FOR HEALTH CARE PROFESSIONALS ONLY

EXPAREL® liposomal
(liposomal bupivacaine)

EXPAREL® delivers targeted pain control for the critical first days post surgery.[1,2]

INDICATION

EXPAREL® liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults.[3]

ADMINISTRATION

EXPAREL® liposomal is given as a prolonged-release dispersion for injection and offers long-acting local anaesthesia that can be administered as a single dose for patients with post-operative pain.[3]

Abbreviated prescribing information can be found at pages 18–19.

1. Howell SB. Clinical applications of a novel sustained-release injectable drug delivery system: DepoFoam® technology. Cancer Journal.2001;7(3):219-227. **2.** 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. **3.** EXPAREL® SmPC January 2021

PP-EX-GB-0012 2021/06 Date of preparation: June 2021

BACKGROUND

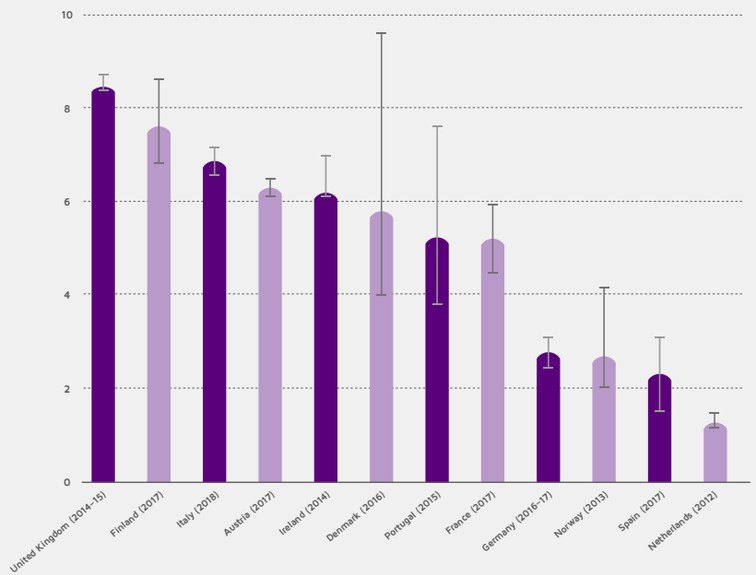
Inadequately managed post-surgical pain has a negative impact on patient outcomes:[1,2]

Studies have shown that not only health costs could increase[2] but also a decreased quality of life, increased length of hospital stay, impaired cardiovascular and respiratory function, insomnia and psychological as well as emotional problems.[1]

Use and misuse of opioids may also cause opioid addiction and opioid related morbidity and mortality.[3]

CURRENT HIGH-RISK OPIOID USE IN EUROPE[4]

Prevalence of high-risk opioid use per 1000 population aged 15–64 years.



EXPAREL® is a non-opioid local anaesthetic agent[5]

Figure adapted from www.emcdda.europa.eu/media-library/prevalence-high-risk-opioid-use-1-000-population-aged-15-64-years-country-most-recent-studies_en September 2020

High-risk opioid use[6]

A high-risk opioid user was defined as a person aged 15–64 years who used opioids, including opioid medicines, weekly or more frequently for at least 6 months of the past 12 months, not according to a medical prescription OR whose use of opioids led to a medical diagnosis of harmful use, dependence or opioid use disorder in the past 12 months according to current DSM or ICD criteria.

1. Apfelbaum JL, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97(2):534-540. **2.** Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg. 2013;26(3):191-196. **3.** National Academies of Sciences, Engineering, and Medicine. 2017. Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781. **4.** www.emcdda.europa.eu/media-library/prevalence-high-risk-opioid-use-1-000-population-aged-15-64-years-country-most-recent-studies_en September 2020 **5.** EXPAREL SmPC January 2021 **6.** https://www.emcdda.europa.eu/system/files/publications/6389/LXAddictions2017_PDU.pdf

INDICATION[1]

EXPAREL® liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults.

ADMINISTRATION

EXPAREL® liposomal is given as a prolonged-release dispersion for injection and offers long-acting local anaesthesia that can be administered as a single dose for patients with post-operative pain.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to local anaesthetic medicinal products of the amide type.
- Obstetrical paracervical block anaesthesia due to risk of foetal bradycardia or death.
- Intravascular administration.
- Intraarticular administration.

Maximum dosage of 266 mg (20mL of unexpanded medicinal product) **must not be exceeded.**

Each vial of 10 or 20 ml contains 133 or 266 mg bupivacaine for injection, respectively.

The recommended dose of EXPAREL® liposomal is based on the following factors:

1. **SIZE** of the surgical site
2. **VOLUME** required to cover the area
3. **INDIVIDUAL** patient factors that may impact the safety of an amide local anesthetic

Guidance in selecting the proper dosing for different procedures, including field block and peripheral nerve block is presented in the SmPC.

1. EXPAREL® SmPC January 2021

PHARMACOKINETICS OF EXPAREL®

EXPAREL® is bupivacaine encapsulated in the multivesicular liposomal drug delivery system. Upon administration, bupivacaine is slowly released from the liposomes over an extended period of time.[1]

Bupivacaine is a commonly used local anaesthetic for post-operative pain management.[2] Bupivacaine is related chemically and pharmacologically to the amide-type local anaesthetics. It is a homologue of mepivacaine and is related chemically to lidocaine.[1]

Local anaesthetics 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.[1]

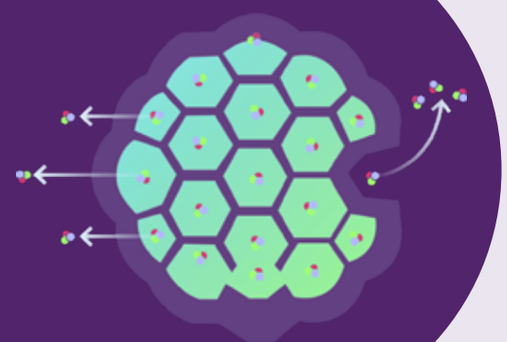
KEY ADMINISTRATION DIFFERENCES BETWEEN TRADITIONAL BUPIVACAINE AND EXPAREL®

EXPAREL® liposomal formulation provides extended analgesic efficacy by reducing the bupivacaine diffusion away from the injection site seen with traditional bupivacaine yet importantly requires more injections to effectively cover the surgical area.[1]

DEPOFOAM® TECHNOLOGY

The DepoFoam® carrier matrix consists of microscopic, spherical, lipid-based particles composed of a honeycomb of numerous, non-concentric, internal aqueous chambers containing the encapsulated drug.

Each chamber is separated from adjacent chambers by lipid membranes. Following injection, the DepoFoam® particles release the drug over an extended period of time due to erosion and/or reorganization of the lipid membranes.[3]



EXPAREL® utilizes DepoFoam® technology and delivers targeted pain control for the critical first days post surgery.[4,5]

EXPAREL® when injected into the peri-surgical sites, blocks the generation and conduction of nerve impulses, numbing the area where surgery has occurred for several days.[6]

1. EXPAREL SmPC January 2021. **2.** Miller RD. Basics of Anesthesia. 2006. Churchill Livingstone. **3.**Mantripragada S. A lipid based depot (DepoFoam® R technology) for sustained release drug delivery. Progress in Lipid Research. 2002;41:392–406injectable drug delivery system: DepoFoam® technology. Cancer Journal.2001;7(3):219-227. **4.** Howell SB. Clinical applications of a novel sustained-release injectable drug delivery system: DepoFoam® technology. Cancer Journal.2001;7(3):219-227. **5.** Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bu-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. **6.** Bramlett K, et al. 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

FOR HOW LONG IS EXPAREL® AVAILABLE IN THE BLOODSTREAM?[1]

EXPAREL® exhibited dose-proportional pharmacokinetics following single administrations via wound infiltration.

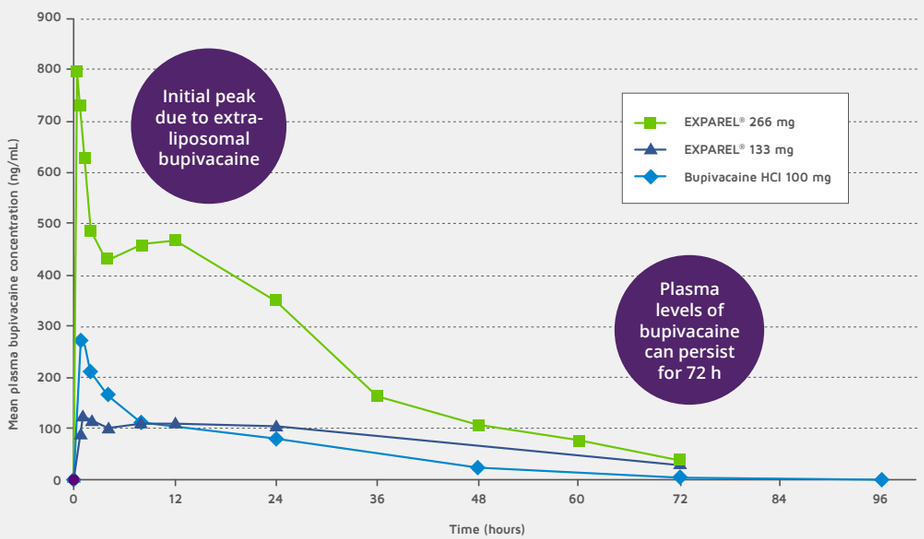


Figure adapted from 1. Hu D, et al. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig. 2013;33(2):109-115.

1. Hu D, et al. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig. 2013;33(2):109-115. **2.** IMS sales data March 2021. **3.** Viscusi ER, et al. The safety of liposome bupivacaine, a novel local analgesic formulation. Clin J Pain. 2014;30(2):102-110. **4.** Bardsley H, et al. 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. **5.** 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. **6.** EXPAREL SmPC January 2021.

SAFETY

EXPAREL® has been used in over 8 million patients since 2012.[2]

The safety data of EXPAREL® was pooled from 10 randomized, double-blind clinical studies involving local administration into the surgical site, with 823 patients undergoing various surgical procedures, which included the following: Haemorrhoidectomy, bunionectomy, inguinal hernia repair, breast augmentation, total knee arthroplasty.[3]

The most common adverse reactions (≥5%) associated with EXPAREL® in clinical trials were dysgeusia (6.0%) and hypoaesthesia oral (6.5%).[4]

The most important serious adverse reactions associated with EXPAREL® were systemic toxic reactions. Systemic toxic reactions usually present shortly after administration of bupivacaine but may be delayed in some cases.[4]

Severe central nervous system toxicity due to EXPAREL® may result in convulsions (< 0.001% from post-marketing data). Severe cardiac toxicity due to EXPAREL® may result in serious dysrhythmia (0.7% in clinical trials), serious hypotension (0.7% in clinical trials), and/or cardiac arrest (< 0.001% from post-marketing data).[4]

The thresholds for central nervous system and cardiac effects are 2000 ng/mL and 4000 ng/mL, respectively[1,4–5]

Symptoms of toxicity have been reported at levels as low as 800ng/ml[6]

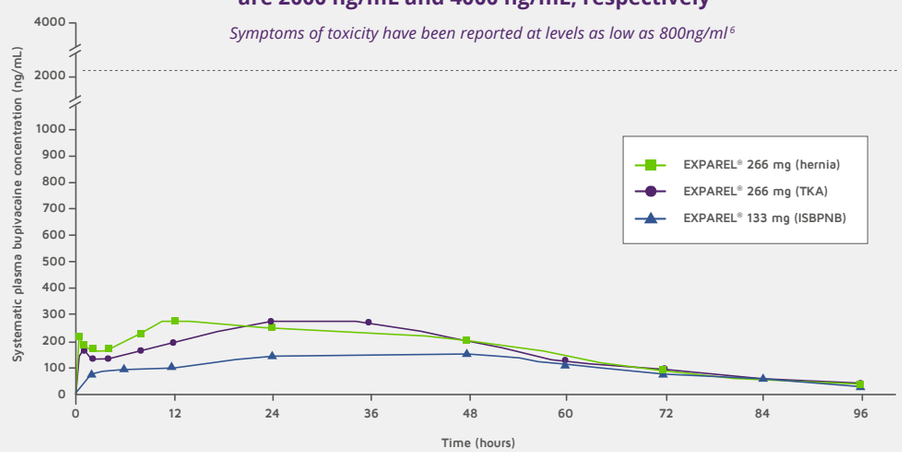


Figure adapted from ref 1, 4 and 5.

SUMMARY OF KEY PAIN ENDPOINT RESULTS IN PHASE 3 STUDIES

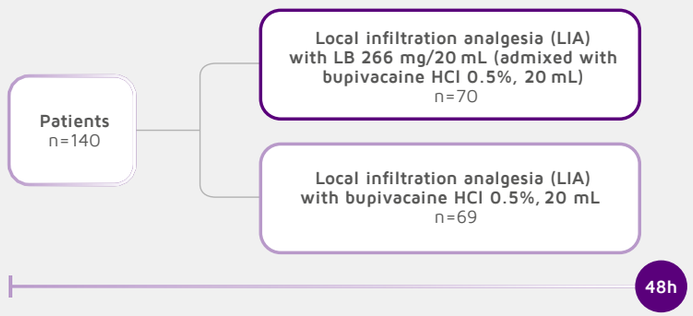
STUDY / SURGERY TYPE	EXPAREL LIPOSOMAL DOSE (N) / CONTROL (N)	PRIMARY ENDPOINT	TREATMENT DIFFERENCE (95% CI)	PAIN SCORE PLACEBO	PAIN SCORE EXPAREL	P-VALUE[a]
SUMMARY OF KEY PAIN ENDPOINT RESULTS IN LOCAL ANALGESIA STUDIES						
Field Block/ Haemorrhoidectomy	266 mg (94)/Placebo (93)	AUC NRS-R_{0-72}	-61 (-90, -31)	**203**[2]	**142**[2]	<0.0001
Field Block/Bunionectomy	106 mg (97)/Placebo (96)	AUC NRS-R_{0-24}	-22 (-35, -10)	**146**[3]	**125**[3]	0.0005
SUMMARY OF KEY PAIN ENDPOINT RESULTS IN REGIONAL ANALGESIA STUDIES						
Femoral Nerve Block/TKA[b]	266 mg (92) / Placebo (91)	AUC NRS-R_{0-72}	-96.5 (-144, -49)	**516**[4]	**419**[4]	<0.0001
Brachial Plexus Nerve Block/ TSA/RCR	133 mg (69) / Placebo (71)	AUC VAS_{0-48}	-118 (-151, -84)	**254**[5]	**136**[5]	<0.0001

a: non-inferiority p-value; b: TKA study was a combined Phase 2 (Part 1) and Phase 3 (Part 2) study; only phase 3 results are displayed here. AUC: area under the curve; NRS-R: numeric rating scale at rest; TKA: total knee arthroplasty; VAS: visual analogue scale; TSA: total shoulder arthroplasty; RCR: rotator cuff repair; (n): number of subjects.

1. EXPAREL® SmPC January 2021. **2.** Gorfine SR, et al. 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. **3.** Golf M, et al. A phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv Ther. 2011;28(9):776-788. **4.** Hadzic A, Minkowitz HS, Melson TI, et al. Liposome bupivacaine femoral nerve block for postsurgical analgesia after total knee arthroplasty. Anesthesiology 2016;124(6):1372–83. **5.** Patel M, 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 Medicine, 2019;21(2):387-400.

TOTAL KNEE ARTHROPLASTY (TKA)[1]

Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty compared to LIA with bupivacaine: results of a randomized controlled trial (PILLAR)



Results from a liposomal bupivacaine (LB) phase 4, double-blind, randomised, active-controlled, parallel group study that compared the efficacy and safety of liposomal bupivacaine (LB) 266 mg (20 mL; n=70) and bupivacaine HCl (n=69) in a TKA study.

Primary end points: Area under the curve (AUC) of visual analogue scale (VAS) pain intensity scores 12 to 48 hours after surgery; total opioid consumption 0 to 48 hours after surgery.

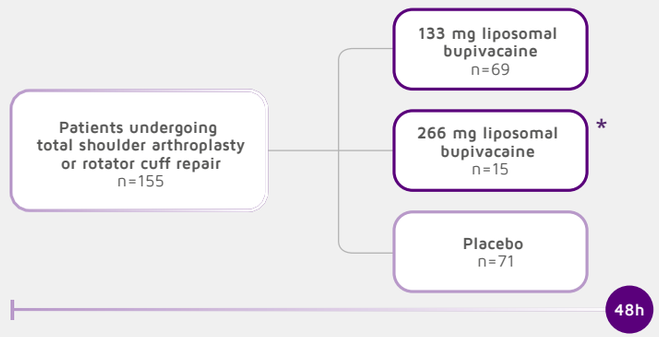
Conclusion: This study provides data on local infiltration analgesia (LIA) with EXPAREL® administered using optimal techniques specific to TKA.

In this setting, LIA with EXPAREL® significantly improved postsurgical pain, opioid consumption, and time to first opioid rescue, with more opioid-free patients and no unexpected safety concerns compared to LIA with bupivacaine.

Rates and types of adverse events were similar between treatment groups. The most common adverse events in the liposomal bupivacaine group were nausea, muscle spasms and vomiting.

SHOULDER SURGERY[2]

Brachial plexus block with Liposomal Bupivacaine for shoulder surgery improves analgesia and reduces opioid consumption compared to placebo



* This part of the study was only for pharmacokinetic and safety analyses

Results from a phase 3, double-blind, randomised, controlled trial that compared the postsurgical analgesia efficacy, safety, and pharmacokinetics of EXPAREL® 133 mg (10 mL) and placebo in 155 patients undergoing total shoulder arthroplasty or rotator cuff repair.

Primary and secondary end points: pain intensity through 48 hours after surgery, as measured by area under the curve (AUC) of visual analogue scale (VAS) pain intensity scores, and total postsurgical opioid consumption.

Conclusion: Single-injection ultrasound-guided brachial plexus block with EXPAREL® 133 mg provided analgesia through 48 hours postsurgery with reduced opioid use compared with placebo after shoulder surgery.

Adverse event incidence was comparable between groups. The proportion of patients with one or more treatment emergent adverse events (TEAEs) was similar between groups. Nausea was the most commonly reported AE, followed by constipation.

1. Mont MA, et al. 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. **2.** Patel M, 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 Medicine, 2019;21(2):387-400.

STORAGE AND PREPARATION[1]

From a microbiological point of view EXPAREL® should be used immediately.

- **Do not** freeze the product.
- **Unopened vials** have a shelf-life of two (2) years and should be stored in a refrigerator (2°C to 8°C). Unopened vials may also be stored at room temperature (below 25°C) for up to 30 days. Vials should not be re-refrigerated.
- **After first opening** Chemical and physical in-use stability of EXPAREL® liposomal withdrawn from vials and transferred into polypropylene syringes has been demonstrated for 48 hours when stored in a refrigerator (2°C to 8°C), or 6 hours when stored at room temperature (below 25°C). From a microbiological point of view, the product should be used immediately.
- **EXPAREL® vials** are intended for single use only and should be visually inspected prior to administration. They should be gently inverted multiple times to re-suspend the particles in the dispersion immediately prior to withdrawal from the vial.
- **EXPAREL® can be** administered in the ready to use dispersion or expanded (the expansion is explained in the SmPC).
- **EXPAREL® and bupivacaine HCl** being co-administered should not exceed 400 mg equivalents of bupivacaine HCl.

HOW TO INJECT EXPAREL® FOR INFILTRATION

1. Use a 25-gauge or larger-bore needle to maintain the structural integrity of the liposomal particles.[1]
2. Inject EXPAREL® slowly and deeply (generally 1–2 mL per injection) into soft tissues using a moving needle technique (ie, inject while withdrawing the needle).[1]
3. Infiltrate above and below the fascia and into the subcutaneous tissue.[2]
4. Aspirate frequently to minimize risk of intravascular injection.[2]
5. Inject frequently in small areas (0.5–1.0 cm apart) to ensure overlapping analgesic coverage.[2]

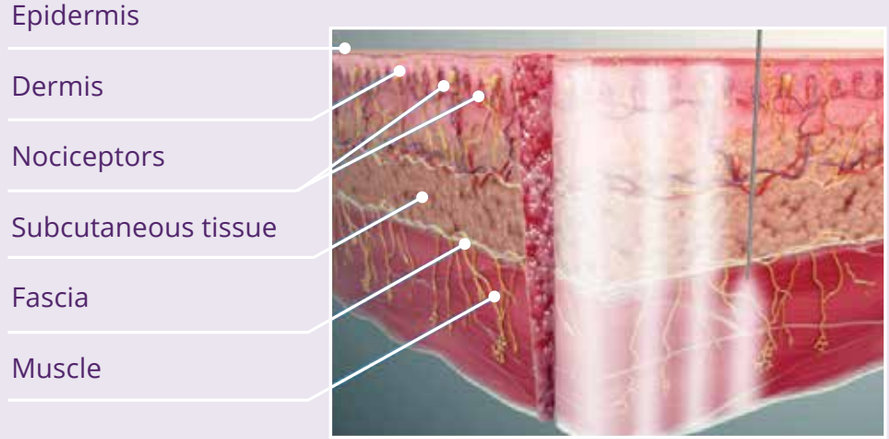


Image source: Pacira

1. EXPAREL® SmPC January 2021
2. Joshi GP, et al. Surgical site infiltration for abdominal surgery: A novel neuroanatomical-based approach. Plast Reconstr Surg Open. 2016: 23;4(12):e1181.

WARNINGS AND PRECAUTIONS SPECIFIC FOR EXPAREL®[1]

- **EXPAREL® is not recommended** for epidural and intrathecal routes of administration.
- **EXPAREL® should only be** admixed with bupivacaine. When EXPAREL® is admixed with lidocaine it leads to an immediate displacement and release of bupivacaine. This can be prevented by ensuring that EXPAREL® is administered at least 20 minutes after administering lidocaine.
- **The addition of local anaesthetics** administered within 96 hours following administration of EXPAREL® should take into account the total bupivacaine exposure.
- **EXPAREL® is for adults** (>18 years) and is not recommended during pregnancy and in women of childbearing potential not using contraception. There is no available information on effects of the medicinal product in the breastfed infant or effects of the medicinal product on milk production. Either discontinue breast feeding or abstain from EXPAREL®.

1. EXPAREL® SmPC January 2021

CONCLUSION/SUMMARY

EXPAREL® is an agent that blocks nerve impulses associated with pain.

- **Controlling post-operative pain** is important for ensuring a good patient experience, optimising post-operative outcomes and enhancing recovery, and the prevention of chronic post-surgical pain in the longer term.[1,2]
- **EXPAREL® is liposomal bupivacaine** used as a local analgesic to alleviate pain in a particular location of the body.[3]
- **The numbing effects** of traditional bupivacaine are short lived, as the molecules are small and rapidly redistributed from the site of injection.[3] When bupivacaine is combined with larger carriers such as liposomes, it remains at the injection site for longer and the local anaesthetic is released gradually over several days.[4]
- **Post-surgical pain is managed effectively**, and opioid consumption is likely to be reduced which further promotes earlier patient mobilisation.[3,5–6]

EXPAREL® is given as a prolonged-release dispersion for injection and offers long-acting local anaesthesia that can be administered as a single dose for patients with post-operative pain.[3]

1. Apfelbaum JL, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97(2):534-540. **2.** Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg. 2013;26(3):191-196. **3.** EXPAREL SmPC January 2021 **4.** Hu D, et al. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig. 2013;33(2):109-115. **5.** Kampman S, et al. Cost and Quality Impact of Multi-Modal Pain Regimens. Washington, DC: The Advisory Board Company; 2014; **6.** Shaffer EE, et al. Adv Ther. 2017;33(12):2211-2228.

EXPAREL LIPOSOMAL 133 MG/10 ML PROLONGED-RELEASE DISPERSION FOR INJECTION, EXPAREL LIPOSOMAL 266 MG/20 ML PROLONGED-RELEASE DISPERSION FOR INJECTION (BUPIVACAINE) - ABBREVIATED PRESCRIBING INFORMATION (API)

Prescribers are recommended to consult the summary of product characteristics before prescribing. Additional information is available on request.

Presentations

Each mL contains 13.3 mg bupivacaine in a multivesicular liposomal dispersion. Each 10 mL vial contains 133 mg bupivacaine, and each 20 mL vial contains 266 mg bupivacaine.

Indication

EXPAREL liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults.

Posology and method of administration

Recommended dosage: The recommended dose of EXPAREL liposomal is based on the size of the surgical site, volume required to cover the area, and individual patient factors. A maximum dosage of 266 mg (20 mL of undiluted medicinal product) must not be exceeded. Refer to full SmPC for dosage examples for different procedures.

Co-administration with other local anaesthetics: EXPAREL liposomal should be used with caution including monitoring for neurologic and cardiovascular effects related to local anaesthetic systemic toxicity. It should not be used interchangeably with other formulations of bupivacaine. Bupivacaine hydrochloride (immediate release formulations) and EXPAREL liposomal may be administered simultaneously in the same syringe as long as the ratio of the mg dose of bupivacaine solution to EXPAREL liposomal does not exceed 1:2. If preparing admixture, the total amount of bupivacaine used (EXPAREL liposomal + bupivacaine HCl) should not exceed 400mg equivalents of bupivacaine HCl.

Elderly patients: Care should be taken in dose selection of EXPAREL liposomal in elderly patients because 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. No dosage adjustment is required; however, greater sensitivity of some older individuals cannot be ruled out. The risk of falls may increase for the elderly patients.

Hepatic/renal impairment: The risk of toxic reactions may be greater in patients with impaired renal function therefore care should be taken when performing dose selection of EXPAREL liposomal. No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5-6) or moderate hepatic impairment (Child-Pugh score 7-9). There are insufficient data to recommend the use of EXPAREL liposomal in patients with severe (Child-Pugh score ≥10) hepatic impairment.

Paediatrics: The safety and efficacy of EXPAREL liposomal in children aged 1 to less than 18 years have not yet been established. EXPAREL liposomal should not be used in children aged less than 1 year of age because neonates and infants have a decreased ability to metabolize anaesthetics due to an immature hepatic system.

Method of administration: EXPAREL liposomal is for administration by infiltration or perineural use only. It is intended for single-dose administration only.

Refer to full SmPC for full information on posology and administration.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to local anaesthetic medicinal products of the amide type.
- Obstetrical paracervical block anaesthesia due to risk of foetal bradycardia or death.
- Intravascular administration.
- Intra-articular administration.

Special warnings and precautions for use

Local anaesthetic systemic toxicity: As there is a potential risk of severe life-threatening adverse reactions associated with the administration of bupivacaine, EXPAREL liposomal 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. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be performed after injection of bupivacaine.

Toxic local anaesthetic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmia, and cardiac arrest, which can be fatal. In addition, toxic local anaesthetic blood concentrations depress myocardial contractility and cause peripheral vasodilation, leading to decreased cardiac output and arterial blood pressure.

No correlation of cases of potential local anaesthetic systemic toxicity with surgical procedure or route of administration has been found with EXPAREL liposomal, but redosing of EXPAREL liposomal, overdose, or concomitant use with other local anaesthetics may increase the risk.

Neurologic effects: 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, excitation 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 include nausea, vomiting, chills, and constriction of the pupils.

Neurologic effects following field block may include persistent anaesthesia, paraesthesias, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Cardiovascular function impairment: Use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of atrioventricular conduction produced by these medicinal products.

Hepatic impairment: Use cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Increased monitoring for local anaesthetic systemic toxicity should be considered in subjects with moderate to severe hepatic disease.

Renal impairment: Bupivacaine metabolites are known to be extensively excreted by the kidney. Thus, the risk of toxic reactions to this medicinal product may be greater in patients with impaired renal function.

Allergic reactions: Allergic-type reactions may rarely occur as a result of hypersensitivity to the local anaesthetic or to other formulation ingredients.

Chondrolysis: Intra-articular infusions of local anaesthetics, including EXPAREL liposomal, following arthroscopic and other surgical procedures are contraindicated. There have been post-marketing reports of chondrolysis in patients receiving such infusions.

Methaemoglobinaemia: Patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methaemoglobinaemia, cardiac or pulmonary compromise, or concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anaesthetics must be used in these patients, close monitoring for symptoms and signs of methaemoglobinaemia is recommended.

Warnings and precautions specific to EXPAREL liposomal: It is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL liposomal and vice versa, and no substitution with other bupivacaine containing products should be made.

Caution is advised when co-administering EXPAREL liposomal and bupivacaine HCl, particularly when administering to highly vascular areas where higher systemic absorption is expected.

Using EXPAREL liposomal followed by other bupivacaine formulations has not been studied in clinical trials. EXPAREL liposomal has not been evaluated and is therefore not recommended for epidural or intrathecal use. It is also not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan due to potential for temporary sensory and/or motor loss which may last for up to 5 days.

Excipients with known effect – sodium: contains 21 mg sodium per 10 mL vial and 42 mg sodium per 20 mL vial, equivalent to 1.1% and 2.1%, respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Refer to full SmPC for further information on warnings and precautions.

Interaction with other medicinal products and other forms of interaction

Use of EXPAREL liposomal with other local anaesthetics: EXPAREL liposomal should be used with caution in patients receiving other local anaesthetics or active substances structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive.The addition of local anaesthetics administered within 96 hours following administration of EXPAREL liposomal should take into account the total bupivacaine exposure.

Oxidizing medicinal products: Patients that are administered local anaesthetics may be at increased risk of developing methaemoglobinamia when concurrently exposed to the following oxidizing medicinal products:

- Nitrates/Nitrites - nitroglycerin, nitroprusside, nitric oxide, nitrous oxide
- Local anaesthetics - benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine, ropivacaine
- Antineoplastic medicinal products - cyclophosphamide, flutamide, rasburicase, isofamide, hydroxyurea
- Antibiotics - dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid
- Antimalarials - chloroquine, primaquine
- Anticonvulsants - phenytoin, sodium valproate, phenobarbital
- Other medicinal products - acetaminophen, metoclopramide, sulfa medicines (e.g., sulfasalazine), quinine

Other medicinal products: When a topical antiseptic, such as povidone iodine, is applied, the site should be allowed to dry before EXPAREL liposomal is administered into the site. EXPAREL liposomal should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Refer to full SmPC for further information on interactions.

Fertility, pregnancy and lactation

Pregnancy: There are no or limited amount of data from the use of bupivacaine in pregnant women. Studies in animals have shown reproductive toxicity. EXPAREL liposomal is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding: Bupivacaine and its metabolite, pipecoloxylidide, are present in human milk at low levels. There is no available information on effects of EXPAREL liposomal in the breastfed infant or on milk production. A decision must be made whether to discontinue breast-feeding or to discontinue EXPAREL liposomal therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility: There are no clinical data on the effects of EXPAREL liposomal on fertility.

Effects on ability to drive and use machines

Bupivacaine could have a major influence on the ability to drive and use machines. Patients should be informed in advance that bupivacaine liposomal dispersion can cause temporary loss of sensation and/or motor function in varying degrees and duration (depending on site of injection, route of administration (i.e. field block or nerve block) and dosage administered), and may last for up to 5 days.

Undesirable effects

For full list of side effects, consult SmPC. 'Common' and 'serious' side effects are included in this prescribing information.

Common side effects (≥1/100 to <1/10): dysgeusia, vomiting, constipation, hypoaesthesia oral, nausea. Serious uncommon (≥1/1000 to <1/100): motor dysfunction, bradycardia, tachycardia, blood creatinine increased, alanine aminotransferase increased, aspartate aminotransferase increased; Serious Rare (≥1/10,000 to <1/1000): monoplegia, atrial fibrillation, tachyarrhythmia, sinus tachycardia, apnoea, hypoxia, atelectasis, dyspnoea, haematochezia, drug eruption, electrocardiogram ST segment elevation, hepatic enzyme increased, white blood cell count increased; Serious Frequency unknown (cannot be estimated from the available data): hypersensitivity, seizure, palsy, cardiac arrest, local anaesthetic systemic toxicity (LAST).

Overdose

Systemic toxic reactions, primarily involving the central nervous system and the cardiovascular system may occur following high blood concentrations of local anaesthetics.

Refer to full SmPC for further information on overdose and management of local anaesthetic overdose.

Legal Category

Prescription only medicine.

Pack quantities and costs

Available in packs of 10 vials 10ml and 10 vials 20ml.
EXPAREL 10ml x 10 Vials: £1,349.00
EXPAREL 20ml x 10 Vials: £2,418.00

Marketing Authorisation Holder

Ireland
Pacira Ireland Ltd
Unit 13, Classon House
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Dundrum
Dublin 14, D14W9Y3
Ireland

UK
Pacira Ltd
Wessex House, Marlow Road
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Buckinghamshire, SL8 5SP
United Kingdom

Marketing Authorisation Number

EU/1/20/1489/001-004 (Ireland)
PLGB 34175/0003 (UK)
PLGB 34175/0004 (UK)

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store for the UK and at hpra.ie/homepage/about-us/report-an-issue for Ireland. **Adverse events should also be reported via drugsafety@pacira.com**

Date of last revision of the API text

May 2021

PACIRA
BIOSCIENCES, INC.

Pacira Biosciences Inc. is a global pharmaceutical company and a leading provider of non-opioid pain management and regenerative health solutions dedicated to advancing and improving patient outcomes. Pacira is setting new expectations for clinicians and patients alike, providing innovative alternatives to opioids for pain management.

EXPAREL® is Pacira´s first pharmaceutical product approved for Europe.

EXPAREL® liposomal
(liposomal bupivacaine)