NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

OMFS FAQ

FREQUENTLY ASKED QUESTIONS

Find information on the efficacy and safety of EXPAREL, including results from the Infiltration Trial in Third Molar Extraction Observing the Analgesic Effect of EXPAREL (INNOVATE) trial in oral surgery, as well as guidance on administration.

- What is EXPAREL?
- Can EXPAREL be used with pediatric patients?
- Has EXPAREL been studied in clinical trials?
- Has EXPAREL been studied in oral surgery?
- Which oral surgery procedures are appropriate for EXPAREL?
- What are the general guidelines on infiltration technique with EXPAREL?
- Where is EXPAREL infiltrated?
- Can I split a vial of EXPAREL?
- Can I use lidocaine with EXPAREL?
- Can I use bupivacaine HCl with EXPAREL?
- How much bupivacaine is released over time?
- Are there potential concerns with toxicity when administering EXPAREL with bupivacaine HCl?
- Is EXPAREL available in cartridge form?
- Can I expand EXPAREL with normal saline or lactated Ringer's solution to achieve greater volume and analgesic coverage?
- How is dosing for EXPAREL calculated?
- Is EXPAREL reimbursed?

Please refer to Important Safety Information on page 8. For more information, please visit www.EXPAREL.com or call 1-855-793-9727.

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What is EXPAREL?

EXPAREL is a long-acting non-opioid local analgesic for postsurgical pain management. EXPAREL utilizes the proprietary DepoFoam® drug delivery technology to consistently deliver safe levels of bupivacaine, which is encapsulated in multivesicular liposomes to extend the duration of analgesia.[1,2]

More than 8 million adult patients have received EXPAREL since 2012.[3]

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Can EXPAREL be used with pediatric patients?

EXPAREL is the first and only FDA-approved long-acting local analgesic for ages 6 and above.[4]

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Has EXPAREL been studied in clinical trials?

In multiple clinical trials, EXPAREL demonstrated significant, long-lasting pain control while reducing opioid use.*

Study 1: A phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study comparing EXPAREL vs placebo for the management of postsurgical pain following bunionectomy.[5]

14.7% reduction in average pain scores (P=0.0005)

19.1% reduction in overall opioid consumption (P=0.0077)

- Significant delay to first opioid rescue (7.2 vs 4.3 hours; P<0.0001)

Study 2: A phase 3, multicenter, parallel-group, randomized, double-blind study comparing EXPAREL vs placebo for postsurgical pain relief in patients undergoing hemorrhoidectomy.[2]

30% reduction in cumulative pain scores (P<0.0001)

45.7% reduction in overall opioid consumption (P≤0.0006)

- Significantly fewer patients required rescue medication (28% vs 10%; P<0.0008)
- A significant 13-hour difference in median time to first opioid rescue between treatment groups

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

Continue to see more studies

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Has EXPAREL been studied in clinical trials? (cont'd)

Study 3: A phase 3, multicenter, randomized, double-blind study comparing EXPAREL vs placebo for brachial plexus nerve block following total shoulder arthroplasty (TSA) or rotator cuff repair (RCR).[6]

Significant reduction in mean AUC and VAS pain intensity (*P*<0.0001)

78% reduction in postsurgical opioid consumption (*P*<0.0001)

- More opioid-free patients (9 patients vs 1 patient; *P*=0.008)
- Significant increase to time of first opioid rescue (4.2 hours vs 0.6 hours; *P*<0.0001)

Phase 4 clinical study—PILLAR: A parallel-group, randomized, double-blind, active-controlled study comparing local infiltration analgesia (LIA) with EXPAREL vs LIA with bupivacaine HCl in patients undergoing total knee arthroplasty (TKA).[7]

14% reduction in mean AUC and VAS pain intensity (180.8 vs 209.3; *P*=0.0381)

78% reduction in postsurgical opioid consumption (18.7 mg vs 84.9 mg; *P*=0.0048)

- Time to first opioid rescue ranged from 0.25 to 48 hours with EXPAREL vs 0.27 to 33 hours without EXPAREL
  - Time to rescue of 50% of patients was 4.1 and 2.9 hours, respectively, with a significant difference between the survival curves (*P*=0.0230)

EXPAREL significantly increased the proportion of opioid-free patients and significantly delayed time to first opioid rescue compared with placebo. The percentage of opioid-free patients through 48 and 72 hours (or discharge) was significantly greater (*P*<0.01) with EXPAREL compared with placebo.[7]

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Has EXPAREL been studied in oral surgery?

Phase 3 clinical study—INNOVATE: The safety, efficacy, and pharmacokinetics of EXPAREL were evaluated in a multicenter, Phase 3, 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).[8]

Significant reduction in mean AUC of NRS through 48 hours in the per-protocol analysis population (120.8 vs 183.3, *P*=0.023)

Significant reduction in cumulative pain scores at 24, 72, and 96 hours after surgery in the per-protocol analysis population (*P*<0.05)

Retrospective study: A retrospective cross-sectional study of 600 patients undergoing third-molar extraction (≥1 partial bony or full bony impacted mandibular third molar) and receiving EXPAREL 133 mg (n=300) were prescribed significantly fewer opioids than patients who did not (n=300), with a lower opioid prescription refill rate.[9]

59% fewer prescribed MMEs than the non-EXPAREL group (47.1 MME vs 113.8 MME, *P*<0.0001)

Significantly lower opioid prescription refill rate (3.3% vs 7.7%, *P*=0.028)

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Which oral surgery procedures are appropriate for EXPAREL?

EXPAREL is indicated for single-dose infiltration in patients aged 6 years and older to produce postsurgical local analgesia and in adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

The indication encompasses use for postsurgical 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 also indicated as an interscalene brachial plexus nerve block in adults to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

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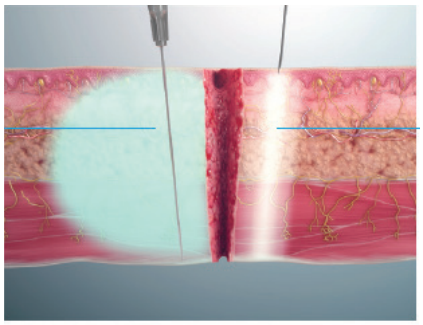
What are the general guidelines on infiltration technique with EXPAREL?



Note: Graphic is for illustrative purposes only.

EXPAREL should be injected slowly with frequent aspiration to check for blood and minimize the risk of inadvertent intravascular injection.

For tissue infiltration using EXPAREL, utilize a deep tissue and moving needle technique to distribute the liposomes across the entire surgical site.

Administer EXPAREL with a 25-gauge or larger-bore needle to maintain the structural integrity of the liposomes. Since EXPAREL stays precisely where placed, inject frequently, 1 to 2 mL per injection, in small areas roughly 1 to 1.5 cm apart.

For more details on administration and injection into the maxilla and mandible, see this case report in which EXPAREL was used in a third-molar extraction.

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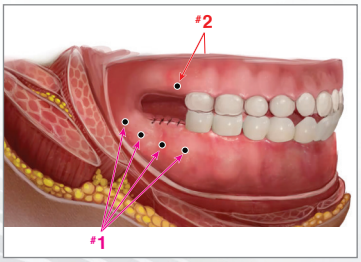
Where is EXPAREL infiltrated?

Infiltrate EXPAREL into the buccal aspect and into the palatal aspect[8]:

1. Lateral aspect of the mandible bilaterally

2. The buccal aspect of the upper third molars bilaterally



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Can I split a vial of EXPAREL?

EXPAREL is indicated for single-dose administration only.

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Can I use lidocaine with EXPAREL?

If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine.

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Can I use bupivacaine HCl with EXPAREL?

For early analgesic onset, bupivacaine HCl can be administered immediately before EXPAREL or admixed as part of the total expanded volume.*

The ratio of milligram dose of bupivacaine HCl solution to EXPAREL should not exceed 1:2.

Admixing may affect the PK and pharmacodynamic properties of EXPAREL and this effect is concentration dependent.

Do not admix EXPAREL with any other local anesthetic because it may affect the release of bupivacaine from the DepoFoam.

*Bupivacaine HCl is approved for use in ages 12 and over.[10]

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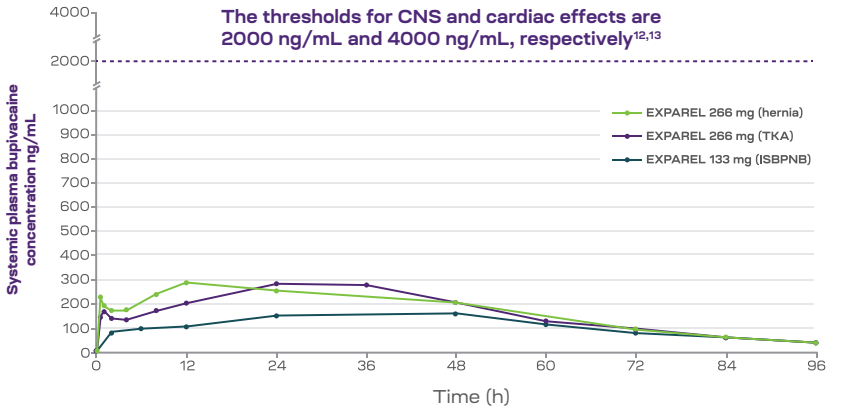
How much bupivacaine is released over time?

DepoFoam technology provides reliable slow release of bupivacaine over 96 hours.[6,11] At both maximum doses of EXPAREL (266 mg for infiltration and 133 mg for interscalene brachial plexus nerve block), the plasma levels of bupivacaine remain below toxicity thresholds[6,11-13]

- Central nervous system symptoms occur at a plasma concentration of ≈2000 ng/mL with bupivacaine HCl[12]
- Cardiac toxicity is associated with blood levels of ≥4000 ng/mL[13]
- Pharmacokinetics demonstrate plasma levels of bupivacaine that can persist for 96 hours[14,15]



CNS=central nervous system; TKA=total knee arthroplasty; ISBPNB=interscalene brachial plexus nerve block.

- At all doses studied, plasma bupivacaine levels are maintained well below toxic thresholds[6,11-15]
- 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
- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL
- Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy

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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 neurologic and cardiovascular effects related to local anesthetic systemic toxicity (LAST). Please see the full Prescribing Information for more details.

*EXPAREL is the first and only FDA-approved long-acting local analgesic for ages 6 and above. Bupivacaine HCl is approved for use in ages 12 and over.[4,10]

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Is EXPAREL available in cartridge form?

No. EXPAREL is available in 133 mg (10 mL) and 266 mg (20 mL) single-dose vials.

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Can I expand EXPAREL with normal saline or lactated Ringer's solution to achieve greater volume and analgesic coverage?

Volume may be expanded to accommodate larger surgical sites. EXPAREL can be administered unexpanded or expanded with normal (0.9%) saline or lactated Ringer's solution, but it cannot exceed a 1:14 ratio of EXPAREL (0.89 mg/mL concentration).

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How is dosing for EXPAREL calculated?

The recommended dose of EXPAREL for infiltration and field blocks in adults 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) for infiltration and fascial plane blocks
- Maximum dose of 133 mg (10 mL) for interscalene brachial plexus nerve blocks – for use in adults only

The recommended dose for pediatric patients is 4 mg/kg, based on body weight, and not to exceed 266 mg (20 mL).

For more information about pediatric dosing, please visit our pediatrics page.

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Is EXPAREL reimbursed?

EXPAREL is covered by many insurance plans. Exact reimbursement and coverage can only be determined by the patient's insurance carrier.

Beginning January 1, 2019, D9613 became an active code:

- Infiltration of a sustained-release therapeutic drug – single or multiple sites
- Infiltration of a sustained-release pharmacologic agent for long-acting surgical site pain control (not for local anesthesia purposes)

For more details on reimbursement, visit our reimbursement page.

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To learn more about resources such as procedure videos, case reports, and the practice marketing toolkit, visit the OMFS page on EXPAREL.com.

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Indication

EXPAREL® (bupivacaine liposome injectable suspension) is indicated for single-dose infiltration in patients aged 6 years and older to produce postsurgical local analgesia and in adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

Important Safety Information

EXPAREL is contraindicated in obstetrical paracervical block anesthesia.

Adverse reactions reported in adults with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported in adults with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation.

Adverse reactions with an incidence greater than or equal to 10% following EXPAREL administration via infiltration in pediatric patients six to less than 17 years of age were nausea, vomiting, constipation, hypotension, anemia, muscle twitching, vision blurred, pruritis, and tachycardia.

If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine.

EXPAREL is not recommended to be used in the following patient populations: patients <6 years old for infiltration, patients younger than 18 years old for interscalene brachial plexus nerve block, and/or pregnant patients.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.

Warnings and Precautions Specific to EXPAREL

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks **other than interscalene brachial plexus nerve block**, or intravascular or intra-articular use.

The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.

Warnings and Precautions for Bupivacaine-Containing Products

Central Nervous System (CNS) Reactions: There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression.

Cardiovascular System Reactions: Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to dysrhythmias, sometimes leading to death.

Allergic Reactions: Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients.

Chondrolysis: There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use.

Methemoglobinemia: Cases of methemoglobinemia have been reported with local anesthetic use.

Full Prescribing Information is available at www.EXPAREL.com.

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