. However, this distribution does present limitations in regard to data interpretation.

Given the safety profile of EXAPREL in adults, there was adequate exposure of EXPAREL 4 mg/kg in children aged 6 to less than 17 years to assess the safety of this dose in this population.

8.2.2. Relevant characteristics of the safety population:

In Study 319, the population included children aged 6 to less than 17 years undergoing spine or cardiac surgeries. As described above, all of the subjects in Group 1 and five subjects in Group 2 underwent spine surgery; whereas, the remainder of the subjects in Group 2 underwent cardiac surgery. Overall, the subjects who underwent cardiac surgery had more cardiovascular co-morbidities (i.e. valvular dysfunction and systolic and diastolic dysfunction) with greater risks of cardiorespiratory complications than the subjects who underwent spine surgery.

8.2.3. Adequacy of the safety database:

A total of 80 subjects aged 6 to less than 17 years received EXPAREL in Studies 120 and 319. Data were pooled from Studies 120 and 319. The adverse events findings in pediatric subjects enrolled in these studies were similar to those seen in the adult studies. There was a small number of serious adverse events that were not attributed to EXPAREL, and there were no apparent cases of LAST or delayed LAST in either of these studies. The safety database is considered adequate to support the proposed indication of EXAPREL for single-dose local infiltration in pediatric subjects aged 6 to less than 17 years.

8.2.4. Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

An AE was considered a treatment-emergent adverse event (TEAE) if the date and time of onset was between the start time of study drug administration and the final Day 30 visit.

Adverse Events were categorized as TEAEs, treatment-emergent serious adverse events

(TESAEs), and TEAEs of special interest (TEAESIs).

The following is a table of TEAESIs as defined by MedDRA.

Table 15. Treatment-Emergent Adverse Events of Special Interest

Group	Protocol term	MedDRA 21.1 Dictionary Preferred Term
Cardiac	Chest pain	Chest Pain
	Abnormal/irregular heart rate	Heart Rate Irregular
	Shortness of breath requiring intervention	Dyspnoea
Neurologic	Seizure	Seizure
	Altered mental status	Mental Status Changes
	Altered sensorium	Depressed Level of Consciousness
	Rigidity	Muscle Rigidity
	Dysarthria	Dysarthria
	Tremors	Tremor
	Tinnitus	Tinnitus
	Visual disturbance	Visual Impairment
	Dizziness[1]	Dizziness
Other	Dizziness[2]	Dizziness
	Hyperesthesia[2]	Hyperaesthesia
	Muscular twitching[2]	Muscle Twitching
	Tingling[2]	Paresthesia
	Paresthesia[2]	Paresthesia

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities
1 If severe or worsening
2 If event persisted or occurred 72 hours after start of study treatment dose

Source: Applicant's Study Body Report, submitted May 22, 2020, page 49.

The selection of TEAESIs is appropriate for this study drug and this study population. Cardiac and neurologic adverse events were considered TEAESIs because LAST typically presents with adverse events in these organ systems. The "other" adverse events were considered of special interest because they are often associated with chosen study procedures, spine and cardiac surgeries. For example, spine surgery subjects may report dizziness due to prone positioning or paresthesia and muscle twitching due to instrumentation of the spinal vertebrae near spinal nerve endings. However, dizziness, paresthesia, and muscle twitching may also be symptoms of LAST. Therefore, interpretation of these events in isolation maybe be difficult, as they could be easily attributed to either the surgical procedure or as a manifestation of LAST. The type of procedure, intraoperative and postoperative medications, time of onset, duration, and concomitantly-occurring adverse events must be evaluated to allow for clinical interpretation and distinction of surgically-related AEs versus LAST-related AEs.

8.2.5. Routine Clinical Tests

Clinical laboratory assessments (i.e., hematology, chemistry, and urinalysis) were collected at baseline (i.e., Day 1 prior to the end of study drug administration) and 96 hours after study drug administration. Refer to Section 6.1.1 "Study Procedures" for additional information.

8.3. Safety Results

The following several sections will discuss, in detail, all relevant safety results.

8.3.1. Deaths

There were no deaths reported in Study 319 or Study 120.

8.3.2. Treatment-Emergent Serious Adverse Events

Study 120

The following table summarizes the TESAEs in Study 120.

Table 16. Summary of Incidence of TESAEs in Study 120

System Organ Class Preferred Term	Total [N=15] n(%)
Subjects with at least one serious TEAE	3 (20.0)
Musculoskeletal and connective tissue disorders	2 (13.3)
Flank pain	1 (6.7)
Muscular weakness	2 (13.3)
Nervous system disorders	1 (6.7)
Paresthesia	1 (6.7)

CSR: clinical study report; TESAE: treatment-emergent serious adverse event
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, Page 20

Three subjects in Study 120 experienced a TESAE after spine surgery. One subject had decreased motor signals in the lower extremities after EXPAREL administration and prior to subcutaneous closure. A wake-up test demonstrated that the subject was unable to move the lower extremities, and a TESAE of muscular weakness was recorded. The spinal fusion instrumentation was removed, and new instrumentation was placed. The subject had improved motor signals in both lower extremities prior to wound closure. Therefore, this TESAE was more likely due to the instrumentation in the spinal vertebrae than to local nerve toxicity or systemic toxicity from EXPAREL. Another subject reported the TESAEs of muscular weakness and flank pain on Day 5. A computerized tomogram revealed a T4 screw encroaching on the spinal canal. The subject returned to the operating room, and the screw was removed. The muscular weakness and the flank pain resolved on Day 58. Similarly to the first case, the TESAEs in this subject were more likely due to the instrumentation in the spinal vertebrae than to local or systemic toxicity from EXPAREL. The third subject reported paresthesia in the right lower extremity on Day 1, which did not resolve until Day 105. Paresthesias are commonly associated with spine surgery, and this subject did not report any other signs or symptoms of LAST on Day 1. Therefore, this TESAE was also unlikely related to EXPAREL.

Study 319

There were no subjects in Group 1 (12 to less than 17 years) in Study 319 who experienced a treatment-emergent serious adverse event.

Two subjects in Group 2 (6 to less than 12 years), both in the cardiac surgery group, experienced at least one TESAE. The TESAEs were considered by the Investigator not to be related to the investigational drug and did not result in discontinuation from the study.

The following table summarizes the TESAEs in Study 319, which all occurred in Group 2 (6 to 12 years old).

Table 17. Summary of Incidence of TESAEs in Study 319 in Group 2

System Organ Class Preferred Term	Spine Surgery [N=5] n (%)	Cardiac Surgery [N=29] n (%)
Subjects with at least one Serious TEAE	0	2 (6.9)
Gastrointestinal disorders	0	1 (3.4)
Vomiting	0	1 (3.4)
Infections and infestations	0	1 (3.4)
Wound infection fungal	0	1 (3.4)
Respiratory, thoracic and mediastinal disorders	0	1 (3.4)
Dyspnea	0	1 (3.4)

CSR: clinical study report; TEAE: treatment-emergent adverse event
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 33

Two subjects who underwent cardiac surgery for congenital heart disease had TESAEs. One of these subjects had a sternal wound fungal infection on Day 1 and vomiting on Day 8. The culture for the infection was obtained prior to the administration of EXPAREL, and the vomiting occurred beyond the expected duration of EXPAREL (i.e., 72 hours). The first SAE occurred prior to the administration of EXPAREL, and the second SAE occurred beyond the expected duration of EXPAREL. Therefore, it is unlikely that either SAE was related to EXPAREL. The other subject experienced dyspnea on Day 11. The timing of the SAE of dyspnea was well beyond the expected duration of EXPAREL, and therefore, it is also unlikely that this event was related to EXPAREL.

8.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 120

In Study 120, there were no dropouts or discontinuations.

Study 319

In Study 319, there was one subject who was discontinued from the study due to an adverse

event. This subject was in Group 2 (6 to less than 12 years) and underwent spine surgery. During the procedure, motor signals were lost prior to administration of the study drug. The procedure was aborted, a wound vacuum-assisted closure device was placed, and the procedure was completed at a later date. The study drug was not administered due to this adverse event.

8.3.4. Treatment-Emergent Adverse Events of Special Interest

Study 120

The following table summarizes the treatment-emergent adverse events of special interest in Study 120.

Table 18. Summary of Incidence of TEAESIs in Study 120

System Organ Class Preferred Term	Total [N=15] n (%)
Subjects with at least one TEAE of special interest	14 (93.3)
Cardiac disorders	11 (73.3)
Bradycardia	4 (26.7)
Tachycardia	8 (53.3)
Ventricular extrasystoles	1 (6.7)
Eye disorders	1 (6.7)
Vision blurred	1 (6.7)
Gastrointestinal disorders	2 (13.3)
Hypesthesia oral	2 (13.3)
Musculoskeletal and connective tissue disorders	5 (33.3)
Muscle spasms	2 (13.3)
Muscle twitching	4 (26.7)
Muscular weakness	1 (6.7)
Nervous system disorders	4 (26.7)
Dizziness	1 (6.7)
Hypesthesia	2 (13.3)
Paresthesia	1 (6.7)

CSR: clinical study report; TEAESI: treatment-emergent adverse event of special interest
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 21

Fourteen of the 15 subjects in Study 120 experienced a TEAESI; however, all 15 subjects completed the study. The most common TEAESI was transient tachycardia, which was most likely a reflex response to hypotension from postoperative anemia, observed in all 15 subjects. One subject had transient premature ventricular contractions, recorded as ventricular extrasystoles, which resolved without treatment. This subject had a Cmax of 433 ng/mL, which is below plasma levels associated with local anesthetic systemic toxicity. Another subject reported muscular weakness, which resolved after rod removal, and therefore, was unlikely related to EXPAREL. The rest of the TEAESIs were similar to the adverse events observed in Study 319 and in adult studies. The mean Cmax for the 14 subjects with TEAESIs was 391 ng/mL, and the mean Cmax for all 15 subjects was 410 ng/mL (min 78.8 ng/mL, max 559 ng/mL), which is below plasma levels typically associated with local anesthetic systemic toxicity.

Study 319

Five subjects in Group 1 (two received EXPAREL, three received bupivacaine) had a treatment-emergent adverse events of special interest (TEAESI). These TEAESIs were not considered related to the investigational drug by the investigator and did not result in discontinuation from the study.

There were no TEAESI in Group 2 (6 to less than 12 years).

The following table summarizes the treatment-emergent adverse events of special interest in Study 319, which all occurred in Group 1.

Table 19. Summary of Incidence of TEAESIs in Study 319 in Group 1 (12 to less than 17 years)

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with at least one TEAE of Special Interest	2 (6.5)	3 (10.0)
Musculoskeletal and connective tissue disorders	1 (3.2)	2 (6.7)
Muscle twitching	1 (3.2)	2 (6.7)
Nervous system disorders	1 (3.2)	0
Dizziness	1 (3.2)	0
Cardiac disorders	0	1 (3.2)
Tachycardia	0	1 (3.2)

CSR: clinical study report; TEAE: treatment-emergent adverse event; TEAESI: treatment-emergent adverse event of special interest

Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 33

Two subjects who underwent spine surgery for idiopathic scoliosis had TEAESIs. One subject had mild dizziness on Day 2 that did not resolve until Day 21, which is beyond the expected duration of EXPAREL. This subject also had moderate postoperative anemia on Day 2, which is more likely to be the cause of this TEAESI than systemic toxicity from EXPAREL. In addition, this subject's PK level on Day 2 was 214 ng/mL, which is below plasma levels typically associated with local anesthetic systemic toxicity. The other subject had muscle twitching at the incision, which resolved without treatment on Day 5. Transient muscle twitching often occurs after spine surgery and is unlikely associated with systemic toxicity. This subject did not report any other adverse events, which also suggests that this TEAESI was not associated with systemic toxicity. In addition, this subject's PK level on Day 2 was 155 ng/mL, which is below plasma levels typically associated with local anesthetic systemic toxicity.

8.3.5. Other Treatment Emergent Adverse Events and Adverse Reactions

Study 120

The following table summarizes all of the TEAEs for all subjects in Study 120.

Table 20. Summary of TEAEs in Study 120

Number of	Total [N=15] n (%)
Subjects with any TEAE[a]	15 (100)
Maximum Severity of Mild	3 (20.0)
Maximum Severity of Moderate	12 (80.0)
Maximum Severity of Severe	0
At least one Related TEAE[b]	15 (100)
At least one Serious TEAE	3 (20.0)
At least one TEAE of Special Interest	14 (93.3)
Subjects Discontinued due to TEAE	0
Died on Study	0

CSR: clinical study report; TEAE: treatment-emergent adverse event
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 18

All 15 subjects experienced at least one TEAE during the study. No subjects were discontinued from the study due to a TEAE.

The following table summarizes the incidence of TEAEs in Study 120.

Table 21. Summary of Incidence of TEAEs in Study 120

System Organ Class Preferred Term	Total [N=15] n (%)
Subjects with at least one TEAE	15 (100)
Blood and lymphatic system disorders	15 (100)
Anemia	15 (100)
Cardiac disorders	12 (80.0)
Bradycardia	5 (33.3)
Tachycardia	8 (53.3)
Eye disorders	4 (26.7)
Vision blurred	3 (20.0)
Gastrointestinal disorders	14 (93.3)
Constipation	7 (46.7)
Hypesthesia oral	2 (13.3)
Nausea	9 (60.0)
Vomiting	8 (53.3)
General disorders and administration site conditions	3 (20.0)
Pyrexia	3 (20.0)
Musculoskeletal and connective tissue disorders	12 (80.0)
Back pain	2 (13.3)
Muscle spasms	3 (20.0)
Muscle twitching	9 (60.0)
Muscular weakness	2 (13.3)
Nervous system disorders	7 (46.7)
Dizziness	3 (20.0)
Hypesthesia	3 (20.0)
Renal and urinary disorders	2 (13.3)
Hematuria	2 (13.3)
Respiratory, thoracic and mediastinal disorders	7 (46.7)
Tachypnea	6 (40.0)
Skin and subcutaneous tissue disorders	6 (40.0)
Pruritus	6 (40.0)
Vascular disorders	14 (93.3)
Hypotension	14 (93.3)

CSR: clinical study report; TEAE: treatment-emergent adverse event
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 19

The most common TEAEs (> 10%) in Study 120 (n=15) were postoperative anemia, hypotension, tachycardia, nausea, and muscle twitching. Postoperative anemia and hypotension, also observed in Study 319, were likely due to significant blood loss and fluid shifts that often occur during spine surgery. Transient tachycardia is likely a reflex response to the anemia and hypotension. GI adverse events (i.e., nausea) are well documented in adults who received EXPAREL and were the most common adverse event reported among subjects in Study 319. Transient muscle twitching is also commonly observed in spine surgery subjects. Overall, the adverse event profile of EXPAREL in Study 120 was very similar to that of Study 319 and did not produce any new safety concerns.

Study 319

The following table summarizes all of the TEAEs for all subjects in Study 319.

Table 22. Summary of TEAEs in Study 319

	Group 1 (12 to <17 years)		Group 2 (6 to <17 years)	
Number of	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)	Spine Surgery [N=5] n (%)	Cardiac Surgery [N=29] n (%)
Subjects with any TEAE	19 (61.3)	22 (73.3)	5 (100)	9 (31.0)
Maximum Severity of Mild	12 (38.7)	14 (46.7)	3 (60.0)	6 (20.7)
Maximum Severity of Moderate	7 (22.6)	7 (23.3)	2 (40.0)	3 (10.3)
Maximum Severity of Severe	0	1 (3.3)	0	0
At least one Related TEAE	2 (6.5)	5 (16.7)	3 (60.0)	0
At least one Serious TEAE	0	0	0	2 (6.9)
At least one TEAE of Special Interest	2 (6.5)	3 (10.0)	0	0
Subjects Discontinued due to TEAE	0	0	0	0
Died on Study	0	0	0	0

Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 27

In Group 1, nineteen of 31 subjects who received EXPAREL and 22 of 30 subjects who received Bupivacaine HCl experienced a TEAE. In Group 2, all five subjects who underwent spine surgery and nine of 29 subjects who underwent cardiac surgery experienced a TEAE. No subjects were discontinued from the study due to a TEAE.

The following two tables summarize the incidence of TEAEs in Group 1 in Study 319.

Table 23. Summary of Incidence of TEAEs in Study 319 in Group 1 (12 to less than 17 years)

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with at least one TEAE	19 (61.3)	22 (73.3)
Gastrointestinal disorders	14 (45.2)	15 (50.0)
Constipation	8 (25.8)	9 (30.0)
Nausea	10 (32.3)	6 (20.0)
Vomiting	9 (29.0)	5 (16.7)
Hypesthesia oral	1 (3.2)	3 (10.0)
Diarrhea	2 (6.5)	0
Dyspepsia	1 (3.2)	0
Musculoskeletal and connective tissue disorders	6 (19.4)	11 (36.7)
Muscle twitching	2 (6.5)	8 (26.7)
Muscle spasms	3 (9.7)	0
Muscular weakness	0	3 (10.0)
Musculoskeletal pain	1 (3.2)	0
Pain in extremity	0	1 (3.3)
Eye disorders	7 (22.6)	6 (20.0)
Vision blurred	4 (12.9)	3 (10.0)
Visual impairment	2 (6.5)	2 (6.7)
Diplopia	1 (3.2)	0
Lacrimation increased	0	1 (3.3)
Nervous system disorders	3 (9.7)	8 (26.7)
Dizziness	2 (6.5)	2 (6.7)
Dysgeusia	1 (3.2)	1 (3.3)
Headache	0	2 (6.7)
Hypesthesia	0	2 (6.7)
Paresthesia	0	2 (6.7)
Syncope	1 (3.2)	0
Vascular disorders	2 (6.5)	8 (26.7)
Hypotension	2 (6.5)	7 (23.3)
Hot flush	0	1 (3.3)
Systolic hypertension	0	1 (3.3)
Injury, poisoning and procedural complications	6 (19.4)	1 (3.3)
Anemia postoperative	4 (12.9)	0
Incision site hemorrhage	1 (3.2)	0

Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 28

Table 24. Summary of Incidence of TEAEs in Study 319 in (Group 1: 12 to <17 years) – continued

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Joint dislocation	1 (3.2)	0
Procedural hemorrhage	0	1 (3.3)
Cardiac disorders	2 (6.5)	4 (13.3)
Tachycardia	1 (3.2)	4 (13.3)
Bradycardia	1 (3.2)	0
Respiratory, thoracic and mediastinal disorders	2 (6.5)	2 (6.7)
Bradypnea	0	1 (3.3)
Hypopnea	1 (3.2)	0
Hypoxia	1 (3.2)	0
Pleural effusion	0	1 (3.3)
Tachypnea	0	1 (3.3)
Skin and subcutaneous tissue disorders	2 (6.5)	2 (6.7)
Pruritus	1 (3.2)	2 (6.7)
Pruritus generalized	1 (3.2)	0
Ear and labyrinth disorders	2 (6.5)	1 (3.3)
Hypoacusis	2 (6.5)	1 (3.3)
General disorders and administration site conditions	2 (6.5)	1 (3.3)
Chest pain	1 (3.2)	0
Generalized edema	0	1 (3.3)
Pyrexia	1 (3.2)	0
Investigations	2 (6.5)	0
Heart rate increased	1 (3.2)	0
Urine output decreased	1 (3.2)	0
Renal and urinary disorders	2 (6.5)	0
Incontinence	2 (6.5)	0
Immune system disorders	0	1 (3.3)
Hypersensitivity	0	1 (3.3)
Infections and infestations	1 (3.2)	0
Ear infection	1 (3.2)	0
Psychiatric disorders	0	1 (3.3)
Anxiety	0	1 (3.3)

CSR: clinical study report; HCl: hydrochloride; TEAE: treatment-emergent adverse event
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 29

In Group 1, the most common TEAEs (>10%) in the EXPAREL group were nausea, vomiting, constipation, blurred vision, and postoperative anemia. These findings are consistent with the most common adverse events in adult subjects who received EXPAREL via local infiltration, except for blurred vision, which was a less common TEAE in adults. The greater frequency of blurred vision in the pediatric population may be due to prone positioning during spine surgery. Overall, these TEAEs do not present any new safety concerns.

In comparison, in the bupivacaine group, the most common TEAEs (>10%) were constipation, muscle twitching, hypotension, nausea, vomiting, tachycardia, oral hypesthesia, muscular weakness, and blurred vision. Besides postoperative anemia, which is likely due to surgical blood loss, these adverse events are similar to those in the EXPAREL group. Blurred vision and oral hypesthesia are likely due to prone positioning, and muscle twitching and muscular weakness are likely due to instrumentation in the spinal vertebrae near spinal nerve endings.

The following table summarizes the incidence of TEAEs in Group 2 in Study 319.

Table 25. Summary of Incidence of TEAEs in Study 319 in Group 2 (6 to less than 12 years)

System Organ Class Preferred Term	Spine Surgery [N=5] n (%)	Cardiac Surgery [N=29] n (%)
Subjects with at least one TEAE	5 (100)	9 (31.0)
Gastrointestinal disorders	4 (80.0)	7 (24.1)
Constipation	1 (20.0)	4 (13.8)
Vomiting	1 (20.0)	4 (13.8)
Hypesthesia oral	3 (60.0)	0
Nausea	1 (20.0)	2 (6.9)
Diarrhea	1 (20.0)	0
Eye disorders	3 (60.0)	1 (3.4)
Vision blurred	3 (60.0)	1 (3.4)
Metabolism and nutrition disorders	0	3 (10.3)
Acidosis	0	1 (3.4)
Hyperglycemia	0	1 (3.4)
Hypomagnesaemia	0	1 (3.4)
Metabolic acidosis	0	1 (3.4)
Musculoskeletal and connective tissue disorders	2 (40.0)	1 (3.4)
Muscle twitching	1 (20.0)	1 (3.4)
Muscle spasms	1 (20.0)	0
Vascular disorders	2 (40.0)	1 (3.4)
Hypotension	2 (40.0)	0
Hypertension	0	1 (3.4)
Cardiac disorders	1 (20.0)	1 (3.4)
Bradycardia	1 (20.0)	0
Sinus tachycardia	0	1 (3.4)
Injury, poisoning and procedural complications	2 (40.0)	0
Anemia postoperative	1 (20.0)	0
Delayed recovery from anesthesia	1 (20.0)	0
Seroma	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1 (3.4)
Dyspnea	0	1 (3.4)
Tachypnea	1 (20.0)	0
Skin and subcutaneous tissue disorders	2 (40.0)	0
Pruritus	2 (40.0)	0
General disorders and administration site conditions	0	1 (3.4)
Face edema	0	1 (3.4)
Infections and infestations	0	1 (3.4)
Wound infection fungal	0	1 (3.4)

CSR: clinical study report; TEAE: treatment-emergent adverse event
Source: Applicant's Clinical Summary of Safety, submitted May 22, 2020, page 30

In Group 2, there were numerous TEAEs occurring in greater than 10% of subjects in the spine surgery cohort. However, since the number of subjects in this cohort was very low (n=5), it was difficult to interpret the clinical significance of these events, particularly because there was no comparator group. The following TEAEs were considered further in the context of LAST: oral hypesthesia, blurred vision, hypotension, and pruritus. Based on the type of surgery and lack of additional TEAEs that would be concerning for LAST in each subject, these events did not appear to represent LAST and were more likely due to the surgical procedure. The most frequently occurring TEAEs (> 10%) in the cardiac surgery cohort (n=29) were constipation and vomiting. The subjects in the spine surgery cohort had a higher incidence of blurred vision and oral hypesthesia than the cardiac surgery group. These adverse events are commonly seen in subjects undergoing spine surgery due to extended time in the prone position, and therefore, are unlikely to represent local anesthetic systemic toxicity. The mean Cmax for the spine surgery cohort was 320 ng/mL (min 187 ng/mL, max 595 ng/mL), and the mean Cmax for the

cardiac surgery cohort was 447 ng/mL (min 194 ng/mL, max 1290 ng/mL). The mean Cmax values were below plasma levels typically associated with local anesthetic systemic toxicity. In addition, the subject with a Cmax of 1290 ng/mL, the only subject in both Group 1 and Group 2 with a Cmax over 800 ng/mL, did not experience any TEAEs.

To summarize, the most common TEAEs in subjects who received EXPAREL were nausea, vomiting, constipation, blurred vision, postoperative anemia, oral hypesthesia, muscle spasms, and hypotension in both Group 1 and Group 2. The gastrointestinal TEAEs (i.e., nausea, vomiting, constipation) are consistent with the adverse event findings in adult studies. Transient postoperative anemia and hypotension often occurs after highly vascular surgeries, such as spine and cardiac procedures, due to significant blood loss and fluid shifts. In addition, muscle spasms often occur after spine surgery and are unlikely associated with local anesthetic systemic toxicity in this clinical scenario in the absence of other LAST symptoms. In addition, blurred vision and oral hypesthesia can occur due to prone positioning during spine surgery, and these adverse events were also observed in the bupivacaine group. Therefore, the TEAE findings in Study 319 do not present any new safety concerns related to the administration of EXPAREL via local infiltration in children aged 6 to less than 17 years.

8.3.6. Laboratory Findings

There were no safety concerns regarding the laboratory findings after EXPAREL administration in Study 319 or Study 120. Postoperative anemia (i.e., low hemoglobin and hematocrit) was the most common laboratory abnormalities observed in both studies. This finding is expected because there is typically a significant amount of blood loss and fluid shifts during both spine surgery and cardiac surgery. Hematology and chemistry results were not collected in the adult studies (Studies 117 and 118) for comparison.

8.3.7. Vital Signs

In both Study 319 and Study 120, vital signs were monitored throughout the perioperative period and hospital stay. Hypotension, the most common vital sign abnormality, is frequently observed in patients having cardiac and spine surgery due to a significant amount of blood loss that takes place during these procedures. Transient episodes of hypertension, tachycardia, and bradycardia were also observed. Inadequate pain control may explain the episodes of tachycardia and hypertension. Tachycardia may also be a reflex response to hypotension and postoperative anemia. Bradycardia may also occur and is frequently due to opioid pain medications. These vital sign derangements are commonly seen perioperatively after highly invasive and painful procedures, such as spine and cardiac surgeries, and are unlikely to be associated with administration of EXPAREL.

8.3.8. Electrocardiograms (ECGs)

There were no concerning ECG findings in subjects who received EXPAREL in Study 319 or Study 120. Of note, the ECG assessments in Study 319 may have been confounded in subjects

undergoing cardiac surgery.

8.3.9. QT

There were no QT data was submitted with this sNDA. Refer to Dr. Arthur Simone's amended review of EXPAREL, dated October 7, 2011, for QT data reviewed under the original NDA.

8.3.10. Immunogenicity

No immunogenicity issues related to the use of EXPAREL were identified during the nonclinical and clinical development programs.

8.4. Analysis of Submission-Specific Safety Issues

The safety evaluation of this sNDA submission focused on the safety of EXPAREL 4 mg/kg via local infiltration for children aged 6 to less than 17 years, specifically the risks of local anesthetic systemic toxicity. However, after thorough evaluation of all clinical data, there were no new safety signals identified in children as compared to the previously-reported safety issues in adults.

8.5. Safety Analyses by Demographic Subgroups

Study 120

Study 120 was a pilot study with limited number of subjects. Therefore, no subgroup analyses were performed.

Study 319

There did not appear to be any differences in safety findings between the younger age group (6 to less than 12 years) and the older age group (12 to less than 17 years).

The subjects who underwent spine surgery had a higher incidence of blurred vision and oral hypesthesia than the cardiac surgery group. These adverse events were also present in Study 120, where all patients underwent spine surgery. These adverse events are commonly seen in subjects undergoing spine surgery due to extended time in the prone position, and therefore, are unlikely to represent local anesthetic systemic toxicity due to EXPAREL.

The majority of subjects who underwent cardiac surgery were classified as ASA 3; whereas the majority of subjects who underwent spine surgery were classified as ASA 1 or 2. Subjects with ASA 3 physical status are typically considered to have an increased risk of perioperative adverse events. In addition, underlying cardiac disease predisposes individuals to an increased risk of local anesthetic systemic toxicity from any local anesthetic.[8] However, after evaluation of adverse events in the pediatric cardiac surgery patients compared to those undergoing spine surgery, patients who underwent cardiac surgery did not appear to have any adverse events

associated with local anesthetic systemic toxicity. Furthermore, local anesthetic systemic exposures were comparable in subjects undergoing cardiac surgery to those undergoing spine surgery.

There was an additional safety concern with regard to EXPAREL dosing in obese children with BMIs greater than the 95th percentile. Specifically, concerns for overdose and increased risk for local anesthetic systemic toxicity if EXPAREL was dosed based on total body weight in obese children were expressed to the Applicant. In pooled data from Studies 120 and 319, there were 10 obese subjects (BMI greater than the 95th percentile) who received EXPAREL 4 mg/kg based on total body weight. The mean Cmax for these subjects was 416 ng/mL (min 194 ng/mL, max 723 ng/mL), which is below the plasma levels typically associated with local anesthetic systemic toxicity. In addition, the mean Cmax for all subjects with BMIs less than the 95th percentile who received EXPAREL 4 mg/kg (n=70) was very similar – 404 ng/mL (min 78.8 ng/mL, max 1290 ng/mL). The adverse event findings in these two groups were also similar. There are no specific recommendations for adjusting the dose of local anesthetics in obese children, however, there are recommendations for adjusting the dose of local anesthetics based on lean body weight in obese adults.[9] Although the sample size of 10 obese subjects was small, based on the safety and pharmacokinetic profile of EXPAREL in these subjects, it appears reasonable to dose EXPAREL in children with BMIs greater than the 95th percentile based on total body weight.

8.6. Specific Safety Studies/Clinical Trials

This section is not relevant to this sNDA.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

This section is not relevant to this sNDA.

8.7.2. Human Reproduction and Pregnancy

This section is not relevant to this sNDA.

8.7.3. Pediatrics and Assessment of Effects on Growth

This sNDA is a pediatric efficacy supplement to expand the indication of EXPAREL to children aged 6 to less than 17 years. However, based on the proposed acute indication for EXPAREL, it is not anticipated that EXPAREL would have an effect on growth.

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

The potential for overdose with EXPAREL exists if the drug is injected intravascularly. Bupivacaine, the active ingredient of EXPAREL, is not associated with any abuse; therefore, the risk with EXPAREL is expected to be equally as low. EXPAREL is intended for single dose

administration; therefore, withdrawal and rebound are not issues of concern. Refer to Dr. Arthur Simone's amended review of EXPAREL, dated October 7, 2011, for additional information.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

This section is not relevant to this sNDA.

8.8.2. Expectations on Safety in the Postmarket Setting

This section is not relevant to this sNDA.

8.8.3. Additional Safety Issues From Other Disciplines

This section is not relevant to this sNDA.

8.9. Integrated Assessment of Safety

Study 120, a pilot study, evaluated the safety of a single dose of EXPAREL 4 mg/kg in pediatric subjects aged 12 to less than 17 years undergoing spine surgery. Study 319, a pivotal study, evaluated the safety of a single dose of EXPAREL 4 mg/kg in pediatric subjects aged 6 to less than 17 years undergoing spine or cardiac surgery.

The Applicant selected spine and cardiac procedures, which are in highly vascular anatomical compartments, to evaluate the pharmacokinetics and safety of EXPAREL in areas with the highest potential for drug absorption, and therefore, the highest probability of having high total systemic plasma levels of EXPAREL. Since high systemic plasma levels of local anesthetics are likely to result in signs and symptoms of LAST, these procedures were deemed appropriate to demonstrate the safety of the proposed 4 mg/kg dose of EXPAREL in the pediatric population. In addition, individuals with underlying cardiac disease who are undergoing cardiac surgery are considered to be more susceptible to the risks of local anesthetic systemic toxicity than those without such cardiac conditions.[8] Furthermore, cardiac and spine surgical procedures typically require prolonged hospital stays, which allowed for complete characterization of the pharmacokinetic profile in these pediatric subjects. After evaluating all the pharmacokinetic and safety data, the Applicant concluded that by demonstrating the safety of EXPAREL 4 mg/kg, up to 266 mg, in highly vascular anatomical compartments, this dose of EXPAREL could also be safely administered via infiltration in other less vascular anatomical compartments (e.g., inguinal hernia incision) in any child over the age of 6 years.

The following is a summary of the TESAEs, TEAESIs, and TEAEs in subjects who received EXPAREL in Study 319. Two subjects in the cardiac surgery group (n=29) had SAEs that were unlikely related to EXPAREL. Two subjects in the spine surgery group (n=36) had TEAESIs that were unlikely related to EXPAREL. The most frequently occurring TEAEs in both groups were

gastrointestinal (i.e., nausea, vomiting, constipation), which is consistent with the adverse event findings in adult studies. The pediatric subjects in the spine surgery group had a higher incidence of blurred vision and oral hypesthesia than the cardiac surgery group. These adverse events are commonly seen in subjects undergoing spine surgery due to extended time in the prone position, and therefore, are unlikely to represent local anesthetic systemic toxicity from EXPAREL.

The pharmacokinetic data from Study 319 further support the safety findings. The mean Cmax for the spine surgery subjects was 353 ng/mL (min 187 ng/mL, max 595 ng/mL), and the mean Cmax for cardiac surgery subjects was 447 ng/mL (min 194 ng/mL, max 1290 ng/mL). The mean Cmax values are below typical plasma levels associated with systemic toxicity for bupivacaine.

To support the PK findings in pediatric subjects, the Applicant submitted PK data from Study 117, which was an open-label study evaluating the safety and PK of EXPAREL administered via wound infiltration in adult subjects undergoing spine surgery, and from Study 118, which was an open-label study evaluating the safety and pharmacokinetics of EXPAREL administered via wound infiltration in adult subjects undergoing cardiac surgery. Among the 11 adult spine surgery subjects who had PK sampling in Study 117, the mean Cmax was 513 ng/mL (min 228 ng/mL, max 1150 ng/mL). Among the five adult cardiac surgery subjects who had PK sampling in Study 118, the mean Cmax was 445 ng/mL (min 291 ng/mL, max 621 ng/mL).

The following table provides a comparison of the PK data in children to the PK data in adults undergoing matching procedures.

Table 26. Comparison of the Mean Cmax Values and Absolute Cmax Values in Pediatric Subjects in Study 319 and Adult Subjects in Study 117 and Study 118

Pharmacokinetic Value	Pediatric Spine Surgery Subjects	Pediatric Cardiac Surgery Subjects	Adult Spine Surgery Subjects	Adult Cardiac Surgery Subjects
Mean Cmax (ng/mL)	353	447	513	445
Absolute Cmax (ng/mL)	595	1290	1150	621

As stated above, the mean Cmax values are all below plasma levels typically associated with local anesthetic systemic toxicity and are reasonably close to one another. In addition, the mean systemic exposure in children is also consistent with the mean systemic exposure levels in adults. The differences in absolute Cmax values are likely the result of the high inter-subject variability of PK concentrations in perioperative products, such as EXPAREL. Both the pediatric cardiac surgery subject with a Cmax of 1290 ng/mL and the adult spine surgery subject with a Cmax of 1150 ng/mL were outliers in their respective groups. Neither subject had a TEAE.

To further support the safety of EXPAREL in children, the Applicant submitted safety data from their pediatric pilot study, Study 120. Among the 15 subjects in this study, the most common TEAEs were hypotension, postoperative anemia, tachycardia, muscle twitching, nausea, vomiting, and constipation. Hypotension and anemia are common in highly invasive procedures such as spine surgery due to significant blood loss and fluid shifts, and transient tachycardia is often observed as a reflex response to hypotension and anemia. In addition, transient muscle twitching often occurs after spine surgery and is unlikely associated with systemic toxicity due to EXPAREL. Nausea, vomiting, and constipation are known adverse events associated with EXPAREL from adult studies. Similar to subjects in Study 319, one subject in Study 120 experienced blurred vision and oral hypesthesia likely due to extended time in the prone position. The safety profile of EXPAREL is similar in Studies 120 and 319, and the overall safety profile of EXPAREL via infiltration into the surgical site appears consistent with the safety profile of EXPAREL in adults for the same indication.

After review of all of the available safety data from Studies 120 and 319, these data appear to support the safety of surgical infiltration of EXPAREL 4 mg/kg, up to a maximum of 266 mg, in children greater than 6 years of age, who are undergoing spine or cardiac procedures. A subgroup analysis of this dose in obese pediatric subjects was also performed. The data from the subgroup analysis support the safety of the EXPAREL 4 mg/kg dose in obese children, and no alteration in the dosing regimen is recommended. In addition, the safety profile of EXPAREL in all pediatric subjects in Studies 120 and 319 was similar to the general safety profile of EXPAREL in adults. Furthermore, the pharmacokinetic data collected in Study 319 were similar to the pharmacokinetic data collected in adults in matching surgical procedures (Studies 117 and 118). Based on the totality of safety and pharmacokinetic data, it is reasonable to believe that the safety profile of EXPAREL for surgical wound infiltration would also be similar in less vascular surgical sites in children aged 6 to less than 17 years.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The following is the approved indication in Section 1 of the package insert for EXPAREL (verbatim):

> EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

The Applicant proposed the following changes to the indication in Section 1 (verbatim):

> EXPAREL is indicated for single-dose infiltration in patients *aged 6 years and older* to produce postsurgical local analgesia and *in adults* as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

The proposed indication is reasonable. The Applicant proposed an EXAPREL dose of 4 mg/kg, up to 266 mg, for pediatric subjects over 6 years of age undergoing any surgical procedure that is amendable to surgical wound infiltration. Based on our assessment of the safety and pharmacokinetic data in children undergoing spine or cardiac surgeries in Studies 120 and 319, including similar pharmacokinetic profiles in adults who had matching surgical procedures, it is reasonable to conclude that the safety profile of EXPAREL 4 mg/kg administration would be similar at less vascular surgical sites. Refer to Section 8.10, "Integrated Assessment of Safety," for additional discussion.

We also note labeling changes to Section 6, Section 8.4, and Section 14.3.

In Section 6.1, "Adverse Reactions," the Applicant added a section entitled, "Adverse Reactions Reported in All Local Infiltration Clinical Studies in Pediatric Patients Aged 6 to Less Than 17 Years." This section includes all of the observed adverse events in Studies 120 and 319.

In Section 8.4, "Pediatric Use," the Applicant proposed the following labeling insertion: "Safety and effectiveness have not been established in pediatric patients aged less than 6 years old for local infiltration or less than 18 years old for interscalene brachial plexus nerve block."

We agree with this labeling insertion, and we recommend adding the following language to Section 8.4:

> The safety and effectiveness of EXPAREL for single-dose infiltration to produce postsurgical local anesthesia have been established in pediatric patients aged 6 years and older. Use of EXPAREL for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 6 years and older [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)].

In Section 14.3, "Study in Pediatric Patients Aged 6 Years and Older," the Applicant provided a description of the design of Study 319. The Applicant concluded with the following statement,

(b) (4)

(b) (4) We recommend removing this concluding statement (b) (4)

In addition, we recommend the following labeling insertion in Section 14.3:

> These studies evaluated the safety of EXPAREL for local infiltration for pediatric subjects aged 6 and older [see Adverse Reactions (6.1), Pediatric Use (8.4), and Clinical Pharmacology (12.3).]
>
> The efficacy of EXPAREL for local infiltration for pediatric subjects (6 to less than 17 years of age) was extrapolated from the efficacy of EXPAREL for local infiltration for adult subjects.

10.2. Nonprescription Drug Labeling

This section is not relevant to this sNDA.

11. Risk Evaluation and Mitigation Strategies (REMS)

This section is not relevant to this sNDA.

12. Postmarketing Requirements and Commitments

There are no postmarketing requirements for this sNDA.

13. Appendices

13.1. References

1. Berde CB, Walco GA, Krane EJ, et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. Pediatrics. 2012;129(2):354-64.
2. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. N Engl J Med. 2002;347(14):1094-103.
3. Gerik SM. Pain management in children: developmental considerations and mind-body therapies. South Med J. 2005;98(3):295-302.
4. Verghese ST, Hannallah RS. Postoperative Pain Management in Children. Anesthesiol Clin North Am. 2005; 23(1):163-84.
5. Oda Y. Pharmacokinetics and systemic toxicity of local anesthetics in children. J. Anesth.

2016;30:547–550.
6. Knudsen K, Suurkula B, Blomberg S, et al. Central Nervous and Cardiovascular Effects of I.V. Infusions of Ropivacaine, Bupivacaine and Placebo in Volunteers. Br J Anaesth. 1997;78(5):507-14.
7. Mohaty SP, Kumar MN, Nand Kishore BG, et al. The timing of spinal fusion in adolescent idiopathic scoliosis. J Orthop Surg Res. 2001;9(2):7-14.
8. El-Boghdadly K, Chin KJ. Local anesthetic systemic toxicity: Continuing Professional Development. Can J Anaesth. 2016;63:330–349
9. Nightingale CE, Margarson MP, Shearer E, et al. Peri-operative management of the obese surgical patient. Anaesthesia. 2015;70:859-76

13.2. Financial Disclosure

Covered Clinical Studies (by study number):
402-C-319
402-C-120
402-C-117
402-C-118

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 122		
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) 0		
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/

ERIN L ZENILMAN
02/16/2021 04:32:51 PM

ALLA T BAZINI
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