NON-OPIOID

EXPAREL®

(bupivacaine liposome injectable suspension)

APPROVED FOR POSTSURGICAL PAIN MANAGEMENT IN PEDIATRICS

THE FIRST AND ONLY FDA-APPROVED LONG-ACTING LOCAL ANALGESIC FOR AGES 6 AND ABOVE[1]

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.

Demonstrated in PLAY, a clinical trial centered uniquely on safety in children[2]

Pediatric patients in the EXPAREL study were defined as 6 to <17 years of age.

Please see Important Safety Information throughout and refer to the full Prescribing Information, which is available at www.EXPAREL.com.

THE RISKS AND COMPLICATIONS OF ADULT-BASED PAIN MANAGEMENT APPROACHES MAY BE MAGNIFIED IN CHILDREN[3,4]

Opioids, short-acting local anesthetics, and delivery devices are the mainstay despite safety implications and limited studies in children[3]

Even so...

50%

of children report moderate to severe pain in the hospital after surgery[5]

~20%

of children experience chronic pain 12 months after surgery[5]

Opioids can be **attributed to 50% of postsurgical respiratory failure events** in children **and may also hinder recovery, extend hospital stay, and negatively impact both patient and parent experience.**[4,6,7]

Potential side effects and complications with current modalities

Opioids[3]	Device-based platforms (ie, pumps and catheters)
Nausea/vomiting	Accidental removal[8]
Constipation	Overdose[9]
Urinary retention	Leakage[10]
Cognitive impairment	Infection[11]
Dependence	Unpredictability or malfunction[8-10]

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.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

MEDICAL SOCIETIES RECOMMEND NON-OPIOID ANALGESICS AND A MULTIMODAL APPROACH TO PAIN MANAGEMENT FOR PEDIATRIC PATIENTS[12]

American Society of Anesthesiologists™

American Society of Anesthesiologists Task Force on Acute Pain Management[13]: *"Analgesic therapy [for pediatric patients] should depend upon age, weight, and comorbidity, and unless contraindicated should involve a multimodal approach."*

Society for Pediatric Anesthesia
education • research • patient safety

Guidelines from the Society for Pediatric Anesthesia[14]:
"...clinicians should use all methods possible to minimize the use of opioids... Use of nonopioid analgesia is encouraged including regional analgesia techniques..."

JAMA®

Expert panel* guidelines that include the American College of Surgeons Education Committee[15]:
"...health care professionals caring for children who require surgery must recognize the risks of opioid misuse associated with prescription opioids, [and] nonopioid analgesic use should be optimized in the perioperative period..."

ERAS protocols enable rapid recovery after surgery, improve clinical and economic outcomes, and remove the risks associated with opioids[16]

ERAS protocols are patient-centered, evidence-based multimodal pathways for perioperative care that include regional analgesia to help accelerate recovery and reduce[12,16,17]:

- Pain scores
- Opioid consumption
- Postsurgical nausea and vomiting
- Respiratory complications

Important Safety Information (continued)

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, pruritus, 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.

*This guideline was developed by the American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee, in addition to a geographically diverse multidisciplinary team composed of leaders in pediatric opioid stewardship from academic and community hospitals and representatives from the American College of Surgeons (ACS) Education Committee, the American Academy of Pediatrics Section on Surgery, pediatric anesthesia, pediatric nursing, general surgery residency, pediatric surgery physician assistants, and addiction science.[15]

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

EXPAREL IS A LONG-LASTING ANALGESIC PROVEN TO MANAGE POSTSURGICAL PAIN AND REDUCE OPIOID USE

EXPAREL delivers long-acting pain control and offers versatility of administration without the use of pumps or catheters

Surgical site infiltration (for local analgesia)

To produce local analgesia across surgical procedures.

Fascial plane infiltration (for regional analgesia)

To produce regional analgesia using regional techniques such as TAP, ESP, and QL.

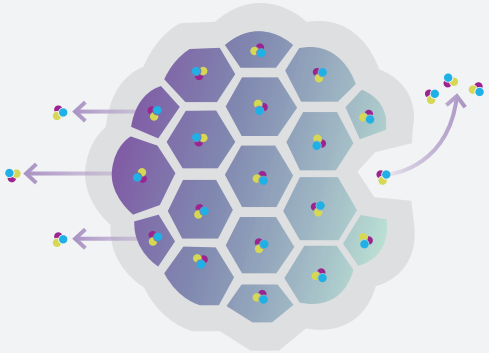
EXPAREL uses DepoFoam®, an innovative drug delivery technology, to extend analgesia[18]

COMPOSED
of naturally occurring biodegradable and biocompatible lipids[19-21]

ENCAPSULATES
bupivacaine in a multivesicular liposomal drug delivery technology

RELEASES
bupivacaine over time as lipid membranes reorganize[18]

UTILIZES
membrane components that are cleared by normal metabolic pathways[19-21]



DELIVERS
targeted local analgesia at the surgical site

DESIGNED
to consistently deliver safe levels of bupivacaine to extend analgesic duration[22]

ELIMINATES
the need for catheters and pumps that may hinder recovery

PROVIDES
long-lasting pain control while reducing the need for opioids[23]

Important Safety Information (continued)

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.

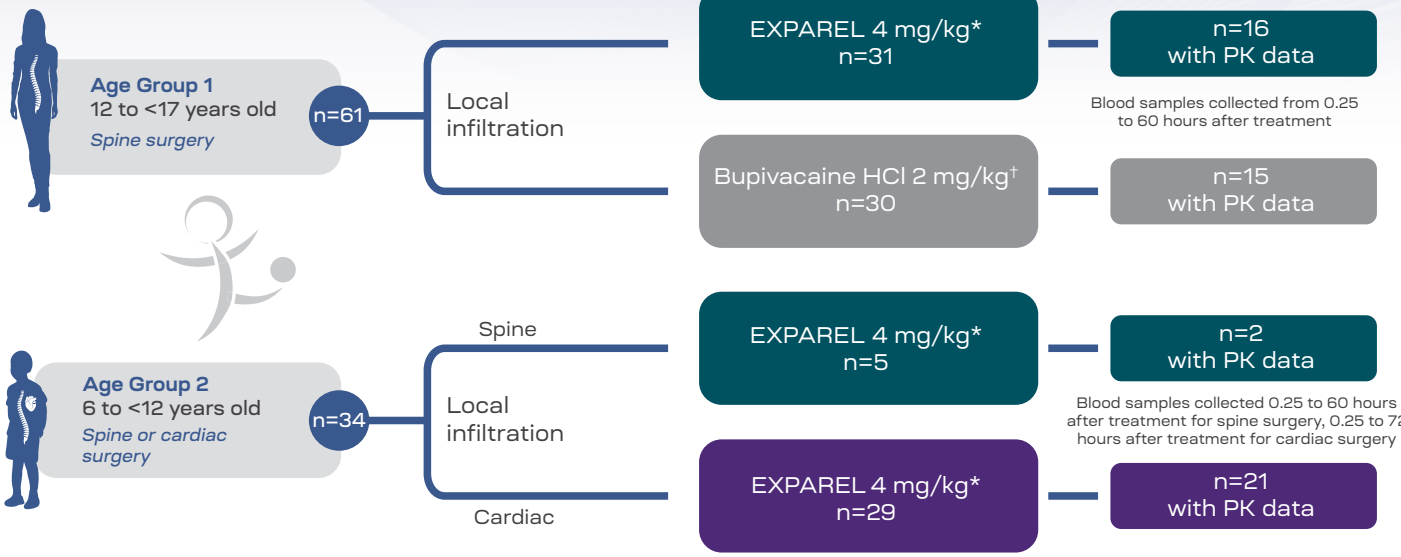
ESP, erector spinae plane; TAP, transversus abdominis plane; QL, quadratus lumborum.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

THE PLAY STUDY WAS DESIGNED TO ESTABLISH THE SAFETY AND PHARMACOKINETICS (PK) OF EXPAREL IN PEDIATRIC PATIENTS[2]

A multicenter, open-label, phase 3 trial with 2 parts including pediatric patients 6 to <17 years of age



Study End Points

Part 1: PK and safety

Part 2: Long-term safety

- AEs up to 30 days after surgery
- Neurologic assessments
- Clinical laboratory tests
- Vital signs

Baseline characteristics were generally comparable among groups.
*Maximum total dose of 266 mg.
†Maximum total dose of 175 mg.

Important Safety Information (continued)

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.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

THE SAFETY OF EXPAREL WAS COMPARABLE TO BUPIVACAINE AND CONSISTENT ACROSS TREATMENT GROUPS

EXPAREL was well tolerated for all age groups, with TEAEs being mild or moderate and no discontinuations[24]

Overview of TEAEs With EXPAREL Greater Than or Equal to 10%

	Patients aged 6 to <17 years old	Patients aged 6 to <12 years old
	Spine surgery EXPAREL 4 mg/kg; n=36 (%)	Cardiac surgery EXPAREL 4 mg/kg; n=29 (%)
Vision blurred	7 (19.4)	1 (3.4)
Constipation	9 (25)	4 (13.8)
Nausea	11 (30.6)	2 (6.9)
Hypoesthesia oral	4 (11.1)	0
Vomiting	10 (27.8)	4 (13.8)
Anemia postoperative	5 (13.9)	0
Muscle spasms	4 (11.1)	0
Hypotension	4 (11.1)	0

There were no treatment-related cardiac or nervous system adverse events in the EXPAREL arms[25]

Important Safety Information (continued)

Warnings and Precautions Specific to EXPAREL (continued)

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.

TEAE, treatment-emergent adverse event.
There is not enough evidence to determine if the numbers associated with spine surgery in patients aged 12 to <17 years old are indicative of differences in the surgery types.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

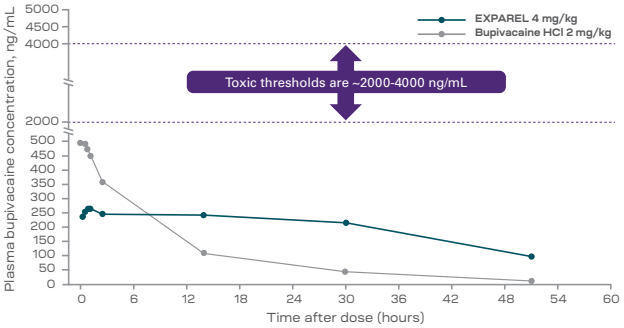
NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

DEMONSTRATED SAFETY WITH PK PROFILES THAT WERE WELL BELOW TOXIC THRESHOLDS AND BUPIVACAINE PK LEVELS[24]

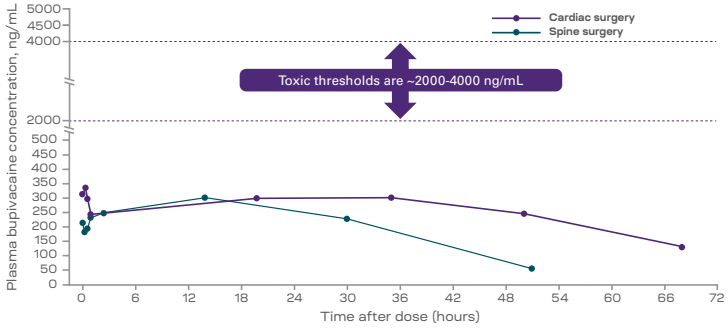
The PK profile of EXPAREL in pediatric patients was:

- Comparable across age groups
- Generally consistent with the EXPAREL PK profile in adults

Group 1 PK Plot of Mean Concentrations (ng/mL) Over Time With EXPAREL and Bupivacaine[24]



Group 2 PK Plot of Mean Concentrations (ng/mL) Over Time With EXPAREL[24]



Mean C_{max}

- Bupivacaine HCl Spine (12 to <17): 564 ng/mL
- EXPAREL Spine (12 to <17): 357 ng/mL
- EXPAREL Cardiac surgery: 447 ng/mL
- EXPAREL Spine surgery: 320 ng/mL

The PK curve represents the **mean plasma concentrations** of bupivacaine (ng/mL) for all patients **at each time point**.

C_{max} is calculated as the mean of the **maximum plasma concentrations** of bupivacaine (ng/mL) **for all patients**.

Important Safety Information (continued)

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.

C_{max}, maximum concentration.
The bupivacaine HCl data is for reference purposes only and does not reflect an active comparator in the study.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

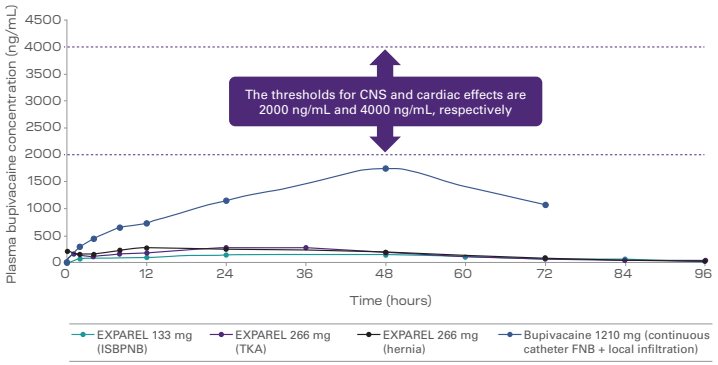
EXPAREL HAS A LEGACY OF SAFETY IN ADULTS THAT IS ALSO PROVEN IN PEDIATRIC PATIENTS

At both doses of EXPAREL (266 mg and 133 mg), the plasma levels of bupivacaine in adults remain below toxicity thresholds[22,26-28]

EXPAREL has a unique PK profile in adults

- PK demonstrates plasma levels of bupivacaine that can persist for 96 hours[22,26,27,29]
- At all doses studied, plasma bupivacaine levels are maintained well below toxic thresholds[22,26,27,29]
- The rate of systemic absorption of bupivacaine is dependent upon the total dose of the drug administered, the route of administration, and the vascularity of the administration site
- Avoid additional use of local anesthetics within 96 hours
- Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy

DepoFoam® Delivers a Consistent Slow Release of Bupivacaine Over Time to Maintain Plasma Levels Below Cardiac and Neuro Toxic Thresholds[26,27,29-31]



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

Important Safety Information (continued)

Warnings and Precautions for Bupivacaine-Containing Products (continued)

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

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

EXPAREL PROVIDES LONG-LASTING, S IGNIFICANT PAIN CONTROL WHILE REDUCING OPIOID USE IN ADULTS*

EXPAREL vs placebo in ISBPNB for total shoulder arthroplasty and rotator cuff repair[26]

78% FEWER OPIOIDS

Postsurgical opioid consumption over 48 hours
P<0.0001

SIGNIFICANTLY BETTER PAIN CONTROL

Cumulative pain scores over 48 hours
P<0.0001

Results from a phase 3, double-blind, randomized, placebo-controlled trial that compared the postsurgical analgesia efficacy, safety, and PK of EXPAREL 133 mg (10 mL) (n=69) and placebo (n=71) in patients undergoing total shoulder arthroplasty or rotator cuff repair. Primary and secondary end points: pain intensity through 48 hours postsurgery, as measured by area under the curve (AUC) of visual analog scale (VAS) pain intensity scores, and total postsurgical opioid consumption. Rescue opioids for pain were available upon patient request. Incidence of adverse events (AEs) was comparable between groups, with the most common being nausea, headache, pyrexia, and constipation.

EXPAREL vs bupivacaine HCl in TKA[32]

78% FEWER OPIOIDS

Overall opioid consumption over 48 hours
P=0.0048

SIGNIFICANTLY BETTER PAIN CONTROL

Cumulative pain scores from 12 to 48 hours
P=0.0381

Results from a phase 4, double-blind, randomized, placebo-controlled trial that compared the efficacy and safety of EXPAREL 266 mg (20 mL) (n=70) and bupivacaine HCl (n=69) in a TKA study. Primary end points: AUC of VAS pain intensity scores 12 to 48 hours postsurgery; total opioid consumption 0 to 48 hours postsurgery. Rescue opioids for pain were available upon patient request. Rates and types of AEs were similar between treatment groups. The most common AEs in the EXPAREL group were nausea, muscle spasms, and vomiting.

EXPAREL vs placebo in hemorrhoidectomy[33,34]

45% FEWER OPIOIDS

Overall opioid consumption over 72 hours
P=0.0006†

SIGNIFICANTLY BETTER PAIN CONTROL

Cumulative pain scores over 72 hours
P=0.0001†

Results from a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial that evaluated the safety and efficacy of EXPAREL 300 mg (30 mL) (n=95) and placebo (n=94) in subjects undergoing 2- or 3-column excisional hemorrhoidectomy. Primary end point: cumulative pain score reflected in AUC 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. Rates of AEs were comparable between groups. The most common AEs were gastrointestinal.

EXPAREL vs bupivacaine HCl in TAP block for C-section[35]

52% FEWER OPIOIDS

Postsurgical opioid consumption at 72 hours
P=0.0117

72 HOURS PAIN CONTROL

Comparable pain control to bupivacaine through 72 hours

Results from a randomized, active-controlled, double-blind investigation using a multimodal protocol with EXPAREL in a TAP block vs standard bupivacaine in patients undergoing elective C-section and given spinal anesthesia. Primary end point: total postsurgical opioid consumption (mg) in oral morphine-equivalent dosing through 72 hours. Patients were randomized in a blinded 1:1 ratio to receive TAP infiltration with EXPAREL 266 mg (20 mL) plus bupivacaine HCl (n=97) or active bupivacaine HCl alone (n=89). Rescue opioids for pain were available upon patient request. The safety profile was similar between groups, with the most common AEs being pruritus, nausea, vomiting, and headache.

Important Safety Information (continued)

Warnings and Precautions for Bupivacaine-Containing Products (continued)

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.

*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.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

EXPAREL IS ADMINISTERED DIFFEREN TLY THAN BUPIVACAINE HCl, ALLOWING FOR PRECISE DELIVERY OF ANALGESIA

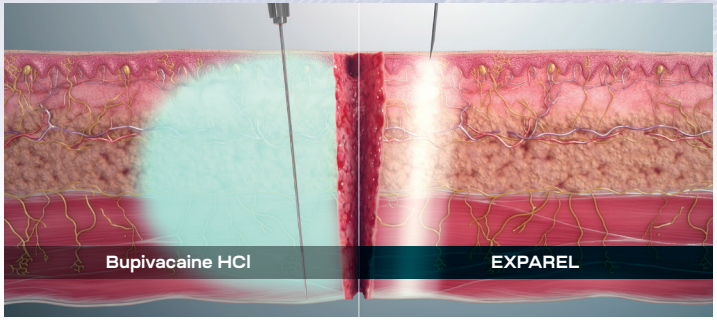
Dosing for EXPAREL in pediatrics is weight based: 4 mg/kg weight. Dosing cannot exceed one 20 mL vial or 266 mg. EXPAREL may also be expanded with normal (0.9%) saline or lactated Ringer's solution.

- Total volume is based on a 1:14 ratio

Due to the proprietary technology of DepoFoam®, EXPAREL releases bupivacaine over time

Bupivacaine is an aqueous solution.

- Readily diffuses into surrounding tissue throughout the site
- Requires fewer injections for adequate pain-receptor coverage



EXPAREL is a suspension composed of multivesicular liposomes that carry bupivacaine.

- **Stays precisely where placed; does not readily diffuse into surrounding tissue**
- **Requires more injections to ensure adequate pain-receptor coverage**

Contact your Pacira representative for dosing and administration guidance and in-service or case support

Important Safety Information (continued)

Warnings and Precautions for Bupivacaine-Containing Products (continued)

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.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID EXPAREL® (bupivacaine liposome injectable suspension)

REFERENCES

1. Pacira BioSciences. Pacira BioSciences announces FDA acceptance of sNDA for EXPAREL use in pediatric patients [press release]. Pacira website. https://investor.pacira.com/news-releases/news-release-details/pacira-biosciences-announces-fda-acceptance-snda-exparel-use. Published August 4, 2020. Accessed September 1, 2021. **2.** Multicenter study for pediatric subjects evaluating pharmacokinetics and safety of EXPAREL (PLAY). US National Library of Medicine website. https://clinicaltrials.gov/ct2/show/study/NCT03682302?term=exparel+pediatric&recrs=e&draw=2&rank=1. Accessed September 1, 2021. **3.** Diwan RM. Acute pain management. NYSORA website. https://www.nysora.com/foundations-of-regional-anesthesia/sub-specialties/pediatric-anesthesia/acute-chronic-pain-management-children/. Accessed September 1, 2021. **4.** Chidambaran V, Sadhasivam S, Mahmoud M. Codeine and opioid metabolism—implications and alternatives for pediatric pain management. *Curr Opin Anaesthesiol.* 2017;30(3):349-356. **5.** Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and predictors of chronic postsurgical pain in children: a systematic review and meta-analysis. *J Pain.* 2017;18(6):605-614. **6.** Gandhi K, Viscusi E. Multimodal pain management techniques in hip and knee arthroplasty. *J NYSORA.* 2019;13(12):1-10. **7.** Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Physician.* 2001;63(10):1979-1984. **8.** Capdevila X, Pirat P, Bringuier S, et al; French Study Group on Continuous Peripheral Nerve Blocks. Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and complications in 1,416 patients. *Anesthesiology.* 2005;103(5):1035-1045. **9.** Remerand F, Vuitton AS, Palud M, et al. Elastomeric pump reliability in postoperative regional anesthesia: a survey of 430 consecutive devices. *Anesth Analg.* 2008;107(6):2079-2084. **10.** Marhofer D, Marhofer P, Triffterer L, Leonhardt M, Weber M, Zeitlinger M. Dislocation rates of perineural catheters: a volunteer study. *Br J Anaesth.* 2013;111(5):800-806. **11.** Simić D, Stević M, Stanković Z, et al. The safety and efficacy of the continuous peripheral nerve block in postoperative analgesia of pediatric patients. *Front Med (Lausanne).* 2018;5(57):1-4. **12.** Modrzyk A, Pasierbek MJ, Korlacki W, Grabowski A. Introducing enhanced recovery after surgery protocol in pediatric surgery. *Adv Clin Exp Med.* 2020;29(8):937-942. **13.** American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116(2):248-273. **14.** Cravero JP, Agarwal R, Berde C, et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. *Ped Anesthesia.* 2019;29:547-571. **15.** Kelley-Quon LI, Kirkpatrick MG, Ricca RL, et al. Guidelines for opioid prescribing in children and adolescents after surgery: an expert panel opinion. *JAMA Surg.* 2021;156(1):76-90. **16.** Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the enhanced recovery after surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg.* 2019;55:91-115. **17.** Brindle ME, Heiss K, Scott MJ, et al. Embracing change: the era for pediatric ERAS is here. *Ped Surg Int.* 2019;35:631-634. **18.** Lambert WJ, Los K. DepoFoam® multivesicular liposomes for the sustained release of macromolecules. In: Rathbone MJ, Hadgraft J, Roberts MS, Lane ME, eds. *Modified-Release Drug Delivery Technology.* 2nd ed. New York, NY: Informa Healthcare USA; 2008:207-214. **19.** Angst MS, Drover DR. Pharmacology of drugs formulated with DepoFoam: a sustained release drug delivery system for parenteral administration using multivesicular liposome technology. *Clin Pharmacokinet.* 2006;45(12):1153-1176. **20.** Kohn FR, Malkmus SA, Brownson EA, Rossi SS, Yaksh TL. Fate of the predominant phospholipid component of DepoFoam drug delivery matrix after intrathecal administration of sustained-release encapsulated cytarabine in rats. *Drug Deliv.* 1998;5(2):143-151. **21.** Richard BM, Newton P, Ott LR, et al. The safety of EXPAREL (bupivacaine liposome injectable suspension) administered by peripheral nerve block in rabbits and dogs. *J Drug Deliv.* 2012;2012:962101. **22.** Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. *Knee.* 2012;19(5):530-536. **23.** Grissinger M. Improved safety needed in handling elastomeric reservoir balls used for pain relief. *P T.* 2013;38(5):243-245. **24.** Tirotta C, de Armendi AJ, Horn ND, et al. Play: a phase 3 study of pharmacokinetics and safety of liposomal bupivacaine for pediatric surgery. Poster presented at: the Anesthesiology Annual Meeting of the American Society of Anesthesiologists; October 5, 2020. **25.** Data on File. 6539. Parsippany, NJ: Pacira BioSciences, Inc.; March 2021. **26.** Patel MA, Gadsden JC, Nedeljkovic SS, et al. Brachial plexus block with liposomal bupivacaine for shoulder surgery improves analgesia and reduces opioid consumption: results from a multicenter, randomized, double-blind, controlled trial. *Pain Med.* 2020;21(2):387-400. **27.** Gadsden J. Local anesthetics: clinical pharmacology and rational selection. In: Hadzic A, ed. *Hadzic's Peripheral Nerve Blocks.* 2nd ed. New York, NY: The McGraw-Hill Companies, Inc. 2012. **28.** Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol.* 1998;46(3):245-249. **29.** Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin Drug Investig.* 2013;33(2):109-115. **30.** Knudsen K, Beckman Suurküla M, Blomberg S, Sjövall J, Edvardsson N. Central nervous and cardiovascular effects of IV infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth.* 1997;78(5):507-514. **31.** Marino J, Scuderi G, Dowling O, Farquhar R, Freycinet B, Overdyk F. Periarticular knee injection with liposomal bupivacaine and continuous femoral nerve block for postoperative pain management after total knee arthroplasty: a randomized controlled trial. *J Arthroplasty.* 2019;34(3):495-500. **32.** Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ. Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: results of a randomized controlled trial. *J Arthroplasty.* 2018;33(1):90-96. **33.** Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum.* 2011;54(12):1552-1559. **34.** Data on File. 2363. Parsippany, NJ: Pacira BioSciences, Inc.; June 2017. **35.** Nedeljkovic SS, Kett A, Vallejo MC, et al. Transversus abdominis plane block with liposomal bupivacaine for pain after cesarean delivery in a multicenter, randomized, double-blind, controlled trial. *Anesth Analg*. 2020;131(6):1830-1839.

Important Safety Information (continued)

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, pruritus, 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.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

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.

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, pruritus, 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.

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

EXPAREL: PROVEN SAFE IN PEDIATRIC AND ADULT PATIENTS

The first and only FDA-approved long-acting local analgesic for ages 6 and above[1]

With experience in more than 9 million patients, EXPAREL is proven to provide:

- Reduction or elimination of opioids[26,32,33,35,*]
- Effective pain management designed with safety in mind for pediatric patients[26,32,33,35]
- Versatility of administration, including surgical site infiltration and fascial plane infiltration (regional field blocks)
- Extended analgesia powered by DepoFoam® technology, delivering precise pain control for the critical first few days after surgery to enable enhanced recovery[18,33]

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

Important Safety Information (continued)

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.

Please refer to the full Prescribing Information for complete Dosage and Administration information before using EXPAREL.

PACIRA BIOSCIENCES, INC.

Parsippany, NJ 07054 PP-EX-US-7041 09/21

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)