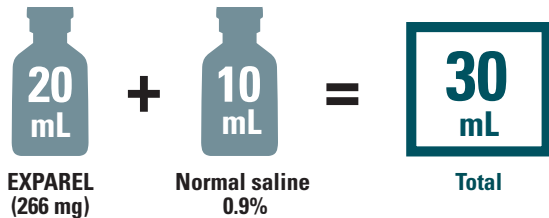


EXPAREL for hemorrhoidectomy:

Infiltration technique and clinical efficacy results

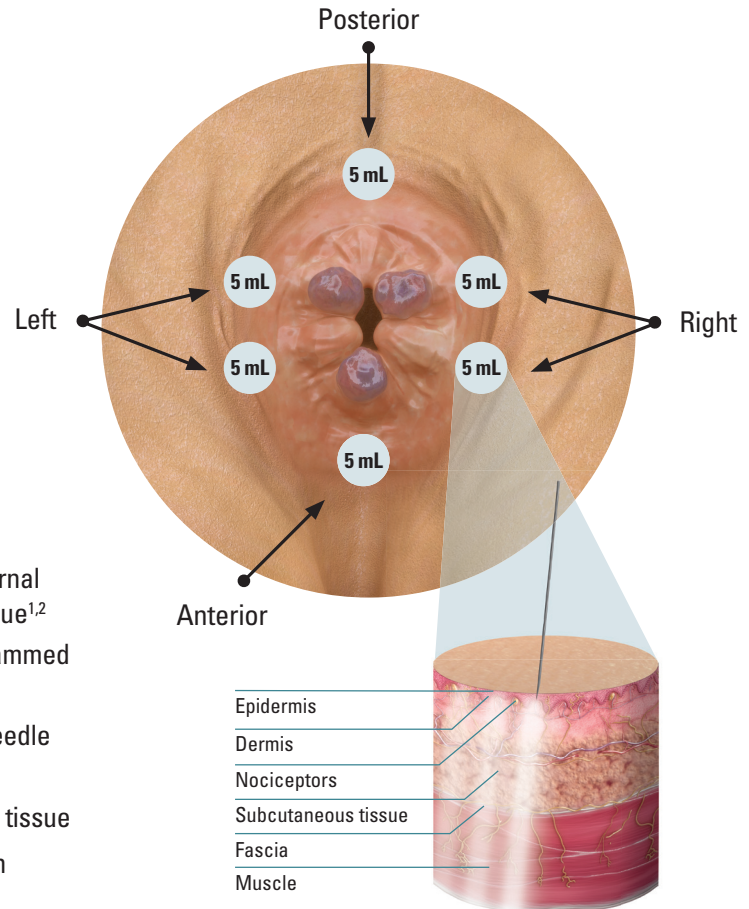
Dose of EXPAREL and total volume used



- EXPAREL was administered at the conclusion of surgery as part of a standard field block with local anesthesia
- Bupivacaine HCl can be admixed with EXPAREL in a 1:2 ratio to provide early onset analgesic coverage
- Avoid non-bupivacaine local anesthetics within 20 minutes of administration of EXPAREL

Infiltration technique protocol

- Surgery was a 2- or 3-column excisional hemorrhoidectomy for internal or internal/external hemorrhoids using the Milligan-Morgan technique^{1,2}
- A field block was created by visualizing the anal sphincter as diagrammed and 5 mL was infiltrated at each infiltration point as indicated below
 - Injected slowly and deeply into the soft tissues using a moving needle technique (ie, injecting while withdrawing the needle)¹
 - Infiltrated above and below the fascia and into the subcutaneous tissue
 - Aspirated frequently to minimize the risk of intravascular injection



Clinical efficacy results^{1,3*}

Significantly lower
OPIOID USE*

45% lower overall opioid consumption

$P=0.0006^{\dagger}$

Significantly better
PAIN CONTROL

30% lower cumulative pain scores

$P<0.0001^{\dagger}$

Results from a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial that evaluated the safety and efficacy of 266 mg (20 mL) EXPAREL in 186 patients undergoing 2- or 3-column excisional hemorrhoidectomy. Primary end point: cumulative pain score reflected in area under the curve of numeric rating scale through 72 hours. Placebo was preservative-free saline for injection. Opioid rescue medication (up to 10 mg morphine administered intramuscularly) was available to all patients.^{1,3}

*The clinical benefit of the decrease in opioid consumption was not demonstrated in the pivotal trials.

[†]Through 72 hours. Opioid reduction was calculated based on geometric mean ratio.³

- 28% of EXPAREL patients were opioid free ($P<0.0008$)

Non-opioid EXPAREL provides significant long-lasting pain control *while* reducing opioid use^{1,3*}

- Approved for use across surgical procedures in various surgical settings
- Critical component of a multimodal, opioid-minimizing pain management strategy⁴
- The infiltration indication includes regional field or interfascial plane blocks such as, but not limited to, Transversus Abdominis Plane (TAP) block, Pectoralis (PEC) and Serratus plane blocks, Erector Spinae Plane (ESP) block, Thoraco-Lumbar Interspinal Plane (TLIP) block, interspace between the Popliteal Artery and Capsule of the Posterior Knee (iPACK), and Quadratus Lumborum (QL) block

Please see Important Safety Information on reverse and refer to accompanying full Prescribing Information, which is also available at www.EXPAREL.com.

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

Regional Analgesia via Interscalene Brachial Plexus Nerve Block

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

2.3 Injection Instructions

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

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

2.4 Compatibility Considerations

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

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately

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

Storage

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

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

Handling

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

17 PATIENT COUNSELING INFORMATION

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

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.