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)
Initial U.S. Approval: 1972

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	(04/2018)
Dosage and Administration (2.1, 2.2, 2.3)	(04/2018)
Warnings and Precautions, Methemoglobinemia (5.1)	(11/2018)

----------INDICATIONS AND USAGE----------

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia (1).

Limitations of Use

Safety and efficacy have not been established in other nerve blocks.

----------DOSAGE AND ADMINISTRATION----------

- EXPAREL is intended for single-dose administration only (2.1).
- Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. It is not possible to convert dosing from other formulations of bupivacaine to EXPAREL (2.1, 2.5).
- DO NOT dilute EXPAREL with water for injection 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 (20 mL). See Full Prescribing Information for guidance on dose selection (2.2).
- The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL) (2.2).
- See Full Prescribing Information for important injection instructions and compatibility considerations (2.3, 2.4).

----------DOSAGE FORMS AND STRENGTHS----------

Injectable suspension:
266 mg/20 mL (13.3 mg/mL) single-dose vial (3)
133 mg/10 mL (13.3 mg/mL) 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 were nausea, constipation, and vomiting (6.1).

Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via nerve block were nausea, pyrexia, and constipation (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).
- Do not dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

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

Limitations of Use

Safety and efficacy have not been established in other nerve blocks.

2. DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- EXPAREL is intended for single-dose administration only.
- Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL [*see Dosage and Administration (2.5)*].
- DO NOT dilute EXPAREL with water for injection or other hypotonic agents, as it will result in disruption of the liposomal particles.
- Use suspensions of EXPAREL diluted with preservative-free normal (0.9%) saline for injection or lactated Ringer's solution within 4 hours of preparation in a syringe.
- 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.

2.2 Recommended Dosing in Adults

Local Analgesia via Infiltration

The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266 mg (20 mL), 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 dosing, two examples of infiltration dosing are provided:

- In 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.
- In patients undergoing 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.

Regional Analgesia via Interscalene Brachial Plexus Nerve Block

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL), and is based upon one study of patients undergoing either total shoulder arthroplasty or rotator cuff repair.

2.3 Injection Instructions

EXPAREL should be injected slowly (generally 1 to 2 mL per injection) with frequent aspiration to check for blood and minimize the risk of inadvertent intravascular injection. Do not exceed a maximum dosage of 266 mg (20 mL, 1.3% of undiluted drug) for infiltration and 133 mg (10 mL) for interscalene brachial plexus nerve block.

- Administer EXPAREL undiluted or diluted to increase volume up to a final concentration of 0.89 mg/mL (i.e., 1:14 dilution by volume) with normal (0.9%) saline or lactated Ringer's solution.
- Invert vials of EXPAREL multiple times to re-suspend the particles immediately prior to withdrawal from the vial.
- Administer EXPAREL with a 25 gauge or larger bore needle to maintain the structural integrity of the liposomal bupivacaine particles.

2.4 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 as long as 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.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage.

2.5 Non-Interchangeability with Other Formulations of Bupivacaine

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

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:

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

4. CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. 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 bupivacaine 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 effects 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.

Bupivacaine 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 bupivacaine 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 effects 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 types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks other than interscalene brachial plexus nerve block
- intravascular or intra-articular use

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 18 years old
- 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 dosage 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

Adverse Reactions Reported in All Local Infiltration Clinical Studies

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.

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, 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, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions

In the EXPAREL surgical site infiltration studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.9%) and bradycardia (1.6%).

Adverse Reactions Reported in All Local Infiltration Placebo-Controlled Trials

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 8 mL EXPAREL 1.3% (106 mg) to placebo and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 1.

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

	STUDY 1[a]		STUDY 2[b]	
	EXPAREL	Placebo	EXPAREL	Placebo
System Organ Class Preferred Term	8 mL/1.3% (106 mg) (N=97) n (%)	(N=96) n (%)	20 mL/1.3% (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)
Pruritus Generalized	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)
Alanine Aminotransferase Increased	3 (3.1)	3 (3.1)	1 (1.1)	0 (0.0)
Aspartate Aminotransferase Increased	3 (3.1)	2 (2.1)	0 (0.0)	0 (0.0)
Blood Creatinine Increased	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Body Temperature Increased	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
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 All Nerve Block Clinical Studies

The safety of EXPAREL was evaluated in four randomized, double-blind, placebo-controlled nerve block clinical studies involving 469 patients undergoing various surgical procedures. Patients were administered a dose of either 133 or 266 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, pyrexia, and constipation.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration as a nerve block were muscle twitching, dysgeusia, urinary retention, fatigue, headache, confusional state, hypotension, hypertension, hypoesthesia oral, pruritus generalized, hyperhidrosis, tachycardia, sinus tachycardia, anxiety, fall, body temperature increased, edema peripheral, sensory loss, hepatic enzyme increased, hiccups, hypoxia, and post-procedural hematoma.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration as a nerve block were arrhythmia, atrial fibrillation, atrioventricular block first degree, bradycardia, bundle branch block left, bundle branch block right, cardiac arrest, hearing impaired, vision blurred, 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, mobility decreased, 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.

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 10 mL EXPAREL 1.3% (133 mg) and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 2.

Neurological and Cardiac Adverse Reactions

In the EXPAREL nerve block studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were motor dysfunction (14.9%), dysgeusia (7.2%), headache (5.1%), hypoesthesia (2.3%), and sensory loss (2.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.0%), sinus tachycardia (2.3%), and bradycardia (1.3%).

Table 2: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies

SYSTEM ORGAN CLASS Preferred Term	133 mg (N=168) n (%)	266 mg (N=301) n (%)	Placebo (N=357) n (%)
Number of Subjects 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)
Hypoesthesia Oral	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)
Feeling Cold	0	10 (3.3)	8 (2.2)
Edema Peripheral	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)
Anemia Postoperative	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)
Body Temperature Increased	1 (0.6)	10 (3.3)	4 (1.1)
Hepatic Enzyme Increased	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)
Mobility Decreased	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)
Pruritus Generalized	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)
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.

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 (SOCs): 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 their co-administration 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 may be at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Examples of Drugs Associated with Methemoglobinemia:

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, pipecoloxylidide, 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

Safety and effectiveness in pediatric patients have not been established.

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=531), 241 patients were greater than or equal to 65 years of age and 60 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, this should be considered when performing dose selection of EXPAREL.

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. Therefore, consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease.

8.7 Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. This should be considered when performing dose selection of EXPAREL.

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.

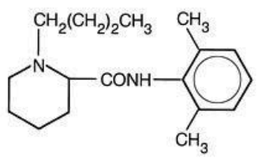
Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

11. DESCRIPTION

EXPAREL is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of multivesicular liposomes (DepoFoam® drug delivery system) containing bupivacaine. Bupivacaine is present at a concentration of 13.3 mg/mL. After injection of EXPAREL, bupivacaine is released from the multivesicular liposomes over a period of time.

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:



Lipid Formulation

The median diameter of the liposome particles ranges from 24 to 31 µm. The liposomes are suspended in a 0.9% sodium chloride solution. 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) (DPPG), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; and 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2 mg/mL. The pH of EXPAREL is in the range of 5.8 to 7.4.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

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

Administration of EXPAREL results in systemic plasma levels of bupivacaine which can persist for 96 hours after local infiltration and 120 hours after interscalene brachial plexus nerve 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 drug 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 were evaluated following surgical procedures. Descriptive statistics of pharmacokinetic parameters of representative EXPAREL doses in each study are provided in Table 3.

Table 3: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL via Local Infiltration and Interscalene Brachial Plexus Nerve Block

Parameters	Surgical Site Administration via Local Infiltration		Interscalene Brachial Plexus Nerve Block
	Bunionectomy 106 mg (8 mL)	Hemorrhoidectomy 266 mg (20 mL)	Total Shoulder Arthroplasty 133 mg (10 mL)
	(N=26)	(N=25)	(N=12)
C_{max} (ng/mL)	166 (92.7)	867 (353)	207 (137)
T_{max} (h)	2 (0.5-24)	0.5 (0.25-36)	48 (3-74)
$AUC_{(0-t)}$ (h x ng/mL)	5864 (2038)	16,867 (7868)	11484 (8615)
$AUC_{(inf)}$ (h x ng/mL)	7105 (2283)	18,289 (7569)	11590 (8603)
$t_{½}$ (h)	34 (17)	24 (39)	11 (5)

Note: Arithmetic mean (standard deviation) except T_{max} where it is median (range).

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 Studies Confirming Efficacy

The efficacy of EXPAREL compared to placebo was demonstrated in three multicenter, randomized, double-blinded clinical studies. For local analgesia via infiltration, one study evaluated the treatment in patients undergoing bunionectomy; the other study evaluated the treatment in patients undergoing hemorrhoidectomy. For regional analgesia, one study 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), however, only two subjects had nerve blocks via the supraclavicular approach. Three additional studies did not provide sufficient efficacy and/or safety data to support a nerve block indication: two studies evaluated the use of EXPAREL via femoral block in patients undergoing total knee arthroplasty (TKA), and one study evaluated the use of EXPAREL via intercostal nerve block for patients undergoing posterolateral thoracotomy.

Study 1: Infiltration for Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial (NCT00890682) evaluated the safety and efficacy of 106 mg (8 mL) EXPAREL in 193 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 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

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

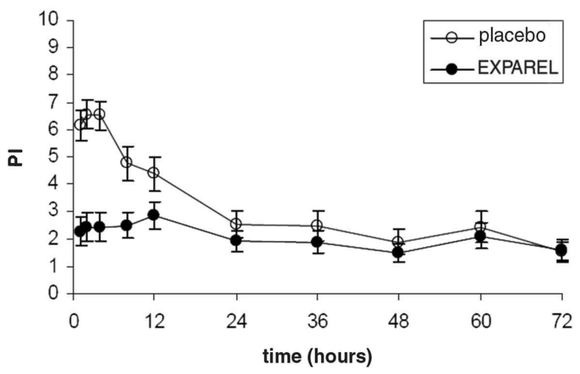
Study medication was administered directly into the site (greater than or equal to 3 cm) at the conclusion of the surgery. Dilution of 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, was divided into six 5-mL aliquots. A field block was performed by visualizing the anal sphincter as a clock 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.

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

A multicenter, randomized, double-blind, placebo-controlled study (NCT02713230) was conducted in 156 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 10 mL of EXPAREL (133 mg) expanded with normal saline to 20 mL as a brachial plexus nerve block 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 1000 mg PO or IV every 8 hours (q8h) 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, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) could be administered every 4 hours or as needed.

In this study, 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 patients treated with EXPAREL and 54 mg for patients treated with placebo and 23 mg with EXPAREL vs. 70 mg for placebo over 72 hours.

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

14.2 Studies That Do Not Support an Indication in Nerve Block

Studies 4 and 5: Femoral Nerve Block in Total Knee Arthroplasty

EXPAREL was administered via a femoral nerve block in two placebo-controlled studies. The results of these studies did not support a femoral nerve block indication due to inadequate safety data (Study 4 and Study 5) or due to inadequate efficacy findings (Study 5). In addition, patient falls were reported only in the EXPAREL treatment groups and none was reported in placebo groups.

Study 4

Study 4, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT01683071), was conducted in 196 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, 20 mL of EXPAREL (266 mg) 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 bupivacaine HCl (0.125%, 1.25 mg/mL) 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 the placebo-treated patients.

Study 5

Study 5, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT02713178), was conducted in 230 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 20 mL of EXPAREL (266 mg) or 10 mL of EXPAREL (133 mg) plus 10 mL of normal saline was administered as a femoral nerve block with ultrasound guidance. In addition to study drug, 8 mL of bupivacaine HCl (0.5%) 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 subject 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 subjects received cyclobenzaprine (a single dose of 10 mg orally or as needed) and acetaminophen/paracetamol (up to 1000 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 mean amount of opioid rescue used over 72 hours was 69 mg for patients treated with EXPAREL 133 mg; 74 mg for patients treated with EXPAREL 266 mg, and 81 mg for patients treated with placebo. The median T_{max} of bupivacaine observed in this study was 72 h with a range of 2.5 h to 108 h. Similarly to Study 4, patient falls only occurred in the EXPAREL-treated patients and not the placebo-treated patients.

Study 6: Intercostal Nerve Block for Posterolateral Thoracotomy

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

After the surgical procedure was completed but prior to the surgical site closure, 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 subject was tolerating oral medication, oral immediate-release oxycodone was administered (but not more than 10 mg every 4 hours). Subjects 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 h with a range of 0.5 h to 50 h.

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.

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)

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

- Invert vials of EXPAREL to re-suspend the particles immediately prior to withdrawal from the vial. Multiple inversions may be necessary to re-suspend the particles if the contents of the vial have settled.
- Visually inspect vials for particulate matter and discoloration before use.
- Do not filter.
- Do not heat before use.
- Do not autoclave.
- Following withdrawal from the vial, store EXPAREL at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration.
- Discard any unused portion in an appropriate manner.

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.

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Patent Numbers:
6,132,766
5,766,627
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For additional information call 1-855-RX-EXPAREL (1-855-793-9727)
or visit www.EXPAREL.com