

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

INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia (1).

DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy	106 mg	8 mL
Hemorrhoidectomy	266 mg	20 mL

Inject EXPAREL slowly into soft tissue via infiltration (2.1).

DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)

10 mL single use vial, 1.3% (13.3 mg/mL) (3)

20 mL single use vial, 1.3% (13.3 mg/mL) (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products (5.1).
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL 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 (5.1).
- Other formulations of bupivacaine should not be administered 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 were nausea, constipation, and vomiting (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Pacira Pharmaceuticals, Inc. at 858-625-2414 ext. 3231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics (7).
- EXPAREL may be administered after at least 20 minutes or more have elapsed following local administration of lidocaine.

USE IN SPECIAL POPULATIONS

Safety and effectiveness in pediatric patients below the age of 18 have not been established (8).

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - Injection Instructions
 - Administration Precautions
 - Non-Interchangeability with Other Formulations of Bupivacaine
 - Dosing in Special Populations
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Warnings and Precautions for Bupivacaine containing Products
 - Warnings and Precautions Specific for EXPAREL
- ADVERSE REACTIONS
 - General
 - Adverse Reactions Reported in All Wound Infiltration Clinical Studies
- DRUG INTERACTIONS
- USE IN SPECIFIC POPULATIONS
 - Pregnancy
 - Labor and Delivery
 - Nursing mothers
 - Pediatric use

- Geriatric use
- Hepatic Impairment
- Renal Impairment
- OVERDOSAGE
- DESCRIPTION
 - Active Ingredient
 - Lipid Formulation
- CLINICAL PHARMACOLOGY
 - Mechanism of action
 - Pharmacodynamics
 - Pharmacokinetics
- NONCLINICAL TOXICOLOGY
 - Carcinogenesis, mutagenesis, impairment of fertility
- CLINICAL STUDIES
 - Bunionectomy
 - Hemorrhoidectomy
- HOW SUPPLIED/STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

EXPAREL has not been studied for use in patients younger than 18 years of age.

2. DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy ¹	106 mg	8 mL
Hemorrhoidectomy ²	266 mg	20 mL

¹Infiltrate 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

²Dilute 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, and divide the mixture into six 5 mL aliquots. Perform the anal block by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers.

2.1 Injection Instructions

EXPAREL should be injected slowly into soft tissues of the surgical site with frequent aspiration to check for blood and minimize the risk of intravascular injection.

- EXPAREL is intended for single-dose infiltration only.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- The maximum dosage of EXPAREL should not exceed 266 mg (20 mL, 1.3% of undiluted drug).
- Do not administer EXPAREL if the product is discolored.
- Do not administer EXPAREL if it is suspected that the vial has been frozen as reflected by the temperature indicator or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection.
- Vials of EXPAREL should be inverted multiple times to re-suspend the particles immediately prior to withdrawal from the vial.

- Diluted suspensions of EXPAREL should be used within 4 hours of preparation in a syringe.

2.2 Administration Precautions

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, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physicochemical properties of the drugs when the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose. EXPAREL contains bupivacaine; therefore, coadministration of both drugs will increase the overall exposure to bupivacaine.
- 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 surgical 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 and does not cause methemoglobinemia.

2.3 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.

2.4 Dosing in Special Populations

EXPAREL has not been studied in patients younger than 18 years of age, pregnant patients or patients who are nursing.

3. DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)

- 10 mL single use vial, 1.3% (13.3 mg/mL)
- 20 mL single use vial, 1.3% (13.3 mg/mL)

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, paresthesias, 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 Warnings and Precautions (5.1) and 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-humerol 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.

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.

Using EXPAREL followed by other bupivacaine formulations has not been studied in clinical trials. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL [*See 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
- intravascular or intra-articular use

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

- patients younger than 18 years old
- pregnant patients
- nursing patients

The ability of EXPAREL to achieve effective anesthesia has not been studied. Therefore, EXPAREL is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

6. ADVERSE REACTIONS

6.1 General

The most commonly encountered acute adverse experiences to bupivacaine and all amide-type local anesthetics that demand immediate counter-measures are related to the central nervous and cardiovascular systems.

High plasma concentrations of bupivacaine can occur from overdose, unintended intravascular injection, or accumulation of bupivacaine in plasma secondary to decreased hepatic metabolic degradation of the drug or diminished plasma protein binding capacity due to acidosis, pathologically lowered plasma protein production, or competition with other drugs for protein binding sites. Although rare, some individuals have a lower tolerance to and are supersensitive

to bupivacaine and other amide-type local anesthetics and may rapidly develop signs of toxicity at low doses [*See Overdosage (10)*].

6.2 Adverse Reactions Reported in All Wound 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, bradycardia, 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 retention, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions Reported in All Wound Infiltration Clinical Studies

In the EXPAREL wound 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 Placebo-Controlled Wound Infiltration Clinical Studies

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%: Placebo-Controlled Studies

System Organ Class Preferred Term	STUDY 1 ^a		STUDY 2 ^b	
	EXPAREL	Placebo	EXPAREL	Placebo
	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)

System Organ Class Preferred Term	STUDY 1 ^a		STUDY 2 ^b	
	EXPAREL	Placebo	EXPAREL	Placebo
	8 mL/1.3% (106 mg) (N=97) n (%)	(N=96) n (%)	20 mL/1.3% (266 mg) (N=95) n (%)	(N=94) n (%)
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.

7. DRUG INTERACTIONS

EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e., 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection. EXPAREL must not be diluted with water or other hypotonic agents as it will result in disruption of the liposomal particles.

EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics.

EXPAREL may be locally administered after at least 20 minutes following local administration of lidocaine.

EXPAREL should not be admixed with other drugs prior to administration.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. EXPAREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride (HCl) produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of EXPAREL at term for analgesia [*See Labor and Delivery (8.2)*].

Bupivacaine HCl was administered subcutaneously to rats and rabbits during the period of fetal organogenesis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Administration of bupivacaine HCl to rats during pregnancy and lactation resulted in decreased offspring survival.

8.2 Labor and Delivery

Bupivacaine hydrochloride is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics 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.

8.3 Nursing mothers

Bupivacaine has been reported to be excreted to some extent in human milk, suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer EXPAREL, taking into account the importance of the drug to the mother.

8.4 Pediatric use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric use

Of the total number of patients in the EXPAREL wound 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. 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, care should be taken in dose selection of EXPAREL.

8.6 Hepatic Impairment

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.

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. Care should be taken in dose selection of EXPAREL.

10. OVERDOSAGE

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)*].

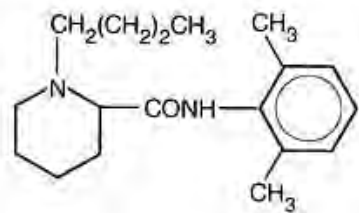
In the clinical study program, maximum plasma concentration (C_{max}) values of approximately 34,000 ng/mL were reported and likely reflected inadvertent intravascular administration of EXPAREL or systemic absorption of EXPAREL at the surgical site. The plasma bupivacaine measurements did not discern between free and liposomal-bound bupivacaine making the clinical relevance of the reported values uncertain; however, no discernable adverse events or clinical sequelae were observed in these patients.

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 into soft tissue, bupivacaine is released from the multivesicular liposomes over a period of time.

11.1 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:



Bupivacaine is present in EXPAREL at a concentration of 13.3 mg/mL.

11.2 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; tricaprilyn, 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

Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours [See *Warnings and Precautions (5.2)*]. 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 administration were evaluated following surgical procedures. Descriptive statistics of pharmacokinetic parameters of representative EXPAREL doses in each study are provided in Table 2.

Table 2: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL

	EXPAREL	
	Bunionectomy 106 mg (8 mL)	Hemorrhoidectomy 266 mg (20 mL)
	(N=26)	(N=25)
C _{max} (ng/mL)	166 (92.7)	867 (353)
T _{max} (h)	2	0.5
AUC _(0-t) (h×ng/mL)	5864 (2038)	16,867 (7868)
AUC _(inf) (h×ng/mL)	7105 (2283)	18,289 (7569)
t _{1/2} (h)	34.1 (17.0)	23.8 (39.4)

Note: Arithmetic mean (standard deviation) except T_{max} (median).

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.

Metabolism

Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecolylxylylidine (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

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.

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 [*See Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

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. Care should be taken in dose selection of EXPAREL [*See Use in Specific Populations (8.7)*].

Age

Various pharmacokinetic parameters of the local anesthetics such as bupivacaine can be significantly altered by the age of the patient.

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 this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of EXPAREL [See *Use in Specific Populations (8.5)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals of most local anesthetics, including bupivacaine, to evaluate the carcinogenic potential have not been conducted. Mutagenic potential and the effect on fertility have not been determined. There is no evidence from human data that bupivacaine may be carcinogenic or mutagenic or that it impairs fertility.

14. CLINICAL STUDIES

The efficacy of EXPAREL was compared to placebo in two multicenter, randomized, double-blinded clinical trials. One trial evaluated the treatments in patients undergoing bunionectomy; the other trial evaluated the treatments in patients undergoing hemorrhoidectomy. EXPAREL has not been demonstrated to be safe and effective in other procedures.

14.1 Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 106 mg EXPAREL in 193 patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72). Study medication was administered directly into the wound at the conclusion of the surgery, prior to wound closure. 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.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity.

14.2 Hemorrhoidectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 266 mg EXPAREL in 189 patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86). Study medication was administered directly into the wound (greater than or equal to 3 cm) at the conclusion of the surgery. 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.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity; however, there was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

16. HOW SUPPLIED/STORAGE AND HANDLING

EXPAREL (bupivacaine liposome injectable suspension) is available in single-use vials for infiltration.

10 mL single use vial, 1.3% (13.3 mg/mL) packaged in cartons of 10 (NDC 65250-133-10)

20 mL single use vial, 1.3% (13.3 mg/mL) packaged in cartons of 10 (NDC 65250-266-20)

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.

Storage

EXPAREL vials should be stored 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 one month in sealed, intact (unopened) vials. Vials should not be re-refrigerated. As a convenience to the hospital pharmacist, each vial label includes space to record the date when the vial has been removed from refrigeration.

EXPAREL should not be frozen as reflected by the temperature indicator or exposed 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 as reflected by the temperature indicator or exposed to high temperatures.

Check the freeze indicator and discard product if it has been triggered. The freeze indicator turns from green to white when exposed to freezing temperatures.

Handling

- Vials of EXPAREL should be inverted 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.
- Vials should be visually inspected before use.
- Do not filter.
- Do not heat before use.
- Do not autoclave.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection.
- Following withdrawal from the vial, EXPAREL may be stored 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

Patients should be informed in advance that bupivacaine-containing products can cause temporary loss of sensation or motor activity in the area infiltrated. Physicians should discuss adverse reactions in the EXPAREL prescribing information with their patients.

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