Frequently asked questions
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**What is EXPAREL?**

EXPAREL is an FDA-approved, long-lasting, non-opioid analgesic that, as part of a multimodal approach to pain management, provides effective postsurgical pain relief and helps reduce the need for opioids after surgery. EXPAREL is indicated for administration into the surgical site to produce postsurgical analgesia. EXPAREL works locally at the surgical site and uses the DepoFoam® drug delivery technology, which encapsulates bupivacaine in multivesicular liposomes. Following injection, DepoFoam particles gradually release bupivacaine over time as the lipid membranes are absorbed, prolonging the duration of action of bupivacaine. More than two million patients have been treated with EXPAREL since 2012. EXPAREL is not indicated for nerve block.

EXPAREL was studied in 2 pivotal trials—hard and soft tissue. In the clinical trial of patients undergoing a soft tissue surgery, EXPAREL demonstrated significant long-lasting pain control. EXPAREL met its primary endpoint: cumulative pain score reflected in area under the curve (AUC) of numeric rating scale (NRS) through 72 hours, showing a 30% reduction in cumulative pain scores versus placebo ($P<0.0001$). EXPAREL also showed a significant decrease in opioid consumption, with a 45% reduction in overall opioid consumption* versus placebo through 72 hours ($P≤0.0006$). Twenty-eight percent of patients in the EXPAREL group did not require any rescue medication throughout the 72-hour study period vs 10% of patients in the placebo group ($P<0.0008$), and there was a significant 14-hour difference in median time to first opioid rescue between treatment groups. *Opioid reduction calculated based on geometric mean ratio in the clinical trials; $P≤0.0006$.

**Has EXPAREL been studied in oral surgery?**

The safety, efficacy and pharmacokinetics of EXPAREL were evaluated in the INfiltratioN Trial In Third MOlar Extraction ObserVing The Analgesic EffecT of EXPAREL (INNOVATE) trial—a randomized, double-blind, placebo-controlled study of local administration of EXPAREL for prolonged postsurgical analgesia in patients undergoing bilateral third molar extraction. EXPAREL was shown to be safe in the safety population (EXPAREL, n=105, placebo, n=57).
What was the study design in the INNOVATE trial?

The study design was a randomized, double-blind, placebo-controlled study. Overall, it included 166 patients (EXPAREL, n=107; placebo, n=59) who were scheduled to undergo elective bilateral third molar extraction under local anesthesia with ≥1 mandibular third molar fully or partially bony impacted, as confirmed by visual or radiographic evidence.4

- Subjects were randomized in a 4:3 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL).4
- Randomized subjects received a nerve block with 2% lidocaine with epinephrine 1:100,000 prior to third molar extraction under local anesthesia.4
- At the end of surgery, EXPAREL or placebo was infiltrated as follows.4
  - A total of 4 mL into the maxilla
  - A total of 6 mL into the mandible
- The numeric rating scale pain intensity assessment was conducted at the following time points after surgery: 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours.4 Patients remained in an inpatient setting for 5 days.
- Times and amounts of opioids required for rescue were recorded throughout the study period through 96 hours.4

Primary endpoint

- Cumulative pain scores vs placebo through 48 hours. Measured by area under the curve (AUC) of numeric rating scale (NRS) pain intensity scores through 48 hours4

Secondary and tertiary endpoints

- AUC of NRS pain intensity scores through 24, 72, and 96 hours4
- Percentage of opioid-free subjects through 24, 48, and 72 hours4
- Total postsurgical opioid consumption through 48 hours4

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What was the size of the INNOVATE trial?

- **Total Patients Randomized**
  - N=166
  - EXPAREL (n=107) Placebo (n=59)

- **Safety Population**
  - N=162
  - EXPAREL (n=105) Placebo (n=57)

- **ITT Population**
  - N=150
  - EXPAREL (n=99) Placebo (n=51)

- **Per-protocol Population**
  - N=89
  - EXPAREL (n=59) Placebo (n=30)

Exclusion:

- 4 patients not treated
- 12 patients did not have baseline NRS collected
- 61 patients who had deviations from protocol
What were the INNOVATE trial results?

- EXPAREL did not meet the primary endpoint cumulative pain score reflected in AUC of NRS through 48 hours in the Intent to Treat (ITT) population (Fig. 1) due to protocol deviations.
  - Therefore, a post hoc per-protocol analysis was conducted (EXPAREL, n=59; placebo, n=30) (Fig. 2).

Fig. 1 ITT results

- No significant reduction in cumulative pain score reflected in AUC of NRS through 48 hours
- No significant difference in mean pain scores (AUC of NRS) at any time points through 96 hours

Fig. 2 Per-protocol results

- A statistically significant reduction in mean AUC of NRS pain scores at 48 hours (EXPAREL=120.8; placebo=183.3, \(P<0.05\))
- Mean AUC of NRS pain scores was significantly lower at all time points through 96 hours for patients who received EXPAREL
- Overall mean opioid consumption was numerically lower for patients who received EXPAREL
Are the INNOVATE trial results consistent with the results seen with EXPAREL in other surgeries?

The efficacy results for oral surgery are consistent with those seen in two multicenter, randomized, double-blind clinical trials of EXPAREL vs placebo. (One trial was conducted in patients undergoing bunionectomy; the other trial was in patients undergoing hemorrhoidectomy.) More information on the pivotal trial results is available at: http://exparel.com/hcp/about-EXPAREL/efficacy.shtml.

EXPAREL has a broad indication for infiltration into the surgical site to produce postsurgical analgesia. EXPAREL is NOT indicated for nerve block.

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What are the safety results for EXPAREL in the INNOVATE trial and overall?

In the INNOVATE trial (EXPAREL, n=105; placebo, n=57), adverse events that occurred in ≥5% of patients were* oral hypoesthesia, dysgeusia, nausea, vomiting, involuntary muscle contractions, dizziness, headache, postprocedural edema, and muscle twitching.

No difference was seen in the incidence or duration of facial numbness and tingling between groups (beyond typical numbness associated with the lidocaine nerve block administered to all patients). There was no difference in incidence of dry socket between groups. EXPAREL had an established safety profile prior to being evaluated in oral surgery. Safety was evaluated in 10 randomized, double-blind clinical studies involving 823 patients undergoing various surgical procedures.

EXPAREL is indicated for administration into the surgical site to produce postsurgical analgesia.

*all subjects received a lidocaine nerve block per study design

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Which oral surgery procedures are appropriate for EXPAREL?

The efficacy of EXPAREL was compared with placebo in two multicenter, randomized, double-blind clinical trials. One trial evaluated the treatment in patients undergoing bunionectomy; the other trial evaluated the treatment in patients undergoing hemorrhoidectomy. In December 2015 the FDA confirmed that EXPAREL has a broad indication for infiltration into the surgical site to produce postsurgical analgesia. The indication encompasses use for postoperative analgesia when administered as local infiltration at the site of oral surgery procedures, including tooth extraction. The indication also includes use as a local anesthetic deposited near a terminal branch of the maxillary or mandibular branch of the trigeminal nerve (periapical injections). EXPAREL is NOT indicated for nerve block.

For more information on the reaffirmation of the broad indication for EXPAREL by the FDA, learn more at PACIRA.com.

How is EXPAREL administered?

EXPAREL should be injected with a 25-gauge or larger-bore needle. It is best administered using a series of injections to effectively cover the surgical area since it does not diffuse throughout tissues in the same manner as traditional bupivacaine.

EXPAREL stays more precisely where placed, requiring more injections to cover the same area.

See Administering EXPAREL and third molar images in EXPAREL in Oral Surgery for more details on administration and injection into the maxilla and mandible.

Can I split a vial of EXPAREL?

EXPAREL is intended for single-dose administration only and is available in single-use vials for infiltration. A vial of EXPAREL should not be used with more than one patient.
Can I use bupivacaine with EXPAREL?

Bupivacaine HCl may be administered immediately before EXPAREL or admixed in the same syringe, as long as the ratio of the milligram dose of bupivacaine HCl to EXPAREL does not exceed 1:2. See Administering EXPAREL for more information.

How much bupivacaine enters the bloodstream after infiltration?

EXPAREL contains a small amount of extra-liposomal bupivacaine (about 3%), with 150 ng/mL available in the plasma serum soon after administration. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.
FAQs

Are there potential concerns with toxicity when administering EXPAREL with bupivacaine HCl?

Please note that the rate of systemic absorption of bupivacaine is dependent on total dose, the route of administration, and the vascularity of the administration site. Also, the toxic effects of these drugs are additive and their administration should be used with caution, including monitoring for neurological and cardiovascular effects related to toxicity. Please see the full Prescribing Information for more details.

Is EXPAREL available in a cartridge?

No. EXPAREL is only available in 10 mL and 20 mL single-use vials.

How much volume is appropriate?

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)

Volume may be expanded to accommodate larger surgical sites. A 20 mL vial of EXPAREL can be administered undiluted or expanded up to a total of 300 mL with normal (0.9%) saline or lactated Ringer's solution.

Proper injection technique of EXPAREL is critical to ensure optimal delivery of EXPAREL for your patients.

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 is best administered using a series of injections in the tissue to effectively cover the surgical area because it does not diffuse throughout tissues in the same manner as traditional bupivacaine.
FAQs

How is EXPAREL paid for?

It is important to inform patients that EXPAREL may not be covered by insurance or coverage may be limited. Some surgeons have had success using the dental codes D9610 (therapeutic parenteral drug [antibiotics, steroids, anti-inflammatory drugs]) and D9612 (therapeutic parenteral drugs, two or more administrations, different medications), although actual coverage will vary based on each individual’s insurance plan.

View the video Discussing EXPAREL with Patients – Value vs Cost for more information.

Where are infiltration points?

In the INNOVATE study, infiltration of 10 mL of EXPAREL followed a lidocaine nerve block and was infiltrated at points illustrated below:

**Maxilla Infiltration Points**
4 mL of EXPAREL on the buccal side
(2 mL right, 2 mL left)

**Mandible Infiltration Points**
6 mL of EXPAREL
(3 mL right, 3 mL left)
EXPAREL is indicated for administration into the surgical site to produce postsurgical analgesia.

Important Safety Information

EXPAREL is contraindicated in obstetrical paracervical block anesthesia.

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

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. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL.

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.

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.

In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting.

Please see the full Prescribing Information.

References


