

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

USDC SDNY
DOCUMENT
ELECTRONICALLY FILED
DOC #:
DATE FILED: 12-15-15

PACIRA PHARMACEUTICALS, INC.,
DR. LOREN J. HARRIS, and DR. JOSEPH
W. BELL,

Plaintiffs,

No. 15 Civ. 7055 (LAK)

v.

STIPULATION AND
~~PROPOSED~~ ORDER

UNITED STATES FOOD & DRUG
ADMINISTRATION; UNITED STATES
OF AMERICA; DR. STEPHEN OSTROFF,
in his official capacity as Acting
Commissioner of Food and Drugs; UNITED
STATES DEPARTMENT OF HEALTH &
HUMAN SERVICES; and SYLVIA
MATHEWS BURWELL, in her official
capacity as Secretary of the Department of
Health & Human Services,

Defendants.

IT IS HEREBY STIPULATED AND AGREED that pursuant to Federal Rule of Civil Procedure 41, and pursuant to the settlement agreement the parties to the above-captioned action entered into on December 14, 2015 (the "Settlement Agreement"), which is attached hereto as Exhibit A, the parties stipulate to dismiss with prejudice all claims asserted in the action, provided that such dismissal shall have no effect on plaintiffs' ability to assert their constitutional rights (including under the First and Fifth Amendments) in connection with or as a defense against any criminal, civil, or administrative investigation into or proceeding against plaintiffs. Each party shall bear its own costs and fees. This Court shall retain jurisdiction over the parties for the purpose of enforcing the terms of the Settlement Agreement.

Dated: New York, New York
December 14, 2015

For Plaintiffs:

ROPES & GRAY LLP

By: 

Joan McPhee
Prudential Tower
800 Boylston Street
Boston, MA 02199
Telephone: (617) 951-7535
joan.mcphee@ropesgray.com

Douglas H. Hallward-Driemeier
2099 Pennsylvania Avenue, NW
Washington, DC 20006
Telephone: (202) 508-4776
douglas.hallward-driemeier@ropesgray.com

For Defendants:

PREET BHARARA
United States Attorney
Southern District of New York

Caleb Hayes-Deats

By: CALEB HAYES-DEATS
Assistant United States Attorney
86 Chambers Street
New York, New York 10007
Tel.: (212) 637-2699
Fax: (212) 637-2686
caleb.hayes-deats@usdoj.gov

BENJAMIN C. MIZER
Principal Deputy Assistant Attorney General
Civil Division

WILLIAM B. SCHULTZ
General Counsel

JONATHAN F. OLIN
Deputy Assistant Attorney General

ELIZABETH H. DICKINSON
Associate General Counsel
Food and Drug Division

MICHAEL S. BLUME
Director
Consumer Protection Branch

ANNAMARIE KEMPIC
Deputy Chief Counsel for Litigation

ANDREW E. CLARK
Assistant Director

ANN M. OXENHAM
Associate Counsel
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel.: (301) 796-8710
ann.oxenham@fda.hhs.gov

MATTHEW J. LASH
Trial Attorney
Consumer Protection Branch
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044
Tel.: (202) 514-3764
matthew.j.lash@usdoj.gov

SO ORDERED:

Lewis A. Kaplan

Hon. Lewis A. Kaplan

Dated: December 15, 2015

enc

SETTLEMENT AGREEMENT AND GENERAL RELEASE

This Settlement Agreement and General Release (the “Settlement Agreement”) is made and entered into as of December 14, 2015 (the “Effective Date”), by and among Pacira Pharmaceuticals, Inc. (“Pacira”), Dr. Loren J. Harris (“Harris”), Dr. Joseph W. Bell (“Bell” and, together with Harris, the “Doctor Plaintiffs”), the United States Food and Drug Administration (“FDA”), the United States of America, Dr. Stephen Ostroff, in his official capacity as Acting Commissioner of Food and Drugs (“Ostroff”), the United States Department of Health and Human Services (“HHS”), and Sylvia Mathews Burwell (“Burwell”), in her official capacity as Secretary of the Department of Health and Human Services (each a “Party” and collectively, the “Parties”).¹

RECITALS

WHEREAS, Pacira, a corporation organized under the laws of the State of Delaware, represents that it is a specialty pharmaceutical manufacturer focused on the clinical and commercial development of non-opioid drug products that meet the needs of acute care practitioners and their patients, for use primarily in hospitals and ambulatory surgery centers;

WHEREAS, Pacira’s product EXPAREL (bupivacaine liposome injectable suspension) is a non-opioid local analgesic;

WHEREAS, FDA is a federal agency within HHS responsible for approving and otherwise regulating drugs, medical devices, and other products;

WHEREAS, FDA approved Pacira’s new drug application (“NDA”) for EXPAREL on October 28, 2011, for the following indication: “administration into the surgical site to produce postsurgical analgesia”;

¹ Collectively, FDA, the United States of America, Ostroff, HHS, and Burwell are referred to herein as the “United States.”

WHEREAS, Pacira marketed EXPAREL to physicians for administration into various surgical sites for postsurgical pain control, including by distributing “administration guides,” documents in which physicians described their experiences using EXPAREL;

WHEREAS, on September 22, 2014, FDA issued to Pacira, and at about the same time published on FDA’s website, a Warning Letter (the “Warning Letter”) objecting to Pacira’s materials promoting EXPAREL for surgeries other than bunionectomy and hemorrhoidectomy and to Pacira’s claims about EXPAREL’s ability to control pain for up to 72 hours;

WHEREAS, on September 8, 2015, Pacira and the Doctor Plaintiffs filed a complaint (the “Complaint”) against the United States in the United States District Court for the Southern District of New York captioned *Pacira Pharmaceuticals, Inc. v. FDA*, No. 15 Civ. 7055 (LAK), seeking declaratory and injunctive relief under the First Amendment, Fifth Amendment, and Administrative Procedure Act (the “Action”);

WHEREAS, FDA has conducted a comprehensive review of the Warning Letter issued to Pacira, as well as the approved labeling for EXPAREL and related materials;

WHEREAS, in light of FDA’s review, on October 13, 2015, FDA withdrew the Warning Letter issued to Pacira and removed it from the agency’s website;

WHEREAS, the Parties desire to settle and dismiss the Action;

NOW, THEREFORE, in consideration of the foregoing as well as the mutual covenants and considerations set forth herein, the sufficiency of which is hereby acknowledged, the Parties agree to the following terms and conditions:

I. Statement Regarding Withdrawal of the Warning Letter

1. Before or simultaneous with the execution of this agreement, FDA shall issue to Pacira a letter clarifying the reasons for the withdrawal of the Warning Letter.

II. Revisions to EXPAREL PI

2. Before or simultaneous with execution of this agreement, FDA shall issue a letter advising Pacira that it has approved Labeling Supplement 019 (S-019) to the EXPAREL NDA 22496, which Pacira submitted to FDA on November 17, 2015 (as amended by NDA Serial No. 0123, submitted November 25, 2015) (the “Labeling Supplement”) under 21 C.F.R. § 314.70(b)(2)(v)(A) & (C). The Prescribing Information (“PI”) that will be approved in the Labeling Supplement (the “Revised PI”), which is attached hereto as Exhibit 1, is intended to describe accurately the scope of the indication initially approved by FDA, which will avoid confusion by the FDA or any other entity about the scope of EXPAREL’s approval by FDA, and is further intended to provide additional information.

III. Confirmation of Scope of EXPAREL’s Indication

3. The United States confirms that EXPAREL has, since October 28, 2011, been approved for “administration into the surgical site to produce postsurgical analgesia” for use in a variety of surgeries not limited to those studied in its pivotal trials.

IV. Regulatory Environment

4. Consistent with the spirit of this Settlement Agreement, Pacira and FDA agree that, in future interactions, they will deal with each other in an open, forthright, and fair manner. This paragraph does not create any independent enforceable obligation.

V. Dismissal of the Action

5. Simultaneous with the execution of this Settlement Agreement, the Parties shall jointly execute the stipulation of dismissal with prejudice to which this Settlement Agreement is attached (the “Stipulation of Dismissal”). As stated in the Stipulation of Dismissal, the Parties agree that the dismissal shall have no effect on Pacira’s or the Doctor Plaintiffs’ ability to assert their constitutional rights (including under the First and Fifth Amendments) in connection with

or as a defense against any criminal, civil, or administrative investigation into or proceeding against Pacira or the Doctor Plaintiffs. No later than 7 days after the Effective Date, Pacira shall file the Stipulation of Dismissal with the Court in the Action.

VI. Mutual Release of Claims

6. Release by Pacira and Doctor Plaintiffs of Claims Against the United States.

Pacira, on behalf of itself and its past, present and future predecessors, successors, assigns, affiliates, subsidiaries, parents, members, managers, principals, owners, officers, directors, employees, agents and representatives, and the Doctor Plaintiffs hereby voluntarily, irrevocably, and forever release, waive, and discharge each and every defendant, its respective agencies, officers, employees, and agents, and all of their successors in interest, from any and all actions, causes of action, suits, charges, claims, demands, liabilities, damages, expenses, attorneys' fees, costs and all other liabilities of any kind or description whatsoever, whether in law or equity, direct or indirect, for relief or damages of every kind, character or description, now or hereafter recognized, that were asserted in the Action, provided, however, that neither this release, this Settlement Agreement, nor the Stipulation of Dismissal shall have any effect on Pacira's or the Doctor Plaintiffs' ability to assert their constitutional rights (including under the First and Fifth Amendments) in connection with or as a defense against any criminal, civil, or administrative investigation into or proceeding against Pacira or the Doctor Plaintiffs.

7. **Acknowledgment by the United States.** Consistent with paragraphs 1-3, the United States acknowledges that the rescission of the Warning Letter and approval of the Labeling Supplement reflect the scope of the indication in the NDA that FDA approved on October 28, 2011.

VII. Miscellaneous

8. Notices: All notices required under this Settlement Agreement shall be delivered or sent by e-mail and registered mail as follows:

To Pacira:

Pacira Pharmaceuticals, Inc.
Attn: Anthony Molloy
5 Sylvan Way, Suite 300
Parsippany, NJ 07054

with a copy to:

Joan McPhee
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199
joan.mcphee@ropesgray.com

To Harris:

Dr. Loren J. Harris
630 First Avenue
Apt. 12G
New York, NY 10016

with a copy to:

Joan McPhee
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199
joan.mcphee@ropesgray.com

To Bell:

Dr. Joseph W. Bell
4602 Jersey Hill Road
Amsterdam, NY 12010

with a copy to:

Joan McPhee
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199
joan.mcphee@ropesgray.com

To FDA:

Ann M. Oxenham
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
ann.oxenham@fda.hhs.gov

with a copy to:

Caleb Hayes-Deats
Assistant United States Attorney
86 Chambers Street, 3rd Floor
New York, NY 10007
caleb.hayes-deats@usdoj.gov

and a copy to:

Matt Lash
Trial Attorney
United States Department of Justice
Consumer Protection Branch
450 Fifth Street, NW, Suite 6400
Washington, DC 20001
matthew.j.lash@usdoj.gov

And to any additional or substitute recipients as any party may specify in writing sent to all notice recipients identified in this paragraph.

9. Entire Agreement: This Settlement Agreement, including its Exhibits, contains

the entire agreement of the Parties, and this Settlement Agreement supersedes and replaces all prior negotiations, proposed agreements and agreements, written or oral.

10. No Inducements or Representations: Except as set forth specifically in this Settlement Agreement, there have been no inducements or representations upon which any Party has relied in entering into this Settlement Agreement.

11. Authority to Bind: Each of the Parties warrants and represents that the person signing this Settlement Agreement on its behalf has the full power and authority to enter into this Settlement Agreement on its behalf.

12. Amendment or Modification: Subject only to the provision in paragraph 8 permitting the designation of additional or substitute notice recipients, this Settlement Agreement may be amended or modified only by a written instrument identified as such and signed by all Parties or their respective successors in interest.

13. Governing Law: The Parties specifically agree that this Settlement Agreement and any disputes arising out of the interpretation or performance of this Settlement Agreement shall be interpreted, enforced, and governed by the laws of the United States, and, to the extent that any state's law may apply, the State of New York, without giving effect to principles of conflicts of laws.

14. Consent to Jurisdiction: The United States District Court for the Southern District of New York shall retain jurisdiction to enforce this Settlement Agreement. Each Party waives the right to trial by jury in any action to enforce the terms and provisions of this Settlement Agreement.

15. No Construing Against Drafter: This Settlement Agreement shall be construed as if the Parties jointly prepared it and any uncertainty or ambiguity shall not be interpreted against

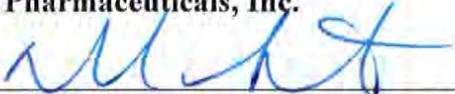
any one Party.

16. Execution in Counterparts: This Settlement Agreement may be executed in counterparts, which when taken together constitute a single agreement among the parties hereto.

17. No Admission: This Settlement Agreement neither may be construed as, nor may be used as, an admission of any fault, wrongdoing or liability whatsoever. Nothing contained in this Settlement Agreement is, or shall be deemed to be, an admission of the merit or validity of any asserted or unasserted claim against any Party, nor will this Settlement Agreement constitute or be construed as an admission of any wrongdoing whatsoever. This Settlement Agreement may not be offered as evidence in any proceeding except in a proceeding to enforce the terms of this Settlement Agreement.

IN WITNESS WHEREOF AND INTENDING TO BE LEGALLY BOUND HEREBY,
the Parties execute this Settlement Agreement.

Pacira Pharmaceuticals, Inc.

By: 
David Stack
Chief Executive Officer & Chairman

Date: December 14, 2015

Loren J. Harris, M.D.

By: _____
Loren J. Harris, M.D.

Date: _____

Joseph W. Bell, M.D.

By: _____
Joseph W. Bell, M.D.

Date: _____

For the United States:

PREET BHARARA
United States Attorney
Southern District of New York

Date: _____

By: _____
CALEB HAYES-DEATS
Assistant United States Attorney
86 Chambers Street
New York, New York 10007
Tel.: (212) 637-2699
Fax: (212) 637-2686
caleb.hayes-deats@usdoj.gov

(continued on next page)

IN WITNESS WHEREOF AND INTENDING TO BE LEGALLY BOUND HEREBY,

the Parties execute this Settlement Agreement.

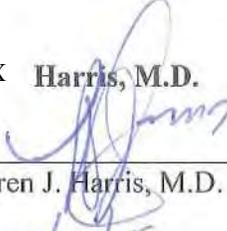
Pacira Pharmaceuticals, Inc.

By: _____

David Stack
Chief Executive Officer & Chairman

Date:

Loren X **Harris, M.D.**

By:  _____
Loren J. Harris, M.D.

Date: 12/11/15

Joseph W. Bell, M.D.

By: _____

Joseph W. Bell, M.D.

Date:

For the United States:

PREET BHARARA
United States Attorney
Southern District of New York

Date: _____

By: CALEB HAYES-DEATS
Assistant United States Attorney
86 Chambers Street
New York, New York 10007
Tel.: (212)637-2699
Fax: (212)637-2686
caleb.hayes-deats@usdoj .gov

{continued on next page}

IN WITNESS WHEREOF AND INTENDING TO BE LEGALLY BOUND HEREBY,
the Parties execute this Settlement Agreement.

Pacira Pharmaceuticals, Inc.

By: _____
David Stack
Chief Executive Officer & Chairman

Date: _____

Loren J. Harris, M.D.

By: _____
Loren J. Harris, M.D.

Date: _____

Joseph W. Bell, M.D.

By: _____
Joseph W. Bell, M.D.

Date: 12/10/15

For the United States:

PREET BHARARA
United States Attorney
Southern District of New York

Date: _____

By: _____
CALEB HAYES-DEATS
Assistant United States Attorney
86 Chambers Street
New York, New York 10007
Tel.: (212) 637-2699
Fax: (212) 637-2686
caleb.hayes-deats@usdoj.gov

(continued on next page)

IN WITNESS WHEREOF AND INTENDING TO BE LEGALLY BOUND HEREBY,
the Parties execute this Settlement Agreement.

Pacira Pharmaceuticals, Inc.

By: _____
David Stack
Chief Executive Officer & Chairman

Date: _____

Loren J. Harris, M.D.

By: _____
Loren J. Harris, M.D.

Date: _____

Joseph W. Bell, M.D.

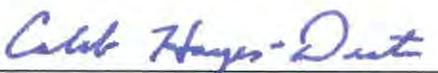
By: _____
Joseph W. Bell, M.D.

Date: _____

For the United States:

PREET BHARARA
United States Attorney
Southern District of New York

Date: Dec. 14, 2015


By: CALEB HAYES-DEATS
Assistant United States Attorney
86 Chambers Street
New York, New York 10007
Tel.: (212) 637-2699
Fax: (212) 637-2686
caleb.hayes-deats@usdoj.gov

(continued on next page)

BENJAMIN C. MIZER
Principal Deputy Assistant Attorney General
Civil Division

WILLIAM B. SCHULTZ
General Counsel

JONATHAN F. OLIN
Deputy Assistant Attorney General

ELIZABETH H. DICKINSON
Associate General Counsel
Food and Drug Division

MICHAEL S. BLUME
Director
Consumer Protection Branch

ANNAMARIE KEMPIC
Deputy Chief Counsel for Litigation

ANDREW E. CLARK
Assistant Director

ANN M. OXENHAM
Associate Counsel
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel.: (301) 796-8710
ann.oxenham@fda.hhs.gov

MATTHEW J. LASH
Trial Attorney
Consumer Protection Branch
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044
Tel.: (202) 514-3764
matthew.j.lash@usdoj.gov

EXHIBIT 1

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)	(12/2015)
Dosage and Administration (2)	(12/2015)
Dosage and Administration, Injection Instructions (2.1)	(12/2015)
Dosage and Administration, Compatibility Considerations (2.2)	(12/2015)
Warnings and Precautions, Warnings and Precautions Specific to EXPAREL (5.2)	(12/2015)

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 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
- Maximum dose of 266 mg (20 mL)

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

DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)
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 1-855-RX-EXPAREL (1-855-793-9727) 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.
- EXPAREL may be administered after at least 20 minutes or more have elapsed following local administration of lidocaine.
- Bupivacaine HCl, when injected immediately before or admixed with EXPAREL, may impact the pharmacokinetic and/or physicochemical properties of the drugs (7).

USE IN SPECIAL POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE**
- DOSAGE AND ADMINISTRATION**
 - Injection Instructions
 - Compatibility Considerations
 - Non-Interchangeability with Other Formulations of Bupivacaine
- DOSAGE FORMS AND STRENGTHS**
- CONTRAINDICATIONS**
- WARNINGS AND PRECAUTIONS**
 - Warnings and Precautions for Bupivacaine Containing Products
 - Warnings and Precautions Specific for EXPAREL
- ADVERSE REACTIONS**
 - Bupivacaine Adverse Reactions
 - Clinical Trial Experience
- DRUG INTERACTIONS**
- USE IN SPECIFIC POPULATIONS**
 - Pregnancy
 - Lactation
 - 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**
 - Study 1
 - Study 2
- 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 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 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
- Maximum dose of 266 mg (20 mL)

As general guidance in selecting the proper dosing for the planned surgical site, two examples of dosing are provided. One example of the recommended dose comes from a study in patients undergoing bunionectomy. A total of 8 mL (106 mg) was administered as 7 mL of EXPAREL infiltrated into the tissues surrounding the osteotomy, and 1 mL infiltrated into the subcutaneous tissue.

Another example comes from a study of patients undergoing hemorrhoidectomy. A total of 20 mL (266 mg) 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.

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 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.
- 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).
- EXPAREL can be administered 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.

- 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.
- Do not administer EXPAREL if the product is discolored.
- 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.

2.2 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 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 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.

3. DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)

- 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. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL [*See Dosage and Administration (2.2) 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
- 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

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 Bupivacaine Adverse Reactions

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 overdosage, 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 Clinical Trial Experience

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

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 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 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%: 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)

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 (%)
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.

7. DRUG INTERACTIONS

EXPAREL can be administered in the ready to use suspension or diluted to a concentration of up to 0.89 mg/mL (i.e., 1:14 dilution by volume) with normal (0.9%) saline or lactated Ringer's solution. 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 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.

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 toxicity [*See Dosage and Administration (2.2), Warnings and Precautions (5.1) and Overdosage (10)*].

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

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 buprenorphine 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, pipercolylxylylidide, 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 surgical site 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)*].

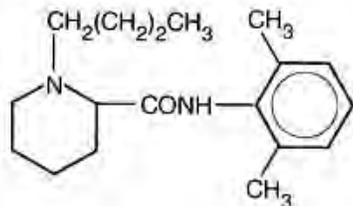
In the clinical study program, maximum plasma concentration (C_{max}) values of approximately 34,000 ng/mL were reported and likely reflected inadvertent intravascular administration of EXPAREL or systemic absorption of EXPAREL at the surgical site. The plasma bupivacaine measurements did not discern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



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

	Surgical Site Administration	
	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 (0.5-24)	0.5 (0.25-36)
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 (17)	24 (39)

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.

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

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

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.

14.1 Study 1

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial 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 ($p < 0.001$).

14.2 Study 2

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial 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).

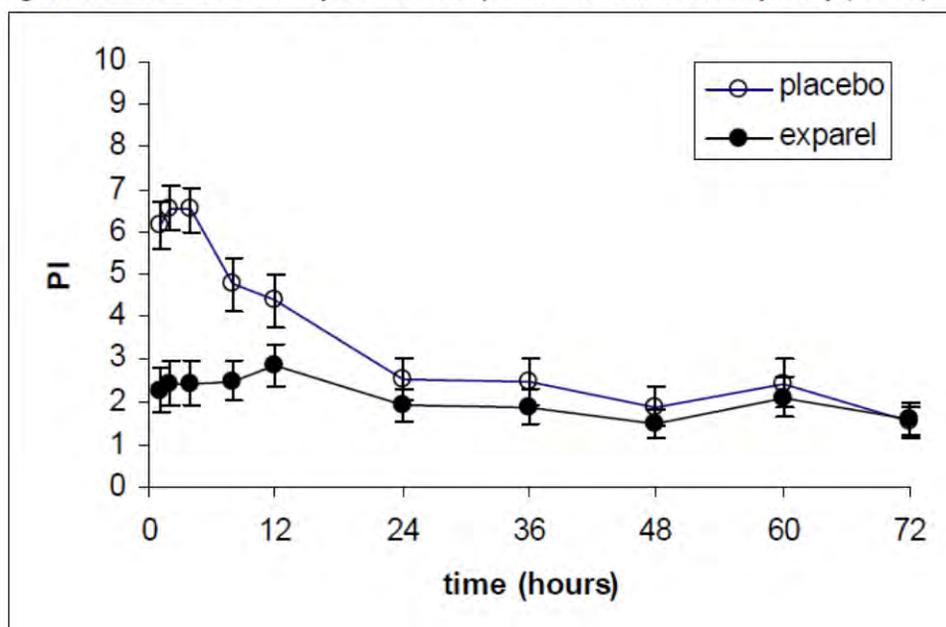
Study medication was administered directly into the site (greater than or equal to 3 cm) at the conclusion of the surgery. Dilution of 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, was divided into six 5 mL aliquots. A field block was performed by visualizing the anal sphincter as a clock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



This resulted in a decrease in opioid consumption, the clinical benefit of which was not demonstrated.

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.

The median time to rescue analgesic use was for 15 hours for patients treated with EXPAREL and one hour for patients treated with placebo.

16. HOW SUPPLIED/STORAGE AND HANDLING

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

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

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 30 days in sealed, intact (unopened) vials. Vials should not be re-refrigerated.

EXPAREL should not be frozen 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 or exposed to high temperatures. Do not use the vial if the stopper is bulging.

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.
- 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.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

6,132,766

5,766,627

5,891,467

8,182,835

Trademark of Pacira Pharmaceuticals, Inc.



For additional information call 1-855-RX-EXPAREL (1-855-793-9727)