

EXPAREL® liposomal
(liposomal bupivacaine)

DOSING GUIDE

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.¹



EXPAREL® should be administered in a setting where trained personnel and appropriate resuscitation equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity.¹

STORAGE¹

Unopened vials

EXPAREL[®] should be refrigerated between 2°C to 8°C. Sealed EXPAREL[®] vials may also be stored at room temperature (below 25°C) for up to 30 days. Vials should not be re-refrigerated. EXPAREL[®] must not be frozen.



Opened vials

Chemical and physical in-use stability of EXPAREL[®] withdrawn from vials and transferred into polypropylene syringes has been demonstrated for 48 hours when stored in a refrigerator (2°C to 8°C), or 6 hours when stored at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. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C unless opening has taken place in controlled and validated aseptic conditions.

After expansion

Chemical and physical in-use stability of EXPAREL[®] when admixed with other formulations of bupivacaine has been demonstrated for 24 hours at room temperature (below 25°C). When admixed with 9 mg/mL (0.9%) sodium chloride or lactated Ringer's solution, chemical and physical in-use stability has been demonstrated for 4 hours when stored in a refrigerator (2°C to 8°C) and at room temperature (below 25°C).

PREPARATION¹

EXPAREL[®] vials should be inspected prior to administration and gently inverted to re-suspend the particles in the dispersion immediately prior to withdrawal from the vial. Multiple inversions may be necessary if the contents of the vial have settled.

EXPAREL[®] vials are intended for single use only.

EXPAREL[®] **must not be expanded** with water or other hypotonic agents as it will result in disruption of the liposomal particles.

EXPAREL[®] **is not recommended** for epidural, intrathecal, intravascular or intraarticular routes of 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.
- Intraarticular administration.

Mixing¹

EXPAREL[®] can be administered in the ready to use dispersion or expanded to a concentration of up to 0.89 mg/mL (i.e. 1:14 expansion by volume) with 9 mg/ml (0.9%) sodium chloride or lactated Ringer's solution.



EXPAREL[®] with bupivacaine¹

If preparing an admixture of EXPAREL[®] with bupivacaine or saline or both, the order in which the components are combined does not matter.

Bupivacaine hydrochloride (immediate release formulations) can be administered simultaneously, as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL[®] does not exceed 1:2 (with strict observance of a combined maximum of 400 mg equivalents of bupivacaine HCl as further described below and opposite).

Bupivacaine amount in EXPAREL[®] is expressed as the free base of bupivacaine, thus, when calculating the total dose of bupivacaine for coadministration, the amount of bupivacaine from EXPAREL[®] should be converted to the equivalent of bupivacaine HCl by multiplying EXPAREL[®] dose with a factor of 1.128.

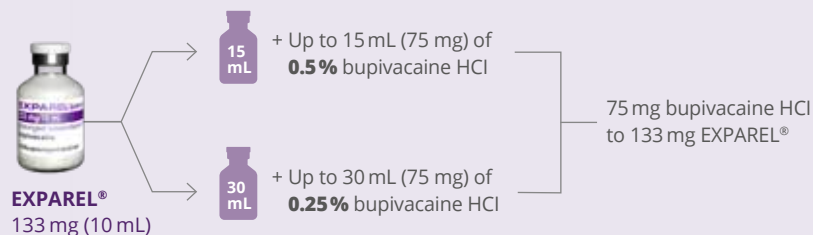
Dosing¹

The recommended dose for local infiltration in adults is based on the following factors:

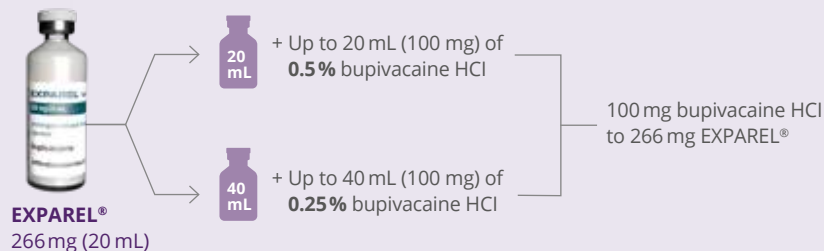
1. **SIZE** of the surgical site
2. **VOLUME** required to cover the area
3. **INDIVIDUAL** patient factors that may impact the safety of an amide local anaesthetic

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

One 10 mL vial contains 133 mg of EXPAREL[®], which is equivalent to 150 mg bupivacaine HCl. This will allow 75 mg of bupivacaine HCl to be added to 133 mg EXPAREL[®]



One 20 mL vial contains 266 mg of EXPAREL[®], which is equivalent to 300 mg bupivacaine HCl. This will allow 100 mg bupivacaine HCl to be added to 266 mg EXPAREL[®]



ADMINISTRATION

– how to inject

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



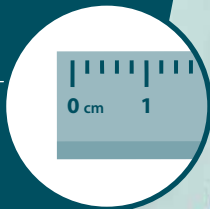
3.

Infiltrate above and below the fascia and into the subcutaneous tissue. Aspirate frequently to minimize risk of intravascular injection.²



4.

Inject frequently in small areas (0.5–1 cm apart) to ensure overlapping analgesic coverage.²



The toxic effects of local anaesthetics are additive and their co-administration, taking into account the dose of local anaesthetic and the extended pharmacokinetic profile of EXPAREL®, should be used with caution including monitoring for neurologic and cardiovascular effects related to local anaesthetic systemic toxicity.¹



Key administration differences exist between traditional bupivacaine and EXPAREL®

EXPAREL® formulation provides extended analgesic efficacy by reducing the bupivacaine diffusion away from the injection site seen with standard bupivacaine yet importantly requires more injections to effectively cover the surgical area.^{1,2}

Effective distribution of EXPAREL® involves adjustment to the infiltration technique where the volume of EXPAREL® may be expanded up to a maximum total of 300 mL using normal saline (0.9%) or lactated Ringer's solution to facilitate complete distribution of the liposomes throughout the surgical site.^{1,2}

- Epidermis
- Dermis
- Nociceptors
- Subcutaneous tissue
- Fascia
- Muscle

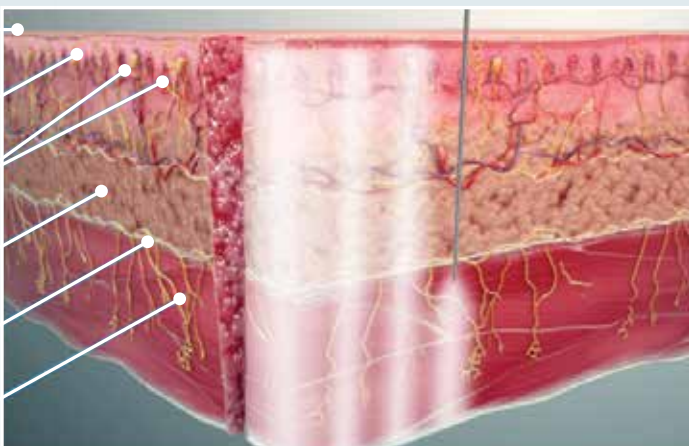


Image source: Pacira

Bunionectomy¹

106 mg (8 mL) of EXPAREL[®]

How to use: 7 mL infiltrated into the tissues surrounding the osteotomy and 1 mL infiltrated into the subcutaneous tissue.

Haemorrhoidectomy¹

266 mg (20 mL) of EXPAREL[®]

How to use: Considering the size of the surgical wound EXPAREL[®] can be expanded with 10 mL of normal saline, total 30 mL. Dosage could be divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block into the subcutaneous tissue.

Shoulder surgery¹

(Total shoulder arthroplasty or rotator cuff repair)

133 mg (10 mL) of EXPAREL[®]

How to use: EXPAREL[®] expanded with 10 mL of normal saline, for a total volume of 20 mL for a brachial plexus nerve block.

Total knee arthroplasty¹

(TKA)

266 mg (20 mL) of EXPAREL[®]
for a femoral nerve block.

EXPAREL[®] is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan. Sensory and/or motor loss may occur with EXPAREL[®] use, however, this is temporary and degree of loss and duration varies depending on the site of injection and dosage administered. As seen during clinical trials, any temporary sensory and/or motor loss may last for up to 5 days.¹

**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 re-dosing 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, paraesthesia, 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. Increa-

sed 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 methaemoglobinemia 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 - dapson, 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, pipercolonylidide, 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 ($\geq 1/100$ to $< 1/10$): dysgeusia, vomiting, constipation, hypoaesthesia oral, nausea. Serious uncommon ($\geq 1/1000$ to $< 1/100$): motor dysfunction, bradycardia, tachycardia, blood creatinine increased, alanine aminotransferase increased, aspartate aminotransferase increased; Serious Rare ($\geq 1/10,000$ 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
Dundrum Business Park
Dundrum
Dublin 14, D14W9Y3
Ireland

UK

Pacira Ltd
Wessex House, Marlow Road
Bourne End
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. 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.

Ordering EXPAREL®

If you would like to purchase EXPAREL®, please contact XXX YYY and order by fax or email:

//PLACEHOLDER: HOW TO ORDER EXPAREL//

For all questions regarding delivery of EXPAREL®, please contact xyz xyz xyz xyz

References

1. EXPAREL® SmPC December 2020.
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.

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