

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22496Orig1s037

Trade Name: **EXPAREL**

Generic or Proper Name: bupivacaine

Sponsor: PACIRA PHARMACEUTICALS, INC

Approval Date: April 02, 2021

Indication: **EXPAREL** contains bupivacaine, an amide local anesthetic, and is indicated to produce postsurgical:

- Local analgesia via infiltration in patients aged 6 years and older
- Regional analgesia via an interscalene brachial plexus nerve block in adults
- Regional analgesia via a sciatic nerve block in the popliteal fossa in adults
- Regional analgesia via an adductor canal block in adults

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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APPROVAL LETTER



NDA 022496/S-037

APPROVAL LETTER

Pacira Pharmaceuticals Inc
Attention: Madhulika Joshi
Associate Director Regulatory Affairs
5 Sylvan Way, Suite 300
Parsippany, NJ 07054

Dear Ms. Joshi:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 9, 2020, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXPAREL (bupivacaine liposome injectable suspension).

This “Changes Being Effectuated in 30 days” supplemental new drug application provides for changes to the manufacturing process for EXPAREL® (bupivacaine liposome injectable suspension) at the Pacira Pharmaceuticals facility in San Diego, California:

[Redacted content] (b) (4)

APPROVAL

We have completed our review of this supplemental application. This supplement is approved.

We remind you that you must comply with reporting requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Teicher Agosto, Regulatory Business Process Manager, at (240) 402 - 3777.

Sincerely,

{See appended electronic signature page}

David B. Lewis, Ph.D.
Branch Chief, B2
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



David
Lewis

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**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXPAREL® safely and effectively. See full prescribing information for EXPAREL.

EXPAREL (bupivacaine liposome injectable suspension), for infiltration or perineural use
Initial U.S. Approval: 1972

RECENT MAJOR CHANGES

Indications and Usage (1) ----- 11/ 2023
Dosage and Administration (2.2) ----- 11/2023

INDICATIONS AND USAGE

EXPAREL contains bupivacaine, an amide local anesthetic, and is indicated to produce postsurgical:

- Local analgesia via infiltration in patients aged 6 years and older (1).
- Regional analgesia via an interscalene brachial plexus nerve block in adults (1).
- Regional analgesia via a sciatic nerve block in the popliteal fossa in adults (1).
- Regional analgesia via an adductor canal block in adults (1).

Limitations of Use

The safety and effectiveness of EXPAREL have not been established to produce postsurgical regional analgesia via other nerve blocks besides an interscalene brachial plexus nerve block, a sciatic nerve block in the popliteal fossa, or an adductor canal block.

DOSAGE AND ADMINISTRATION

- EXPAREL is for single administration only (2.1).
- EXPAREL is not substitutable with other bupivacaine products even if the strength is the same. Therefore, it is not possible to convert a dose from other bupivacaine products to an EXPAREL dose and vice versa (2.1, 2.5).
- Do not dilute EXPAREL with water or other hypotonic solutions (2.1).
- The recommended dose of EXPAREL for:
 - Local infiltration in adults is up to a maximum dose of 266 mg. See Full Prescribing Information for guidance on dose selection (2.2).
 - Local infiltration in pediatric patients aged 6 to less than 17 years is 4 mg/kg, up to a maximum of 266 mg (2.2).
 - Interscalene brachial plexus nerve block in adults is 133 mg (2.3).
 - Sciatic nerve block in the popliteal fossa in adults is 133 mg (2.3).
 - Adductor canal block in adults is 133 mg (10 mL) admixed with 50 mg (10 mL) 0.5% bupivacaine HCl, for a total volume of 20 mL (2.3).
- For all these nerve blocks, administer additional analgesics, which may include other immediate-release local anesthetics, as appropriate (2.3).
- See Full Prescribing Information for important preparation and administration instructions and compatibility considerations (2.4, 2.5).

DOSAGE FORMS AND STRENGTHS

Injectable suspension:
1.3% (266 mg/20 mL) (13.3 mg/mL) in a single-dose vial (3)
1.3% (133 mg/10 mL) (13.3 mg/mL) in a single-dose vial (3)

CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia (4).

WARNINGS AND PRECAUTIONS

- Monitor cardiovascular status, neurological status, and vital signs during and after injection of EXPAREL (5.1).
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, use EXPAREL cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations (5.1).
- Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use (5.1).
- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL (5.2).

ADVERSE REACTIONS

Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via:

- Infiltration in adults were nausea, constipation, and vomiting (6.1).
- Nerve block in adults were nausea, pyrexia, headache, and constipation (6.1).
- Infiltration in pediatric patients six to less than 17 years of age were nausea, vomiting, constipation, hypotension, anemia, muscle twitching, blurred vision, pruritus, and tachycardia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pacira Pharmaceuticals, Inc. at 1-855-RX-EXPAREL (1-855-793-9727) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Lidocaine or other non-bupivacaine local anesthetics:** Do not admix with EXPAREL. EXPAREL may be administered at least 20 minutes or more following local administration of lidocaine (7).
- **Bupivacaine HCl:** Do not exceed a milligram dose of bupivacaine HCl solution to EXPAREL of 1:2 when admixing, as this may impact the pharmacokinetics and/or physicochemical properties of the drugs (7).

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXPAREL is indicated to produce postsurgical:

- Local analgesia via infiltration in patients aged 6 years and older
- Regional analgesia via an interscalene brachial plexus nerve block in adults
- Regional analgesia via a sciatic nerve block in the popliteal fossa in adults
- Regional analgesia via an adductor canal block in adults

Limitations of Use

The safety and effectiveness of EXPAREL have not been established to produce postsurgical regional analgesia via other nerve blocks besides an interscalene brachial plexus nerve block, a sciatic nerve block in the popliteal fossa, or an adductor canal block.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dose, Preparation, and Administration Instructions

- EXPAREL is for single administration only.
- EXPAREL is **not** substitutable with other bupivacaine products even if the strength is the same. Therefore, it is not possible to convert a dose from other bupivacaine products to an EXPAREL dose and vice versa.
- Do **not** dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles.
- Do **not** administer EXPAREL if it is suspected that the vial has been frozen or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- Inspect EXPAREL visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do **not** administer EXPAREL if the product is discolored.
- Do **not** heat or autoclave before use.
- Do **not** filter during administration.

2.2 Recommended Dose for Local Analgesia via Infiltration

Local Analgesia via Infiltration in Adults

The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266 mg, and is based on the following factors:

- Size of the surgical site

- Volume required to cover the area
- Individual patient factors that may impact the safety of an amide local anesthetic

As general guidance in selecting the proper EXPAREL dose for local infiltration in adults, two examples are provided [*see Clinical Studies (14.2)*]. In adult patients undergoing:

- Bunionectomy, a total of 106 mg (8 mL) of EXPAREL was administered, with 7 mL infiltrated into the tissues surrounding the osteotomy, and 1 mL infiltrated into the subcutaneous tissue.
- Hemorrhoidectomy, a total of 266 mg (20 mL) of EXPAREL was diluted with 10 mL of saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

Local Analgesia via Infiltration in Pediatric Patients

The recommended dose of EXPAREL for one-time infiltration in pediatric patients, aged 6 to less than 17 years, is 4 mg/kg (up to a maximum of 266 mg), and is based upon two studies of pediatric patients undergoing either spine surgery or cardiac surgery [*see Use in Specific Populations (8.4)*].

2.3 Recommended Dose for Regional Analgesia

The maximum recommended dose of EXPAREL via perineural use for interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, and adductor canal block is 133 mg. For all these nerve blocks, administer additional analgesics, which may include other immediate-release local anesthetics, as appropriate (for example, Mayo field block for bunionectomy, infiltration between the popliteal artery and capsule of the knee (IPACK) block for total knee arthroplasty).

Regional Analgesia via Interscalene Brachial Plexus Nerve Block in Adults

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg and is based upon one study of patients undergoing either total shoulder arthroplasty or rotator cuff repair [*see Clinical Studies (14.3)*].

Regional Analgesia via Sciatic Nerve Block in the Popliteal Fossa in Adults

The recommended dose of EXPAREL for sciatic nerve block in the popliteal fossa in adults is 133 mg and is based upon one study of patients undergoing bunionectomy [*see Clinical Studies (14.3)*].

Regional Analgesia via Adductor Canal Block in Adults

The recommended dose of EXPAREL for adductor canal block in adults is 133 mg (10 mL) admixed with 50 mg (10 mL) 0.5% bupivacaine HCl, for a total volume of 20 mL, and is based upon one study of patients undergoing total knee arthroplasty [*see Clinical Studies (14.3)*].

2.4 Preparation and Administration Instructions

- Invert vials of EXPAREL multiple times to re-suspend the particles immediately prior to withdrawal from the vial.
- Administer EXPAREL (1) undiluted or (2) diluted to increase volume up to a final concentration of 0.89 mg/mL (i.e., 1:14 dilution by volume) with 0.9% preservative-free Sodium Chloride Injection or lactated Ringer's solution. Use diluted EXPAREL within 4 hours of preparation in a syringe.
- Administer EXPAREL with a 25 gauge or larger bore needle to maintain the structural integrity of the liposomal bupivacaine particles.
- Administer EXPAREL slowly via infiltration or perineural use with frequent aspiration to check for blood and minimize the risk of inadvertent intravascular injection.
- Discard unused portion.

2.5 Compatibility Considerations

Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL. Therefore, admixing EXPAREL with other drugs prior to administration is **not** recommended [see *Drug Interactions (7)*].

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL if the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

The toxic effects of these drugs are additive, and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [see *Warnings and Precautions (5.1) and Overdosage (10)*].

- When a topical antiseptic such as povidone iodine (e.g., Betadine) is applied, the site should be allowed to dry before EXPAREL is administered into the site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

3 DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension) is a white to off-white, milky aqueous suspension that is available in the following vial sizes:

- 1.3% (266 mg/20 mL) (13.3 mg/mL) single-dose vial
- 1.3% (133 mg/10 mL) (13.3 mg/mL) single-dose vial

4 CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia [*see Use in Specific Populations (8.1)*]. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

5 WARNINGS AND PRECAUTIONS

5.1 Warnings and Precautions for Bupivacaine-Containing Products

The safety and effectiveness of EXPAREL, other bupivacaine products, and other amide-containing products depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. As there is a potential risk of severe life-threatening adverse reactions associated with the administration of bupivacaine, any bupivacaine-containing product should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*see Overdosage (10)*].

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of bupivacaine and other amide-containing products. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

EXPAREL, other bupivacaine products, and other amide-containing products should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Injection of multiple doses of EXPAREL, other bupivacaine products, and other amide-containing products may cause significant increases in plasma concentrations with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood concentrations varies with the status of the patient.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Central Nervous System Reactions

The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesia, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered.

Cardiovascular System Reactions

Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure [*See Overdosage (10)*].

Allergic Reactions

Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Chondrolysis

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been postmarketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients

who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue EXPAREL and any oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

5.2 Warnings and Precautions Specific for EXPAREL

As there is a potential risk of severe life-threatening adverse reactions associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these routes of administration or types of analgesia:

- epidural
- intrathecal
- intravascular or intra-articular use
- regional nerve blocks other than interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, and adductor canal block

EXPAREL has not been evaluated for use in the following patient populations and, therefore, is not recommended for administration to these groups.

- patients younger than 6 years old for infiltration

- patients younger than 18 years old for interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, and adductor canal block
- pregnant patients

The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dose administered and may last for up to 5 days as seen in clinical trials.

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with bupivacaine hydrochloride in clinical trials and are described in greater detail in other sections of the labeling:

- Central Nervous System Reactions [*see Warnings and Precautions (5.1)*]
- Cardiovascular System Reactions [*see Warnings and Precautions (5.1)*]
- Allergic Reactions [*see Warnings and Precautions (5.1)*]
- Chondrolysis [*see Warnings and Precautions (5.1)*]
- Methemoglobinemia [*see Warnings and Precautions (5.1)*]
- Accidental intravascular injection [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse Reactions Reported in All Local Infiltration Clinical Studies in Adults

The safety of EXPAREL (local administration into the surgical site) was evaluated in 10 randomized, double-blind, clinical studies (including Studies 1 and 2 [*see Clinical Studies (14.2)*]) that included 823 adult patients who had various surgical procedures. Patients were administered an EXPAREL dose ranging from 66 to 532 mg (two times the maximum recommended dose of 266 mg). In these studies, following EXPAREL administration, the:

- *Most common* adverse reactions (incidence greater than or equal to 10%) were nausea, constipation, and vomiting.
- *Common* adverse reactions (incidence greater than or equal to 2% to less than 10%) were pyrexia, dizziness, peripheral edema, anemia, hypotension, pruritus, tachycardia, headache, insomnia, postoperative anemia, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.
- *Less common* adverse reactions (incidence less than 2%) were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, postural dizziness, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, generalized pruritus,

pruritic rash, hyperhidrosis, cold sweat, urticaria, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, increased body temperature, increased blood pressure (BP), decreased BP, decreased oxygen saturation, urinary incontinence, blurred vision, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions

In the EXPAREL surgical site infiltration studies, following EXPAREL administration adverse reactions with an incidence greater than or equal to 1% in the:

- Nervous System Disorders system organ class were dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoaesthesia (1.5%), and lethargy (1.3%).
- Cardiac Disorders system organ class were tachycardia (3.9%) and bradycardia (1.6%).

Adverse Reactions Reported in All Local Infiltration Placebo-Controlled Trials in Adults

Adverse reactions with an incidence greater than or equal to 2% reported by adult patients in clinical studies who underwent a bunionectomy (Study 1) or hemorrhoidectomy (Study 2) [see *Clinical Studies (14.2)*] that compared 106 mg of EXPAREL (8 mL) to placebo and 266 mg of EXPAREL (20 mL) to placebo are shown in Table 1.

Table 1: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Local Infiltration Placebo-Controlled Studies in Adults (Studies 1 and 2)

System Organ Class Preferred Term	Study 1 ^a		Study 2 ^b	
	EXPAREL	Placebo	EXPAREL	Placebo
	106 mg (N=97) n (%)	(N=96) n (%)	266 mg (N=95) n (%)	(N=94) n (%)
Any TEAE	53 (54.6)	59 (61.5)	10 (10.5)	17 (18.1)
Gastrointestinal Disorders	41 (42.3)	38 (39.6)	7 (7.4)	13 (13.8)
Nausea	39 (40.2)	36 (37.5)	2 (2.1)	1 (1.1)
Vomiting	27 (27.8)	17 (17.7)	2 (2.1)	4 (4.3)
Constipation	2 (2.1)	1 (1.0)	2 (2.1)	2 (2.1)
Anal Hemorrhage	0 (0.0)	0 (0.0)	3 (3.2)	4 (4.3)
Painful Defecation	0 (0.0)	0 (0.0)	2 (2.1)	5 (5.3)
Rectal Discharge	0 (0.0)	0 (0.0)	1 (1.1)	3 (3.2)
Nervous System Disorders	20 (20.6)	30 (31.3)	0 (0.0)	0 (0.0)
Dizziness	11 (11.3)	25 (26.0)	0 (0.0)	0 (0.0)
Headache	5 (5.2)	8 (8.3)	0 (0.0)	0 (0.0)
Somnolence	5 (5.2)	1 (1.0)	0 (0.0)	0 (0.0)
Syncope	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	8 (8.2)	7 (7.3)	0 (0.0)	0 (0.0)
Generalized Pruritus	5 (5.2)	6 (6.3)	0 (0.0)	0 (0.0)
Pruritus	3 (3.1)	1 (1.0)	0 (0.0)	0 (0.0)
Investigations	5 (5.2)	3 (3.1)	4 (4.2)	3 (3.2)
Increased Alanine Aminotransferase	3 (3.1)	3 (3.1)	1 (1.1)	0 (0.0)
Increased Aspartate Aminotransferase	3 (3.1)	2 (2.1)	0 (0.0)	0 (0.0)
Increased Blood Creatinine	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Study 1 ^a		Study 2 ^b	
	EXPAREL	Placebo	EXPAREL	Placebo
	106 mg (N=97) n (%)	(N=96) n (%)	266 mg (N=95) n (%)	(N=94) n (%)
Increased Body Temperature	0 (0.0)	0 (0.0)	3 (3.2)	3 (3.2)
General Disorders And Administration Site Conditions	4 (4.1)	0 (0.0)	1 (1.1)	1 (1.1)
Feeling Hot	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (2.1)	0 (0.0)	1 (1.1)	1 (1.1)
Infections And Infestations	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Fungal Infection	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Swelling	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Decreased Appetite	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)

^a Study 1: Bunionectomy; ^b Study 2: Hemorrhoidectomy; TEAE = treatment-emergent adverse event.

At each level of summation (overall, system organ class, preferred term), patients are only counted once. Preferred terms are included where at least 2% of patients reported the event in any treatment group.

Adverse Reactions Reported in All Local Infiltration Clinical Studies in Pediatric Patients Aged 6 to Less Than 17 Years

The safety of EXPAREL in 110 pediatric patients between the age of 6 and 17 years old who had spine or cardiac surgical procedures was evaluated in one randomized, open-label, clinical study in which EXPAREL was administered by infiltration into the surgical site (Study Peds-1) and one single-arm, open-label study in which EXPAREL was administered by infiltration into the surgical site (Study Peds-2) [see *Use in Specific Populations (8.4)*]. Patients were administered a weight-based dose of EXPAREL at 4 mg/kg (maximum dose of 266 mg) or bupivacaine HCl 2 mg/kg (maximum dose of 175 mg).

In these studies, following EXPAREL administration the:

- *Most common* adverse reactions (incidence greater than or equal to 10%) were nausea, vomiting, constipation, hypotension, anemia, muscle twitching, blurred vision, pruritus, and tachycardia.
- *Common* adverse reactions (incidence greater than or equal to 2% to less than 10%) were bradycardia, muscle spasms, tachypnea, oral hypoesthesia, postoperative anemia, dizziness, pyrexia, diarrhea, hypoacusis, hypoesthesia, back pain, hematuria, incontinence, muscular weakness, and visual impairment.
- *Less common* adverse reactions (incidence less than 2%) were flatulence, abdominal pain, dyspepsia, lip swelling, pain in extremity, musculoskeletal pain, flank pain, musculoskeletal chest pain, hypertension, sinus tachycardia, ventricular extrasystoles, dysgeusia, paresthesia, burning sensation, syncope, diplopia, eye swelling, dyspnea, atelectasis, hypopnea, hypoxia, chest pain, face edema, gait disturbance, generalized pruritus, rash, delayed recovery from anesthesia, fall, incision site hemorrhage, joint dislocation, seroma, hypomagnesemia, acidosis, hyperglycemia, metabolic acidosis, ear

discomfort, decreased urine output, increased heart rate (HR), anxiety, panic attack, ear infection, and fungal wound infection.

Neurological and Cardiac Adverse Reactions in Pediatric Patients Aged 6 to Less than 17 Years Old

In the EXPAREL infiltration studies in pediatric patients aged 6 to less than 17 years old (Studies Peds-1 and Peds-2), following EXPAREL administration adverse reactions with an incidence greater than or equal to 1% in the:

- Nervous System Disorders system organ class were dizziness (6.3%, n=5), and dysgeusia (1.3%, n=1).
- Cardiac Disorders system organ class were tachycardia (11.3%, n=9), bradycardia (8.8%, n=7), sinus tachycardia (1.3%, n=1), and ventricular extrasystoles (1.3%, n=1).

Adverse Reactions Reported in All Local Infiltration Trials in Pediatric Patients Aged 6 to Less than 17 Years Old

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies (Studies Peds-1 and Peds-2) studying 4 mg/kg EXPAREL are shown in Table 2.

Table 2: Treatment-Emergent Adverse Reactions (TEAE) with an Incidence Greater than or Equal to 2%: Local Infiltration Studies in Pediatric Patients Aged 6 to Less than 17 Years Old (Study Peds-1 and Peds-2)

System Organ Class Preferred Term	Study Peds-1 ^a		Study Peds-2 ^b
	Spine Surgery EXPAREL 4 mg/kg ^c (N=36) n (%)	Cardiac Surgery EXPAREL 4 mg/kg ^c (N=29) n (%)	Spine Surgery EXPAREL 4 mg/kg ^c (N=15) n (%)
Patients with at least one TEAE	24 (66.7)	9 (31.0)	15 (100.0)
Blood and lymphatic system disorders	0	0	15 (100)
Anemia	0	0	15 (100)
Cardiac disorders	3 (8.3)	1 (3.4)	12 (80.0)
Bradycardia	2 (5.6)	0	5 (33.3)
Sinus tachycardia	0	1 (3.4)	0
Tachycardia	1 (2.8)	0	8 (53.3)
Ventricular extrasystoles	0	0	1 (6.7)
Ear and labyrinth disorders	2 (5.6)	0	2 (13.3)
Ear discomfort	0	0	1 (6.7)
Hypoacusis	2 (5.6)	0	1 (6.7)
Eye disorders	10 (27.8)	1 (3.4)	4 (26.7)
Diplopia	1 (2.8)	0	0
Eye swelling	0	0	1 (6.7)
Increased Lacrimation	0	0	0
Blurred Vision	7 (19.4)	1 (3.4)	3 (20.0)
Visual impairment	2 (5.6)	0	0
Gastrointestinal disorders	18 (50.0)	7 (24.1)	14 (93.3)
Abdominal Pain	0	0	1 (6.7)
Constipation	9 (25.0)	4 (13.8)	7 (46.7)
Nausea	11 (30.6)	2 (6.9)	9 (60.0)

System Organ Class Preferred Term	Study Peds-1 ^a		Study Peds-2 ^b
	Spine Surgery EXPAREL 4 mg/kg ^c (N=36) n (%)	Cardiac Surgery EXPAREL 4 mg/kg ^c (N=29) n (%)	Spine Surgery EXPAREL 4 mg/kg ^c (N=15) n (%)
Diarrhea	3 (8.3)	0	0
Dyspepsia	1 (2.8)	0	0
Flatulence	0	0	1 (6.7)
Oral Hypoesthesia	4 (11.1)	0	2 (13.3)
Lip Swelling	0	0	1 (6.7)
Vomiting	10 (27.8)	4 (13.8)	8 (53.3)
General disorders and administration site conditions	0	1 (3.4)	3 (20.0)
Chest pain	1 (2.8)	0	0
Face edema	0	1 (3.4)	0
Gait disturbance	0	0	1 (6.7)
Generalized edema	0	0	0
Pyrexia	0	0	3 (20.0)
Infections and infestations	1 (2.8)	1 (3.4)	0
Ear infection	1 (2.8)	0	0
Fungal wound infection	0	1 (3.4)	0
Injury, poisoning and procedural complications	8 (22.2)	0	1 (6.7)
Postoperative Anemia	5 (13.9)	0	0
Delayed recovery from anesthesia	1 (2.8)	0	0
Fall	0	0	1 (6.7)
Incision site hemorrhage	1 (2.8)	0	0
Joint dislocation	1 (2.8)	0	0
Procedural hemorrhage	0	0	0
Seroma	1 (2.8)	0	0
Metabolism and nutrition disorders	0	3 (10.3)	0
Acidosis	0	1 (3.4)	0
Hyperglycemia	0	1 (3.4)	0
Hypomagnesaemia	0	1 (3.4)	0
Metabolic acidosis	0	1 (3.4)	0
Musculoskeletal and connective tissue disorders	8 (22.2)	1 (3.4)	12 (80.0)
Back pain	0	0	2 (13.3)
Flank pain	0	0	1 (6.7)
Muscle twitching	3 (8.3)	1 (3.4)	9 (60.0)
Muscle spasms	4 (11.1)	0	3 (20.0)
Muscular weakness	0	0	2 (13.3)
Musculoskeletal pain	1 (2.8)	0	0
Musculoskeletal chest pain	0	0	1 (6.7)
Pain in extremity	0	0	1 (6.7)
Nervous system disorders	3 (8.3)	0	7 (46.7)
Burning sensation	0	0	1 (6.7)
Dizziness	2 (5.6)	0	3 (20.0)
Dysgeusia	1 (2.8)	0	0
Headache	0	0	0
Hypoesthesia	0	0	3 (20.0)
Paresthesia	0	0	1 (6.7)
Syncope	1 (2.8)	0	0

System Organ Class Preferred Term	Study Peds-1 ^a		Study Peds-2 ^b
	Spine Surgery EXPAREL 4 mg/kg ^c (N=36) n (%)	Cardiac Surgery EXPAREL 4 mg/kg ^c (N=29) n (%)	Spine Surgery EXPAREL 4 mg/kg ^c (N=15) n (%)
Psychiatric disorders		0	2 (13.3)
Anxiety	0	0	1 (6.7)
Panic attack	0	0	1 (6.7)
Renal and urinary disorders	0	0	2 (13.3)
Hematuria	0	0	2 (13.3)
Respiratory, thoracic and mediastinal disorders	3 (8.3)	1 (3.4)	7 (46.7)
Atelectasis	0	0	1 (6.7)
Bradypnea	0	0	0
Dyspnea	0	1 (3.4)	0
Hypopnea	1 (2.8)	0	0
Hypoxia	1 (2.8)	0	0
Pleural effusion	0	0	0
Tachypnea	1 (2.8)	0	6 (40.0)
Skin and subcutaneous tissue disorders	4 (11.1)	0	6 (40.0)
Pruritus	3 (8.3)	0	6 (40.0)
Generalized Pruritus	1 (2.8)	0	0
Rash	0	0	1 (6.7)
Vascular disorders	4 (11.1)	1 (3.4)	14 (93.3)
Hot flush	0	0	0
Hypotension	4 (11.1)	0	14 (93.3)
Hypertension	0	1 (3.4)	0
Systolic hypertension	0	0	0

^a Study 1: Includes spine surgery patients aged 6 to less than 17 years old, and cardiac surgery patients aged 6 to less than 12 years old.

^b Study 2: Includes spine surgery patients aged 12 to less than 17 years old.

^c Patients received EXPAREL 4 mg/kg, not to exceed 266 mg.

At each level of summation (overall, system organ class, preferred term), patients are only counted once. Preferred terms are included where at least 2% of patients reported the event in any treatment group.

TEAE = treatment-emergent adverse event.

Adverse Reactions Reported in Placebo-Controlled Nerve Block Clinical Studies in Adults

The safety of EXPAREL was evaluated in four randomized, double-blind, placebo-controlled nerve block clinical studies (Studies 3, 6, 7, 8) [see *Clinical Studies (14.3, 14.4)*] involving 469 EXPAREL-treated adult patients and 357 placebo-treated patients who had various surgical procedures. Patients were administered placebo or an EXPAREL dose of either 133 or 266 mg (two times the maximum recommended dose for these nerve blocks). In these studies, following EXPAREL administration via nerve block (perineural use) the:

- *Most common* adverse reactions (incidence greater than or equal to 10%) were nausea, pyrexia, and constipation.
- *Common* adverse reactions (incidence greater than or equal to 2% to less than 10%) were muscle twitching, dysgeusia, urinary retention, fatigue, headache, confusional state, hypotension, hypertension, oral hypoesthesia, generalized pruritus, hyperhidrosis, tachycardia, sinus tachycardia, anxiety, fall, increased body temperature, peripheral

edema, sensory loss, increased hepatic enzyme, hiccups, hypoxia, and post-procedural hematoma.

- *Less common* adverse reactions (incidence less than 2%) were arrhythmia, atrial fibrillation, first degree atrioventricular block, bradycardia, left bundle branch block, right bundle branch block, cardiac arrest, impaired hearing, blurred vision, visual impairment, asthenia, chills, hyperthermia, cellulitis, lung infection, pneumonia, procedural nausea, wound dehiscence, wound secretion, electrocardiogram QT prolonged, white blood cell count increased, arthralgia, back pain, joint swelling, decreased mobility, muscle spasms, muscular weakness, musculoskeletal pain, paraesthesia, presyncope, sedation, somnolence, syncope, delirium, dysuria, urinary incontinence, atelectasis, cough, dyspnea, lung infiltration, blister, drug eruption, erythema, rash, urticaria, deep vein thrombosis, hematoma, and orthostatic hypotension.

The *most common* and *common* adverse reactions for the four randomized, double-blind, placebo-controlled nerve block clinical studies (Studies 3, 6, 7, 8) are shown in Table 3.

Neurological and Cardiac Adverse Reactions

In the EXPAREL nerve block placebo-controlled studies, following EXPAREL administration adverse reactions with an incidence greater than or equal to 1% in the:

- Nervous System Disorders system organ class were motor dysfunction (14.9%), dysgeusia (7.2%), headache (5.1%), hypoesthesia (2.3%), and sensory loss (2.3%).
- Cardiac Disorders system organ class were tachycardia (3%), sinus tachycardia (2.3%), and bradycardia (1.3%).

Table 3: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies (Studies 3, 6, 7, and 8)

SYSTEM ORGAN CLASS Preferred Term	EXPAREL 133 mg (N=168) n (%)	EXPAREL 266 mg (N=301) n (%)	Placebo (N=357) n (%)
Number of Patients with at Least One TEAE	152 (90.5)	260 (86.4)	299 (83.8)
Blood and Lymphatic System Disorders	2 (1.2)	22 (7.3)	15 (4.2)
Anemia	2 (1.2)	18 (6.0)	13 (3.6)
Cardiac Disorders	13 (7.7)	34 (11.3)	38 (10.6)
Atrial Fibrillation	1 (0.6)	4 (1.3)	8 (2.2)
Sinus Tachycardia	3 (1.8)	8 (2.7)	4 (1.1)
Tachycardia	3 (1.8)	11 (3.7)	10 (2.8)
Gastrointestinal Disorders	84 (50.0)	154 (51.2)	184 (51.5)
Constipation	29 (17.3)	66 (21.9)	68 (19.0)
Dyspepsia	3 (1.8)	7 (2.3)	7 (2.0)
Oral Hypoesthesia	6 (3.6)	8 (2.7)	7 (2.0)
Nausea	62 (36.9)	111 (36.9)	133 (37.3)
Vomiting	17 (10.1)	55 (18.3)	73 (20.4)
General Disorders And Administration Site Conditions	52 (31.0)	102 (33.9)	91 (25.5)
Fatigue	7 (4.2)	15 (5.0)	15 (4.2)

Table 3: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies (Studies 3, 6, 7, and 8)

SYSTEM ORGAN CLASS Preferred Term	EXPAREL 133 mg (N=168) n (%)	EXPAREL 266 mg (N=301) n (%)	Placebo (N=357) n (%)
Feeling Cold	0	10 (3.3)	8 (2.2)
Peripheral Edema	4 (2.4)	6 (2.0)	8 (2.2)
Peripheral Swelling	3 (1.8)	8 (2.7)	4 (1.1)
Pyrexia	36 (21.4)	70 (23.3)	64 (17.9)
Injury, Poisoning And Procedural Complications	18 (10.7)	44 (14.6)	32 (9.0)
Postoperative Anemia	0	8 (2.7)	10 (2.8)
Contusion	4 (2.4)	1 (0.3)	0
Fall	4 (2.4)	8 (2.7)	1 (0.3)
Post Procedural Hematoma	4 (2.4)	1 (0.3)	0
Procedural Hypotension	2 (1.2)	13 (4.3)	7 (2.0)
Investigations	18 (10.7)	31 (10.3)	31 (8.7)
Increased Body Temperature	1 (0.6)	10 (3.3)	4 (1.1)
Increased Hepatic Enzyme	7 (4.2)	1 (0.3)	3 (0.8)
Metabolism and Nutrition Disorders	13 (7.7)	18 (6.0)	25 (7.0)
Hypokalemia	7 (4.2)	9 (3.0)	14 (3.9)
Musculoskeletal And Connective Tissue Disorders	22 (13.1)	47 (15.6)	41 (11.5)
Decreased Mobility	0	6 (2.0)	5 (1.4)
Muscle Twitching	14 (8.3)	21 (7.0)	25 (7.0)
Nervous System Disorders	72 (42.9)	101 (33.6)	112 (31.4)
Dizziness	8 (4.8)	28 (9.3)	40 (11.2)
Dysgeusia	12 (7.1)	22 (7.3)	21 (5.9)
Headache	14 (8.3)	10 (3.3)	10 (2.8)
Hypoesthesia	6 (3.6)	5 (1.7)	2 (0.6)
Motor Dysfunction	35 (20.8)	35 (11.6)	37 (10.4)
Sensory Loss	4 (2.4)	7 (2.3)	1 (0.3)
Psychiatric Disorders	10 (6.0)	33 (11.0)	44 (12.3)
Anxiety	3 (1.8)	9 (3.0)	6 (1.7)
Confusional State	3 (1.8)	15 (5.0)	14 (3.9)
Insomnia	5 (3.0)	10 (3.3)	19 (5.3)
Renal And Urinary Disorders	9 (5.4)	31 (10.3)	31 (8.7)
Urinary Retention	5 (3.0)	23 (7.6)	22 (6.2)
Respiratory, Thoracic And Mediastinal Disorders	18 (10.7)	30 (10.0)	31 (8.7)
Dyspnea	2 (1.2)	4 (1.3)	8 (2.2)
Hiccups	4 (2.4)	4 (1.3)	1 (0.3)
Hypoxia	4 (2.4)	3 (1.0)	3 (0.8)
Skin And Subcutaneous Tissue Disorders	24 (14.3)	63 (20.9)	84 (23.5)
Hyperhidrosis	1 (0.6)	14 (4.7)	15 (4.2)
Pruritus	10 (6.0)	45 (15.0)	55 (15.4)
Generalized Pruritus	6 (3.6)	7 (2.3)	14 (3.9)
Vascular Disorders	16 (9.5)	30 (10.0)	44 (12.3)
Hypertension	3 (1.8)	15 (5.0)	21 (5.9)

Table 3: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies (Studies 3, 6, 7, and 8)

SYSTEM ORGAN CLASS Preferred Term	EXPAREL 133 mg (N=168) n (%)	EXPAREL 266 mg (N=301) n (%)	Placebo (N=357) n (%)
Hypotension	11 (6.5)	8 (2.7)	19 (5.3)

At each level of summation (overall, system organ class, preferred term), patients are only counted once.

Preferred terms are included where at least 2% of patients reported the event in any treatment group.

TEAE = treatment-emergent adverse event.

Adverse Reactions Reported in Active-Controlled Nerve Block Clinical Studies in Approved Populations

The safety of EXPAREL was evaluated in two randomized, double-blind, active-controlled nerve block clinical studies in 189 adult patients who had a bunionectomy or a total knee arthroplasty (Studies 4 and 5) [see *Clinical Studies (14.3)*]. Via nerve block, patients received 133 mg of EXPAREL, 266 mg of EXPAREL (two times the maximum recommended EXPAREL dose) [see *Dosage and Administration (2.3)*] or 133 mg of EXPAREL admixed with 50 mg of bupivacaine HCl. In both of these studies the active comparator was 50 mg of bupivacaine HCl.

The *most common* adverse reactions (incidence greater than or equal to 10%) in Studies 4 and 5 following:

- EXPAREL administration as a nerve block were nausea and constipation.
- Administration of EXPAREL admixed with bupivacaine as a nerve block were nausea, constipation, muscle spasms, and headache.

The *common* adverse reactions (incidence greater than or equal to 2% to less than 10%) in Studies 4 and 5 following:

- EXPAREL administration as a nerve block were pruritus, vomiting, dyspepsia, headache, peroneal nerve palsy, rash and hypertension.
- Administration of EXPAREL admixed with bupivacaine as a nerve block were vomiting, dyspepsia, heart rate increased, hypokalaemia, hyponatraemia, back pain, disorientation, oropharyngeal pain, hypoesthesia, pruritus, dizziness, insomnia, hypertension, hypoxia, hypotension, pyrexia, and tachycardia.

The *less common* adverse reactions (incidence less than 2%) in Studies 4 and 5 following:

- EXPAREL administration as a nerve block were increased BP, pyrexia, arthralgia, insomnia, muscle spasms, asthenia, increased systolic BP, diarrhea, facial pain, migraine, muscle twitching, throat irritation, post procedural erythema, post procedural edema, dizziness, hypoesthesia, rhinorrhea, and paresthesia.
- Administration of EXPAREL admixed with bupivacaine as a nerve block were increased BP, procedural pain, rash, pruritic rash, anemia, anxiety, arthralgia, atrial fibrillation,

decreased blood potassium, decreased BP, increased systolic BP, increased body temperature, bradycardia, confusional state, decreased appetite, diarrhea, dysarthria, fall, feeling cold, decreased HR, hot flush, joint swelling, leukocytosis, mental status changes, neuralgia, orthostatic hypotension, decreased oxygen saturation, pneumonia, post procedural hematoma, post procedural inflammation, post procedural swelling, pruritic rash, positive staphylococcus test, syncope, and urinary tract infection .

The *most common* and *common* adverse reactions in adult patients in the active-controlled clinical studies are shown in Table 4.

Table 4: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Active-Controlled Studies (Studies 4 and 5)

SYSTEM ORGAN CLASS Preferred Term	EXPAREL 133 mg (N=81) n (%)	EXPAREL 266 mg (N=22) n (%)	EXPAREL 133 mg + Bupi (N = 86) n (%)	Bupi (N=162) n (%)
Number of Patients with at Least One TEAE	42 (51.9)	13 (59.1)	77 (89.5)	116 (71.6)
Cardiac Disorders				
Tachycardia	0	0	4 (4.7)	5 (3.1)
Gastrointestinal Disorders				
Constipation	10 (12.3)	3 (13.6)	30 (34.9)	47 (29.0)
Dyspepsia	2 (2.5)	1 (4.5)	2 (2.3)	2 (1.2)
Nausea	13 (16)	9 (40.9)	34 (39.5)	49 (30.2)
Vomiting	4 (4.9)	5 (22.7)	5 (5.8)	13 (8.0)
General Disorders And Administration Site Conditions				
Pyrexia	0	1 (4.5)	3 (3.5)	3 (1.9)
Investigations				
Increased Heart rate	0	0	3 (3.5)	3 (1.9)
Metabolism and Nutrition Disorders				
Hypokalemia	0	0	2 (2.3)	2 (1.2)
Hyponatremia	0	0	2 (2.3)	2 (1.2)
Musculoskeletal And Connective Tissue Disorders				
Back pain	0	0	2 (2.3)	3 (1.9)
Muscle Spasms	2 (2.5)	0	11 (12.8)	10 (6.2)
Nervous System Disorders				
Dizziness	2 (2.5)	0	4 (4.7)	4 (2.5)
Headache	8 (9.9)	1 (4.5)	13 (15.1)	6 (3.7)
Hypoaesthesia	0	9 (12.7)	2 (2.1)	0
Peroneal Nerve Palsy	3 (3.7)	0	0	0
Psychiatric Disorders				
Disorientation	0	0	2 (2.3)	0
Insomnia	2 (2.5)	0	5 (5.8)	14 (8.6)
Respiratory, Thoracic And Mediastinal Disorders				

Table 4: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Active-Controlled Studies (Studies 4 and 5)

SYSTEM ORGAN CLASS Preferred Term	EXPAREL 133 mg (N=81) n (%)	EXPAREL 266 mg (N=22) n (%)	EXPAREL 133 mg + Bupi (N = 86) n (%)	Bupi (N=162) n (%)
Hypoxia	0	0	4 (4.7)	4 (2.5)
Oropharyngeal Pain	0	0	2 (2.3)	0
Skin And Subcutaneous Tissue Disorders				
Pruritus	6 (7.4)	1 (4.5)	6 (7.0)	9 (5.6)
Rash	4 (4.9)	1 (4.5)	1 (1.2)	1 (0.6)
Vascular Disorders				
Hypertension	3 (3.7)	1 (4.5)	5 (5.8)	7 (4.3)
Hypotension	0	0	3 (3.5)	9 (5.6)

At each level of summation (overall, system organ class, preferred term), patients were only counted once. Preferred terms are included where at least 2% of patients reported the event in any treatment group. TEAE = treatment-emergent adverse event.

Notable Adverse Reactions from Active-Controlled Studies in Unapproved Populations

The safety of EXPAREL was evaluated in a multicenter, randomized, double-blind, active-controlled trial in 119 patients undergoing foot and ankle procedures (Study 9) [see *Clinical Studies (14.3)*]. Patients were administered a dose of either 266 mg EXPAREL, 266 mg EXPAREL admixed with 50 mg bupivacaine HCl, or 100 mg bupivacaine HCl. The following adverse reactions were observed following administration of EXPAREL or EXPAREL admixed with bupivacaine in Study 9 that either were not observed in Studies 4 and 5, or were observed at a higher frequency than was observed in Studies 4 and 5. These include:

- The *most common* adverse reactions (incidence greater than 10%) observed in Study 9 at higher frequencies than Studies 4 and 5: hypoesthesia (21% vs. 1% and 0%, respectively), paresthesia (10% vs. 1% and 0%, respectively).
- The *common* adverse reactions (incidence greater than or equal to 2% to less than 10%) observed in Study 9 but not in Studies 4 and 5: epistaxis, motor dysfunction, pain in extremity, skin abrasion, infusion site pain, muscular weakness.

6.2 Postmarketing Experience

Because adverse reactions reported during postmarketing are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are consistent with those observed in clinical studies and most commonly involve the following system organ classes: Injury, Poisoning, and Procedural Complications (e.g., drug-drug interaction, procedural pain), Nervous System Disorders (e.g., palsy, seizure), General Disorders And Administration Site Conditions (e.g., lack of efficacy,

pain), Skin And Subcutaneous Tissue Disorders (e.g., erythema, rash), and Cardiac Disorders (e.g., bradycardia, cardiac arrest).

7 DRUG INTERACTIONS

The toxic effects of local anesthetics are additive and concomitant use should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.1)*, and *Overdosage (10)*]. Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

Patients who are administered local anesthetics, including EXPAREL, may be at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	Phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

Bupivacaine

Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

Non-Bupivacaine Local Anesthetics

EXPAREL should not be admixed with local anesthetics other than bupivacaine. Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. There are no data to support administration of other local anesthetics prior to administration of EXPAREL.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

Water and Hypotonic Agents

Do not dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies conducted with EXPAREL in pregnant women. In animal reproduction studies, embryo-fetal deaths were observed with subcutaneous administration of bupivacaine to rabbits during organogenesis at a dose equivalent to 1.6 times the maximum recommended human dose (MRHD) of 266 mg. Subcutaneous administration of bupivacaine to rats from implantation through weaning produced decreased pup survival at a dose equivalent to 1.5 times the MRHD [see Data]. Based on animal data, advise pregnant women of the potential risks to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Clinical Considerations

Labor or Delivery

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia. While EXPAREL has not been studied with this technique, the use of bupivacaine for obstetrical paracervical block anesthesia has resulted in fetal bradycardia and death.

Bupivacaine can rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity [See *Clinical Pharmacology (12.3)*]. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Data

Animal Data

Bupivacaine hydrochloride was administered subcutaneously to rats and rabbits during the period of organogenesis (implantation to closure of the hard plate). Rat doses were 4.4, 13.3, and 40 mg/kg/day (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) and rabbit doses were 1.3, 5.8, and 22.2 mg/kg/day (equivalent to 0.1, 0.4 and 1.6 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at the doses tested with the high dose causing increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Decreased pup survival was noted at 1.5 times the MRHD in a rat pre- and post-natal development study when pregnant animals were administered subcutaneous doses of 4.4, 13.3, and 40 mg/kg/day bupivacaine hydrochloride (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) from implantation through weaning (during pregnancy and lactation).

8.2 Lactation

Risk Summary

Limited published literature reports that bupivacaine and its metabolite, pipercoloxylidide, are present in human milk at low levels. There is no available information on effects of the drug in the breastfed infant or effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXPAREL and any potential adverse effects on the breastfed infant from EXPAREL or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of EXPAREL to produce postsurgical local analgesia via infiltration 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, and pharmacokinetic (PK) and safety data in pediatric patients aged 6 years and older from Studies Peds-1 and Peds-2 [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*].

- Study Peds-1 was a multicenter, randomized, open-label, two-part study (NCT03682302) to evaluate the PK and safety of EXPAREL for local infiltration in pediatric patients aged 6 to less than 17 years who were undergoing spine or cardiac surgery (postsurgically, patients were administered opioid rescue medication according to the study site's standard of care).
 - Group 1: 61 patients aged 12 to less than 17 years, undergoing spine surgeries, were randomized 1:1 to receive either EXPAREL 4 mg/kg (maximum 266 mg) or bupivacaine HCl 2 mg/kg (maximum 175 mg).
 - Group 2: 34 patients aged 6 to less than 12 years, undergoing either spine or cardiac surgeries, received open-label EXPAREL 4 mg/kg (maximum up to 266 mg).
- Study Peds-2 was a phase 1, open-label study that evaluated the PK and safety of 4 mg/kg (maximum 266 mg) of EXPAREL (administered intraoperatively prior to wound closure) in 15 pediatric patients aged 12 to less than 17 who were undergoing spinal surgery.

The safety and effectiveness of EXPAREL have not been established to produce postsurgical:

- Local analgesia via infiltration in pediatric patients aged less than 6 years old.
- Regional analgesia via an interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, or adductor canal block in pediatric patients.

8.5 Geriatric Use

Of the total number of patients in the EXPAREL local infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. Of the total number of patients in the EXPAREL nerve block clinical studies (N= 1046), 312 patients were greater than or equal to 65 years of age and 70 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness of

EXPAREL have been observed between patients 65 years of age and older and younger adult patients.

In clinical studies, differences in various pharmacokinetic parameters have been observed between patients 65 years of age and older and younger adult patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of adverse reactions to bupivacaine may be greater in patients with renal impairment than in patients with normal renal function. Because patients 65 years of age and older are more likely to have renal impairment, increase monitoring for EXPAREL-associated adverse reactions [*see Adverse Reactions (6)*].

8.6 Hepatic Impairment

Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity [*see Clinical Pharmacology (12.3)*]. Therefore, consider increased monitoring for local anesthetic systemic toxicity in patients with moderate to severe hepatic disease.

8.7 Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of adverse reactions to EXPAREL may be greater in patients with renal impairment than in patients with normal renal function. Therefore, in patients with renal impairment, increase monitoring for EXPAREL-associated adverse reactions [*see Adverse Reactions (6)*].

10 OVERDOSAGE

Clinical Presentation

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution [*See Warnings and Precautions (5) and Adverse Reactions (6)*].

Signs and symptoms of overdose include CNS symptoms (perioral paresthesia, dizziness, dysarthria, confusion, mental obtundation, sensory and visual disturbances, and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia, and asystole).

Plasma levels of bupivacaine associated with toxicity can vary. Although concentrations of 2,500 to 4,000 ng/mL have been reported to elicit early subjective CNS symptoms of bupivacaine toxicity, symptoms of toxicity have been reported at levels as low as 800 ng/mL.

Management of Local Anesthetic Overdose

At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should

be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine to enhance myocardial contractile force).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

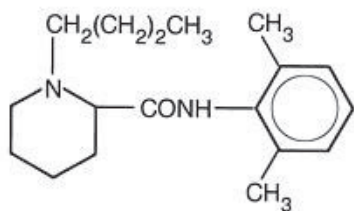
Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

11 DESCRIPTION

EXPAREL (bupivacaine liposome injectable suspension) is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension consisting of multivesicular liposomes containing bupivacaine. Bupivacaine is present at a concentration of 13.3 mg/mL. After injection of EXPAREL, bupivacaine is released from the multivesicular liposomes. EXPAREL is for infiltration or perineural use.

Active Ingredient

Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics. It is a homologue of mepivacaine and is related chemically to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage. Chemically, bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.4. Bupivacaine has the following structural formula:



EXPAREL

The median diameter of the liposome particles in EXPAREL ranges from 24 to 31 μm . The liposomes are suspended in a 0.9% Sodium Chloride Injection. Each vial contains bupivacaine at a nominal concentration of 13.3 mg/mL. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) sodium salt

(DPPG), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2 mg/mL; phosphoric acid to adjust pH; and sodium chloride to adjust tonicity. The pH of EXPAREL is in the range of 5.8 to 7.4.

Bupivacaine in EXPAREL has different functional properties relative to those of the unencapsulated or nonlipid-associated bupivacaine products. Bupivacaine that is released from EXPAREL has a different pharmacokinetic and systemic profile relative to other bupivacaine products. In addition, the nominal weight percent concentration of bupivacaine in EXPAREL is based on bupivacaine free base rather than bupivacaine HCl (100 mg of bupivacaine HCl contains 88.6 mg of bupivacaine free base) [*see Dosage and Administration (2.1)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.2 Pharmacodynamics

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after accidental intravascular injection of bupivacaine.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors, and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

12.3 Pharmacokinetics

After administration of EXPAREL, the systemic plasma levels of bupivacaine were observed for 96 hours after local infiltration, 120 hours after interscalene brachial plexus nerve block, 168 hours after sciatic nerve block in the popliteal fossa, and 168 hours after adductor canal block [*see Warnings and Precautions (5.2)*]. In general, peripheral nerve blocks have shown systemic

plasma levels of bupivacaine for extended duration when compared to local infiltration. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

Absorption

The rate of systemic absorption of bupivacaine is dependent upon the total dose of EXPAREL administered, the route of administration, and the vascularity of the administration site.

Pharmacokinetic parameters of EXPAREL after local infiltration, and following an interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, and adductor canal block were evaluated following surgical procedures. Descriptive statistics of pharmacokinetic parameters of representative EXPAREL doses in each study are provided in Table 5 for adult patients after administration of single doses of EXPAREL via local infiltration; Table 6 for adult patients after administration of single doses of EXPAREL via nerve block; and in Table 7 for pediatric patients aged 6 to less than 17 years old after administration of single doses of EXPAREL via local infiltration.

Table 5: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL via Local Infiltration in Adult Patients

Parameters*	Bunionectomy ¹ 106 mg (8 mL)	Hemorrhoidectomy ² 266 mg (20 mL)	Spine Surgery ³ 266 mg (20 mL)	Cardiothoracic Surgery ⁴ 266 mg (20 mL)
	(N=26)	(N=25)	(N=11)	(N=5)
C _{max} (ng/mL)	166 (93)	867 (353)	513 (268)	445 (120)
T _{max} (h)	2 (0.5, 24)	0.5 (0.25, 36)	0.6 (0.2, 37)	0.6 (0.6, 36)
AUC _{0-40h} (h x ng/mL)	NE	NE	13035 (8782)	9867 (1332)
AUC _(0-last) (h x ng/mL)	5864 (2038) ⁵	16867 (7868) ⁵	17214 (11621) ⁶	14277 (3449) ⁶
AUC _(inf) (h x ng/mL)	7105 (2283)	18289 (7569)	17917 (12187)	15768 (4530)
t _{1/2} (h)	34 (17)	24 (39)	9 (2)	14 (6)

* Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum).

¹Patients undergoing bunionectomy (Study 1)

²Patients undergoing hemorrhoidectomy (Study 2)

³Patients undergoing open posterior spinal fusion or reconstructive surgery

⁴Patients undergoing posterolateral thoracotomy

⁵ AUC_{0-last}, 0-72h; ⁶ AUC_{0-last}, 0-96h

NE: Not evaluated

Table 6: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL via Nerve Block in Adult Patients (Studies 3, 4 and 5)

Parameters*	Interscalene Brachial Plexus Nerve Block ¹	Sciatic Nerve Block in the Popliteal Fossa ²	Adductor Canal Block ³
	EXPAREL 133 mg (10 mL)	EXPAREL 133 mg (10 mL) + BUP as Mayo field block (100 mg ⁶) (Total dose: 221.6 mg bupivacaine)	EXPAREL 133 mg (10 mL) + BUP 50 mg + BUP as IPACK (37.5 mg) + BUP (up to 15 mg) as spinal anesthesia (Total dose: 224 mg bupivacaine)
	(N = 12)	(N = 21)	(N = 24)
C _{max} (ng/mL)	207 (137)	382 (241)	495 (165)
T _{max} (h)	48 (3, 74)	8.1 (1.7, 12)	0.7 (0.4, 72)
AUC _(0-last) (h x ng/mL)	11484 (8615) ⁴	16005 (6740) ⁵	25039 (11921) ⁵
AUC _(inf) (h x ng/mL)	11590 (8603)	17004 (7206)	25109 (11918)
t _{1/2} (h)	11 (5)	28 (14)	11 (3)

* Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum).

¹ Patients undergoing total shoulder arthroplasty (Study 3)

² Patients undergoing bunionectomy (Study 4)

³ Patients undergoing total knee arthroplasty (Study 5)

⁴ AUC_{0-last, 0-120h}; ⁵ AUC_{0-last, 0-168h}

⁶ 100 mg bupivacaine HCl contains 88.6 mg of bupivacaine free base.

BUP: Bupivacaine HCl.

IPACK: Infiltration between the popliteal artery and capsule of the knee

NE: Not evaluated

Table 7: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL via Local Infiltration in Pediatric Patients Aged 6 to Less Than 17 Years Old (Studies Peds-1 and Peds-2)

Parameters*	Spine Surgery	Cardiac Surgery
	EXPAREL 4 mg/kg (Maximum 266 mg)	EXPAREL 4 mg/kg (Maximum 266 mg)
	6 to <17 years (N = 17)	6 to <12 years (N = 21)
C _{max} (ng/mL)	353 (125)	447 (243)
T _{max} (h)	1.2 (0.3-26)	23 (0.2, 55)
AUC _(0-40 h) (h x ng/mL)	8782 (2834)	11286 (4791)

AUC _(0-last) (h x ng/mL)	NR ¹	16776 (7936) ¹
AUC _(inf) (h x ng/mL)	NR ²	NR ²
t _{1/2} (h)	NR ²	NR ²

* Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum).

¹AUC_{0-last, 0-72h}

NR¹ = Not reported, since the last sampling time point varies among different patients.

NR² = Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

Distribution

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation.

Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionized drugs such as bupivacaine readily enter the fetal blood from the maternal circulation.

Elimination

Metabolism

Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxylidide (PPX) is the major metabolite of bupivacaine; approximately 5% of bupivacaine is converted to PPX. Elimination of drug depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic disease. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Excretion

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Only 6% of bupivacaine is excreted unchanged in the urine.

Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Acidifying the urine hastens the renal elimination of local anesthetics. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow.

Specific Populations

Hepatic Impairment

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, the effects of decreased hepatic function on bupivacaine pharmacokinetics following administration of EXPAREL were studied in patients with moderate hepatic impairment. Consistent with the hepatic clearance of bupivacaine, mean plasma concentrations were higher in patients with moderate hepatic impairment than in the healthy control volunteers with approximately 1.5- and 1.6-fold increases in the mean values for C_{max} and the area under the curve (AUC), respectively. [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine have not been conducted.

Mutagenesis

The mutagenic potential of bupivacaine has not been determined.

Impairment of Fertility

The effect of bupivacaine on fertility has not been determined.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies in Adult Patients

In five multicenter, randomized, double-blinded, placebo-controlled clinical studies in adults, the efficacy of EXPAREL was established to produce postsurgical:

- Local analgesia via infiltration: One study evaluated the use of EXPAREL in patients undergoing bunionectomy (Study 1); the other study evaluated the use of EXPAREL in patients undergoing hemorrhoidectomy (Study 2) [see *Clinical Studies (14.2)*].
- Regional analgesia via perineural use: one study (Study 3) evaluated the use of EXPAREL as a brachial plexus nerve block via interscalene or supraclavicular approach in patients undergoing total shoulder arthroplasty (TSA) or rotator cuff repair (RCR) (only two patients had nerve blocks via the supraclavicular approach); one study evaluated the use of EXPAREL as a sciatic nerve block in the popliteal fossa in patients undergoing bunionectomy (Study 4); and one study evaluated the use of EXPAREL as an adductor canal block in patients undergoing total knee arthroplasty (TKA) (Study 5) [see *Clinical Studies (14.3)*].

Four additional studies (Studies 6, 7, 8, and 9) [see *Clinical Studies (14.4)*] did not provide sufficient efficacy and/or safety data to support an indication for the following nerve blocks: femoral block in patients undergoing total knee arthroplasty, intercostal nerve block in patients undergoing posterolateral thoracotomy, and combined sciatic (in popliteal fossa) and saphenous (in adductor canal) nerve block [see *Indications and Usage (1)*].

14.2 Studies in Adults to Produce Postsurgical Local Analgesia

Study 1: Infiltration for Bunionectomy in Adults

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial (NCT00890682) (Study 1) evaluated the safety and efficacy of 106 mg (8 mL) EXPAREL in 193 adult patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72).

Study medication was administered directly into the site at the conclusion of the surgery, prior to closure. There was an infiltration of placebo or 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) out to 72 hours. Postoperatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4 to 6 hours as needed) or, if that was insufficient within the first 24 hours, ketorolac (15 to 30 mg IV). The primary outcome measure was the area under the curve (AUC) of the NRS pain intensity scores (cumulative pain scores) collected over the first 24-hour period. There was a significant treatment effect for EXPAREL compared to placebo.

EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. There was no significant difference in the amount of morphine equivalents used through 72 hours post-surgery, 43 mg versus 42 mg for placebo and EXPAREL, respectively. In addition, there was not a significant difference in the percentage of patients that used ketorolac, 43% versus 31% for placebo and EXPAREL, respectively.

Study 2: Infiltration for Hemorrhoidectomy in Adults

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial (NCT00890721) (Study 2) evaluated the safety and efficacy of 266 mg (20 mL) EXPAREL in 189 adult patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86).

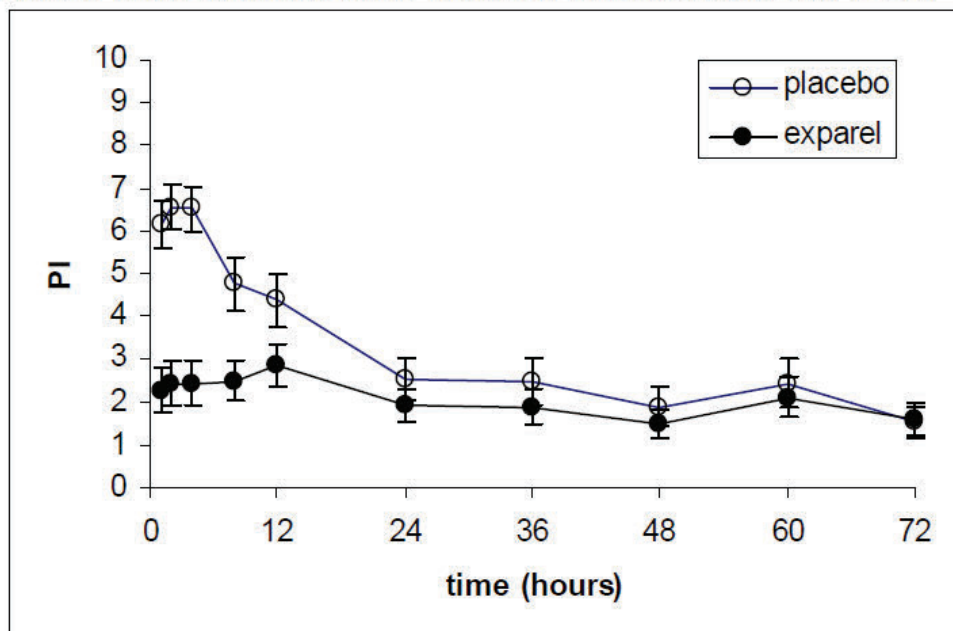
EXPAREL or placebo were administered directly into the site (greater than or equal to 3 cm) at the conclusion of the surgery. Dilution of 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, was divided into six 5-mL aliquots. A field block was performed by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers.

Pain intensity was rated by the patients on a 0 to 10 NRS at multiple time points up to 72 hours. Postoperatively, patients were allowed rescue medication (morphine sulfate 10 mg intramuscular every 4 hours as needed).

The primary outcome measure was the AUC of the NRS pain intensity scores (cumulative pain scores) collected over the first 72-hour period.

There was a significant treatment effect for EXPAREL compared to placebo. See Figure 1 for the mean pain intensity over time for the EXPAREL and placebo treatment groups for the 72-hour efficacy period.

Figure 1. Mean Pain Intensity versus Time plot for hemorrhoidectomy study (C-316)



There were statistically significant, but small differences in the amount of opioid rescue analgesia used across the treatment groups, the clinical benefit of which has not been established. The median time to rescue analgesic use was 15 hours for patients treated with EXPAREL and one hour for patients treated with placebo. Twenty-eight percent of patients treated with EXPAREL required no rescue medication at 72 hours compared to 10% treated with placebo. For those patients who did require rescue medication, the mean amount of morphine sulfate intramuscular injections used over 72 hours was 22 mg for patients treated with EXPAREL and 29 mg for patients treated with placebo.

14.3 Nerve Block Studies in Adults to Produce Postsurgical Regional Analgesia

Study 3: Interscalene Brachial Plexus Nerve Block for Total Shoulder Arthroplasty or Rotator Cuff Repair in Adults

A multicenter, randomized, double-blind, placebo-controlled study (NCT02713230) (Study 3) was conducted in 156 adult patients undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair with general anesthesia. The mean age was 61 years (range 33 to 80). Prior to the surgical procedure, patients received 133 mg (10 mL) of EXPAREL expanded with normal saline to 20 mL or placebo as a brachial plexus nerve block (perineural use) via interscalene or supraclavicular approach with ultrasound guidance. Only two patients received nerve block with EXPAREL by supraclavicular approach. Postsurgically, patients were administered acetaminophen/paracetamol up to 1,000 mg orally or intravenously every 8 hours unless contraindicated. Patients were allowed opioid rescue medication administered initially as oral immediate-release oxycodone (initiating at 5-10 mg every 4 hours or as needed). If a patient could not tolerate oral medication, intravenous morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) could be administered every 4 hours or as needed.

In Study 3, there was a statistically significant treatment effect for EXPAREL compared to placebo in cumulative pain scores through 48 hours as measured by the AUC of the visual analog scale (VAS) pain intensity scores. There were statistically significant, but small differences in the amount of opioid consumption through 48 hours, the clinical benefit of which has not been demonstrated. For those patients who required rescue medication, the mean amount of morphine-equivalent opioid rescue used over 48 hours was 12 mg for EXPAREL-treated patients and 54 mg for placebo-treated patients and 23 mg with EXPAREL-treated patients vs. 70 mg for placebo-treated patients over 72 hours.

Although at 48 hours, 9 patients (13%) in the EXPAREL group remained opioid-free compared to 1 patient (1%) in the placebo group, a difference which was statistically significant, at 72 hours, there were 4 (6%) patients in the EXPAREL group who remained opioid-free compared to 1 (1%) patient in the placebo group, a difference that is not statistically significant.

Study 4: Sciatic Nerve Block in the Popliteal Fossa for Bunionectomy in Adults

A multicenter, randomized, double-blind, active controlled study (NCT05157841) (Study 4) was conducted in 185 adult patients undergoing bunionectomy. The mean age was 49 years (range 18 to 76).

Prior to the surgical procedure, patients received 133 mg of EXPAREL mixed with 20 mL saline OR 50 mg (20 mL) of 0.25% bupivacaine HCl mixed with 10 mL saline via sciatic nerve block (perineural use) in the popliteal fossa. All patients received 100 mg (20 mL) of 0.5% immediate-release bupivacaine HCl as a Mayo field block after study drug administration (i.e., in the operating room immediately prior to surgical incision). All patients also received a dose of 1,000 mg of intravenous (IV) acetaminophen at the time of surgical incision. IV fentanyl was allowed for intraoperative pain control (not exceeding 1 mcg/kg unless deemed medically necessary).

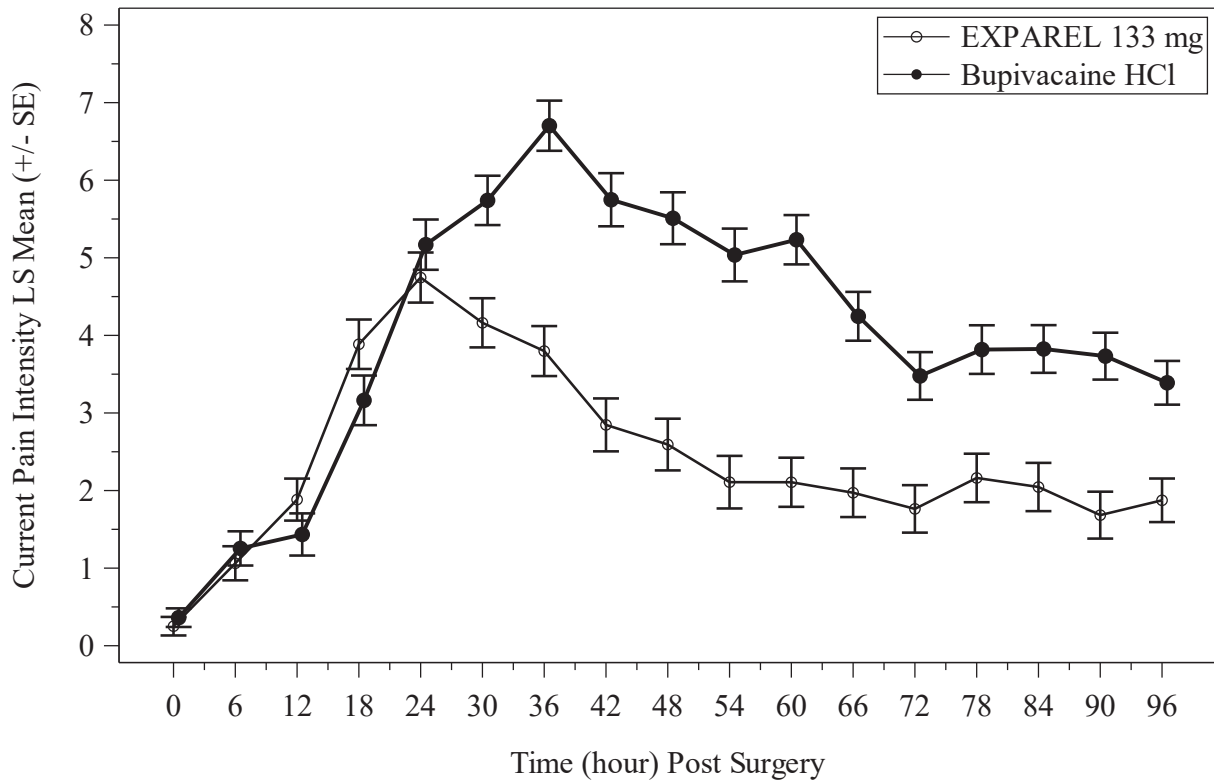
Postsurgically, all patients received one post-operative dose of 1,000 mg IV acetaminophen, administered approximately 8 hours after the first dose (approximately 8 hours after incision). Patients were administered pain medications on an as needed basis; opioids were not given on a pre-determined schedule. Patients were allowed opioid rescue medication administered initially as oral immediate-release oxycodone (initiating at 5 mg and increasing the dose to 10 mg if initial opioid dose was insufficient). If a patient could not tolerate oral medication or the oral oxycodone pain relief was insufficient, IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) could be administered. No NSAIDs or other opioids including tramadol were allowed for the breakthrough pain management and no acetaminophen (other than the scheduled IV acetaminophen) was used for breakthrough pain.

In Study 4, there was a statistically significant treatment effect for EXPAREL (with 0.5% immediate-release bupivacaine HCl as a Mayo field block) compared to bupivacaine HCl (with 0.5% immediate-release bupivacaine HCl as a Mayo field block) in cumulative pain scores through 96 hours as measured by AUC of the NRS pain intensity scores. There were statistically significant differences in the total amount of postsurgical opioid medication used through 96 hours, the clinical benefit of which has not been demonstrated. For those patients who required postsurgical opioid medication, the mean amount of morphine-equivalent opioid rescue used over 96 hours was 18 mg for patients treated with EXPAREL + Mayo field block and 45 mg for patients treated with bupivacaine HCl + Mayo field block. There was also a statistically

significant difference in the percentage of opioid-free patients through 96 hours compared with bupivacaine HCl (24% in the EXPAREL + Mayo field block vs. 6% in the bupivacaine HCl + Mayo field block).

See Figure 2 for the LS mean pain intensity scores after administration of either 133 mg of EXPAREL or 50 mg of 0.25% bupivacaine HCl.

Figure 2. NRS Pain Intensity After Administration of Study Drug by Sciatic Nerve Block in the Popliteal Fossa.



Study 5: Adductor Canal Block for Total Knee Arthroplasty in Adults

A multicenter, randomized, double-blind, active controlled study (NCT05139030) (Study 5) was conducted in 166 adult patients undergoing primary unilateral total knee arthroplasty. The mean age was 62 years (range 37 to 83).

Prior to the surgical procedure, patients received (via adductor canal block) (perineural use):

- 133 mg (10 mL) of 1.3% EXPAREL admixed with 50 mg (10 mL) of 0.5% bupivacaine HCl or
- 50 mg (10 mL) of 0.5% bupivacaine HCl mixed with 10 mL normal saline.

All patients also received 37.5 mg (15 mL) of 0.25% immediate-release bupivacaine HCl as an infiltration between the popliteal artery and capsule of the knee (IPACK) block immediately following study drug administration. All patients received spinal anesthesia immediately prior to surgery with 0.5% bupivacaine HCl (up to 15 mg). All patients also received a dose of 1,000 mg of intravenous (IV) acetaminophen at the time of surgical incision. IV fentanyl was allowed for intraoperative pain control (not exceeding 1 µg/kg unless deemed medically necessary).

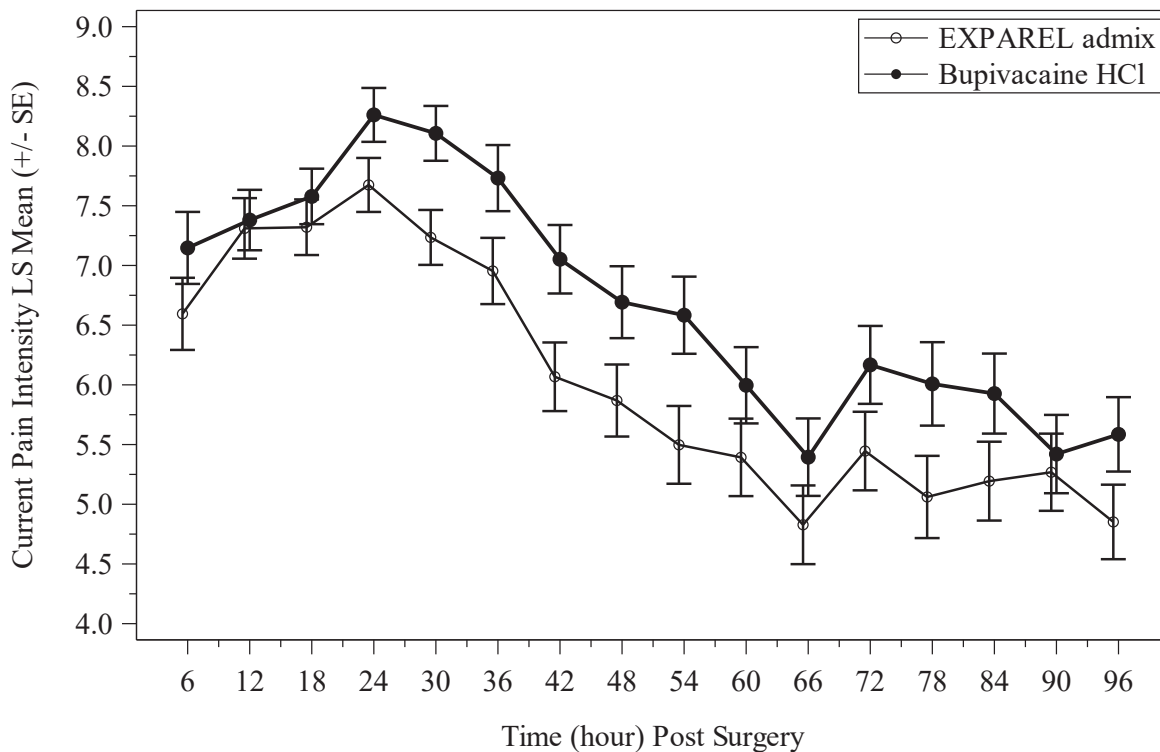
Postsurgically, all patients received one post-operative dose of 1,000 mg IV acetaminophen, administered approximately 8 hours after the first dose (approximately 8 hours after incision). Patients were administered pain medications on an as needed basis for breakthrough pain; opioids were not given on a pre-determined schedule. Patients were allowed opioid rescue medication administered initially as oral immediate-release oxycodone (initiating at 5 mg and increasing the dose to 10 mg if initial opioid dose was insufficient). If a patient could not tolerate

oral medication or the oral oxycodone pain relief was insufficient, IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) could be administered. No NSAIDs or other opioids including tramadol were allowed for the breakthrough pain management and no acetaminophen (other than the scheduled IV acetaminophen) was used for breakthrough pain.

In Study 5, there was a statistically significant treatment effect for EXPAREL + IPACK block compared to bupivacaine HCl + IPACK in cumulative pain scores through 96 hours as measured by AUC of the NRS pain intensity scores. There were statistically significant differences in the total amount of postsurgical opioid medication used through 96 hours, the clinical benefit of which has not been demonstrated. For those patients who required postsurgical opioid medication, the mean amount of morphine-equivalent opioid rescue used over 96 hours was 102 mg for patients treated with EXPAREL + IPACK and 133 mg for patients treated with bupivacaine HCl+ IPACK. The median time to first postsurgical use was 4.2 hours for patients treated with EXPAREL + IPACK and 3.6 hours for patients treated with bupivacaine HCl + IPACK.

See Figure 3 for LS mean pain intensity scores after administration of either 133 mg of 1.3% EXPAREL admixed with 50 mg of 0.5% bupivacaine HCl or 50 mg of 0.5% bupivacaine HCl.

Figure 3. NRS Pain Intensity After Administration of Study Drug by Adductor Canal Block



14.4 Studies That Do Not Support an Indication for Certain Nerve Blocks in Adults

Studies 6 and 7: Inadequate Demonstration of Efficacy and Safety in Femoral Nerve Block in Total Knee Arthroplasty

EXPAREL was administered via a femoral nerve block in two placebo-controlled studies in adults (Studies 6 and 7). The results of these studies did not support a femoral nerve block indication due to inadequate safety data (Study 6) and/or due to inadequate efficacy findings (Study 7). In addition, patient falls were reported only in the EXPAREL treatment groups, and none was reported in placebo groups.

Study 6

Study 6, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT01683071), was conducted in 196 adult patients undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. The mean age was 65 years (range 42 to 88). Prior to the surgical procedure, 266 mg (20 mL) of EXPAREL or placebo was administered as a femoral nerve block with ultrasound guidance. Postsurgically, patients were allowed opioid rescue medication administered initially by intravenous injection of hydromorphone and subsequently by a patient-controlled analgesia (PCA) pump containing morphine or hydromorphone only. Once patients were tolerating oral medication, oral immediate-release oxycodone was administered on an as-needed basis (but not more than 10 mg every 4 hours) or, if that was insufficient, a third rescue of 1.25 mg/mL of 0.125% bupivacaine HCl was administered at a rate of 8 mL per hour via the previously placed femoral nerve catheter.

In this study, there was a statistically significant treatment effect for EXPAREL compared to placebo in cumulative pain scores through 72 hours as measured by the AUC of the NRS pain (at rest) intensity scores.

There was a statistically significant, although small decrease in opioid consumption for the EXPAREL treatment group compared to the placebo group, the clinical benefit of which has not been established. All patients in both the EXPAREL and placebo treatment groups required opioid rescue medication during the first 72 hours. The mean amount of opioid rescue used over 72 hours was 76 mg for patients treated with EXPAREL and 103 mg for patients treated with placebo.

The study was inadequate to fully characterize the safety of EXPAREL when used for femoral nerve block due to patient falls, which occurred only in the EXPAREL-treated patients and not in the placebo-treated patients.

Study 7

Study 7, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT02713178), was conducted in 230 adult patients undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. The mean age was 65 years (range 39 to 89). Prior to the surgical procedure, either 266 mg (20 mL) of EXPAREL or 133 mg (10 mL) of EXPAREL plus 10 mL of normal saline or placebo was administered as a femoral nerve block with ultrasound guidance. In addition to study drug, 8 mL of 0.5% bupivacaine HCl diluted with 8 mL of normal saline was administered by the surgeon as a periarticular infiltration to the posterior capsule (8 mL each behind the medial and lateral condyles) before placement of the prosthesis. Postsurgically, patients were allowed opioid rescue medication consisting of oral immediate-release oxycodone (initiated at 5 to 10 mg every 4 hours or as needed). If a patient could not tolerate oral medication, IV morphine (2.5 to 5 mg) or hydromorphone (0.5 to 1 mg) was permitted every 4 hours or as needed. Patient-controlled analgesia was not permitted. No other analgesic agents, including NSAIDs, were permitted through 108 hours.

However, to reflect the current standard of care of postsurgical multimodal therapy, all patients received cyclobenzaprine (a single dose of 10 mg orally or as needed) and acetaminophen/paracetamol (up to 1,000 mg orally or IV every 8 hours for a maximum total daily dose of 3000 mg) postsurgically.

In this study there were no statistically significant treatment effects for the EXPAREL group compared to the placebo group in cumulative pain intensity scores or total opioid consumption. All patients in the EXPAREL and placebo treatment groups required opioid rescue medication over 72 hours. The median T_{max} of bupivacaine observed in this study was 72 hours with a range of 2.5 to 108 hours. Similar to Study 6, patient falls only occurred in the EXPAREL-treated patients and not the placebo-treated patients.

Study 8: Lack of Efficacy in Intercostal Nerve Block for Posterolateral Thoracotomy

A multicenter, randomized, double-blind, placebo-controlled study was conducted in 191 adult patients undergoing posterolateral thoracotomy under general anesthesia (NCT01802411) (Study 8). The mean age was 58 years (range 18 to 82).

After the surgical procedure was completed but prior to the surgical site closure, 266 mg (20 mL) of EXPAREL was administered by the surgeon as an intercostal nerve block divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve, and administered to each of three nerve segments (index nerve, nerve above, and nerve below). Postsurgically, patients were allowed opioid rescue medication administered initially by intravenous fentanyl 100 mcg, which was to be administered once via bolus only. For the US sites, the second rescue medication was to be PCA-administered morphine or hydromorphone. For the European sites, the second rescue medication was to be intramuscular administered morphine up to 10 mg every 4 hours. At all sites, once a patient was tolerating oral medication, oral immediate-release oxycodone was administered (but not more than 10 mg every 4 hours). Patients who did not achieve adequate pain relief with this regimen were to be withdrawn from the study and followed for safety only.

In this study there were no statistically significant treatment effects for EXPAREL 266 mg compared to placebo in cumulative pain intensity scores or total opioid consumption. Four percent of patients treated with EXPAREL required no rescue medication at 72 hours compared to 1% treated with placebo. For those patients who did require rescue medication, the mean amount of opioid rescue used over 72 hours was 71 mg for patients treated with EXPAREL and 71 mg for patients treated with placebo. The median T_{max} of bupivacaine observed in this study was 1 hour with a range of 0.5 hours to 50 hours.

Study 9: Lack of Efficacy in Combined Sciatic (in popliteal fossa) and Saphenous (in adductor canal) Nerve Block Study in Lower Extremity Surgeries

A multicenter, randomized, double-blind, active-controlled trial (NCT04518462) (Study 9) was conducted in 119 adult patients who underwent foot and ankle procedures (bunionectomy, first metatarsophalangeal fusion, forefoot & hindfoot fusion, total ankle arthroplasty). The mean age was 48 years (range 20 to 72). Prior to the surgical procedure, patients received one of the following three treatments under ultrasound guidance as a sciatic nerve block in the popliteal fossa and a saphenous nerve block in the adductor canal:

- 266 mg of EXPAREL (20 mL) admixed with 20 mL of 0.9% Sodium Chloride Injection (referred to as normal saline (NS)),
- 266 mg of EXPAREL (20 mL) admixed with 50 mg of 0.25% bupivacaine HCl (20 mL), or
- 100 mg of 0.25% bupivacaine (40 mL).

The total volume (40 mL) was divided evenly between the two blocks. All patients received general anesthesia or nonopioid sedation (except fentanyl); were allowed medication for intraoperative nausea/vomiting prevention; and were allowed medication for breakthrough pain postsurgery which followed a step-wise approach starting with acetaminophen or a nonsteroidal anti-inflammatory drug (not exceeding the maximum dose), and, if needed escalating to an initial 5 mg dose of oxycodone, then to a 10 mg dose of oxycodone, and finally to intravenous morphine (initiated at 2 mg) or intravenous hydromorphone (initiated at 0.2 mg).

In Study 9 there was no significant difference in the primary endpoint [least square mean (LSM) area under the curve (AUC) numerical rating scale (NRS) pain score from 0 to 96 hours after surgery] between EXPAREL + NS and the 0.25% bupivacaine HCl treatment groups. Cumulative opioid consumption differences between groups were nonsignificant 0-96 hours after surgery. The LSM amount of opioids received over 96 hours was 21 mg in EXPAREL group and 20 mg in bupivacaine HCl group.

16 HOW SUPPLIED/STORAGE AND HANDLING

EXPAREL (bupivacaine liposome injectable suspension) is a white to off-white milky aqueous suspension that is available in the following single-dose vials.

1.3% (266 mg/20 mL) (13.3 mg/mL) single-dose vial, (NDC 65250-266-20) packaged in cartons of 10 (NDC 65250-266-09) and cartons of 4 (NDC 65250-266-04)

1.3% (133 mg/10 mL) (13.3 mg/mL) single-dose vial, (NDC 65250-133-10) packaged in cartons of 10 (NDC-65250-133-09) and cartons of 4 (NDC 65250-133-04)

Storage

Store EXPAREL vials refrigerated between 2°C to 8°C (36°F to 46°F). EXPAREL may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 30 days in sealed, intact (unopened) vials. Do not re-refrigerate vials.

Do not freeze or expose EXPAREL to high temperatures (greater than 40°C or 104°F) for an extended period. Do not administer EXPAREL if it is suspected of having been frozen or exposed to high temperatures. Do not use the vial if the stopper is bulging.

Handling

See *Dosage and Administration (2.1, 2.4)* for important preparation instructions.

17 PATIENT COUNSELING INFORMATION

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

Inform patients in advance that EXPAREL can cause temporary loss of sensation or motor activity that may last for up to 5 days.

Manufactured for Pacira Pharmaceuticals, Inc., a wholly owned subsidiary of Pacira BioSciences, Inc.
San Diego, CA 92121 USA

Trademark of Pacira Pharmaceuticals, Inc.

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For additional information call 1-855-RX-EXPAREL (1-855-793-9727) or visit
www.EXPAREL.com

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22496Orig1s037

PRODUCT QUALITY REVIEW(S)

**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I, Branch II
Review of Chemistry, Manufacturing, and Controls**

1. **NDA Supplement Number:** NDA-022496-SUPPL-37

2. **Submission(s) Being Reviewed:** SDN 956

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	CBE-30	10/09/2020	10/09/2020	11/13/2020	04/09/2020	03/09/2021

3. **Proposed Changes:** Provides for changes to the manufacturing process for EXPAREL® (bupivacaine liposome injectable suspension) at the Pacira Pharmaceuticals facility in San Diego, California:

(b) (4)

4. **Review #:** 1

5. **Clinical Review Division:** DAAAP

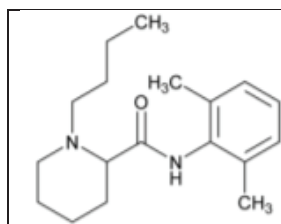
6. **Name and Address of Applicant:**

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr., Building 1
San Diego, CA 92121

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Exparel® (Bupivacaine liposome injectable suspension)	Sterile; Injectable; Liposomal	266 mg/ 20mL and 133 mg/ 10 mL	Injection	Rx	No

8. **Chemical Name and Structure of Drug Substance:**



USAN: Bupivacaine
Chemical name: (1) 2-Piperidinecarboxamide, 1-butyl N-(2,6- dimethylphenyl)-; (2) (2RS)-1-Butyl-N-(2,6-dimethylphenyl) piperidine-2- carboxamide.
Molecular formula: C₁₈H₂₈N₂O.
MW: 288.44

9. **Indication:** Exparel is a liposomal injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

10. Supporting/Relating Documents:

The applicant has submitted the process validation report (in section 3.2.P.3.5), batch analysis (in section 3.2.P.5.4) and stability data (in section 3.2.P.8.3) for the three exhibit batches (b) (4) to support this supplement.

11. Consults:

Consults	Recommendation	Date	Reviewer
Microbiology	Adequate	02/11/2021	Hemlata Tamta, Ph.D.
OPMA (Facility: Pacira Pharmaceuticals Inc, San Diego, FEI# 3002783962)	Approve	12/11/2020	Yifan Wang

12. Executive Summary:

This supplement, submitted and acknowledged as CBE-30, provides for (b) (4) at the Pacira San Diego Facility. (b) (4)

The applicant submitted the process validation report, batch analysis as well as stability results (three months under both long term and accelerated storage conditions) for the three process performance qualification (PPQ) batches (b) (4)

The release, 3-months long-term and accelerated stability test results of all evaluated parameters were well within acceptance criteria of previously approved drug product stability specification {Ref: SDN 846; dated 12/19/2019}. No significant trends are observed.

There are no changes proposed regarding the container closure system, (b) (4) and release/stability specifications. The microbiology review (N022496S037MR01; 02/11/2021); assessed by Hemlata Tamta, Ph.D., was found adequate for sterilization validation of drug product.

The applicant's proposed site, Pacira Pharmaceuticals Inc, San Diego, FEI# 3002783962), for the manufacturing of drug product, has been assessed as approve facility by OPMA assessor (Yifan Wang) on 12/11/2020. The OMIR (overall manufacturing inspection recommendation) is *approve* for the facility added for NDA 022496-SUPPL-37. A copy of the screenshot from Panorama is attached below.

NDA-022496-SUPPL-37 » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Task Summary Task Details Documents Archive Updates Application Life Cycle **Inspection Management Form**

Inspection Management Form

Inspection Management Form

NDA-022496-SUPPL-37

PACIRA PHARMACEUTICALS INC | 3002783962 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility

Overall Manufacturing Inspection Recommendation

Approve
 Withhold
 No Evaluation Necessary

Save Cancel

The applicant's proposed changes and the justifications in this supplement are acceptable from CMC prospective. See further justification in the CMC assessment section of this review.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Rishi Thakur, Ph.D., CMC reviewer, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

(see attached electronic signature)

16. Secondary Reviewer:

David B. Lewis, Ph.D., Branch Chief, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

(see attached electronic signature)



Rishi
Thakur

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David
Lewis

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Date: 3/11/2021 04:32:49PM
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Comments: concur; recommend approval from the standpoint of
CMC

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22496Orig1s037

CLINICAL MICROBIOLOGY/VIROLOGY
REVIEW(S)

CBE Microbiology Review Form

09 February 2021

Applicant: Pacira Pharmaceuticals, Inc. Type of Supplement: CBE-30

NDA/Supplement #:
022496/S037

Drug Product Name:
Exparel® (Bupivacaine liposome Injectable suspension) 266
mg/ 20mL and 133 mg/ 10 mL

Receipt Date: 10 September 2020

Manufacturing Site:
Pacira Pharmaceuticals, Inc.
10450 Science Center Dr., Building 1
San Diego, CA 92121

Method of Sterilization: (b) (4)

Dosage Form, Route of Administration and Strength/Potency:

- Dosage form: Sterile solution for injection
- Route of administration: Parenteral administration
- Strength/Potency: 266 mg/ 20mL and 133 mg/ 10 mL single dose presentations

File Name: N022496S037MR01.doc

Proposed Change(s): (b) (4)

Supporting/Related Documents: Microbiology review N022496S029MR01.docx dated 08/27/2018 (adequate) for sterilization validation of product contact components.

Conclusion:

The supplement is recommended for approval

Information requested (deficiencies to be conveyed to the applicant are listed at the end of the review)

Template: CBE Review Form.doc

Review Notes: The subject CBE-30 supplement provides for (b) (4)
(b) (4) at the Pacira San Diego Facility. (b) (4)
(b) (4)
(b) (4) There are no (b) (4)
changes proposed regarding the container closure system,
and release/stability specifications.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – No change.
- **Drug product composition** – No change.
- **Description of container closure system** – No change from previously approved submission. (b) (4)

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity** - No change in container closure is proposed. (b) (4)

Acceptable

- **Antimicrobial Effectiveness Testing** – No change. The subject drug product is single dose. Antimicrobial effectiveness testing is not required.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers: No Change

Approved: (Manufacturing, packaging, finished product sterility and bacterial endotoxins testing)

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr., Building 1
San Diego, CA 92121

Acceptable

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

(b) (4) However, data was not provided. Since (b) (4) (b) (4) data is 2 years old (from the date of submission) and the (b) (4) (b) (4) recent studies will not be requested.

Acceptable

- **Actions concerning product** (b) (4)
Any contamination shall be investigated in accordance with procedures (not provided), and a product impact risk assessment shall be performed. The contaminating microorganism(s) are isolated and identified to the species level. The investigation shall include a review of all lots (b) (4) (b) (4) unless an assignable cause is identified with a more recent lot. Upon notification of contamination, (b) (4) (b) (4)

Acceptable

P.5 Control of Drug Product

P.5.1 Specification- No change in the currently approved drug product release specifications or procedures.

Test	Test method	Acceptance criteria	Exhibit batch results*
Bacterial endotoxins	(b) (4)-STM-0035	NMT (b) (4)	Pass
Sterility	(b) (4) STM-0040	Sterile	Pass

*Lot # 20-3066, 20-3067, and 20-4076

Acceptable

P.5.2 Analytical Procedures – See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

- **Endotoxins** – No change
- **Sterility** – No change

P.7 Container Closure System - See P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Expiry: 24 months (No change)

P.8.3 Stability Data

(3.2.P.8.1 Stability Summary and Conclusion- (b) (4)
Stability data for three commercial scale exhibit batches of Exparel (bupivacaine liposome injectable suspension; 133 mg/ 10 mL) manufactured and (b) (4) (b) (4) is summarized below. The batches under accelerated under accelerated conditions (25° ± 2°C) and long-term conditions (5° ± 3°C) will

be tested according to the stability schedule. Bacterial endotoxins testing and sterility met the specifications at the initial time point for both long term and accelerated stability studies. The applicant states that accelerated and long-term stability studies are ongoing.

Acceptable

R REGIONAL INFORMATION

R.1 Executed Batch Record

Batch # 20-3066 (b) (4) and 20-3067 (b) (4) were (b) (4)
(b) (4) on 03/19/2020. Batch # 20-4068 was (b) (4)
(b) (4) on 03/20/2020.

Acceptable

R.2 Comparability Protocol – No CP was included in the application.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY
(CTD-Q)
MODULE 1**

A. PACKAGE INSERT – No change

Acceptable

Primary Reviewer: Hemlata Tamta, Ph.D.

Secondary Reviewer: Denise Miller, SPQA, Senior Microbiologist



Hemlata
Tamta

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Denise
Miller

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