EXPAREL Liposomal Bupivacaine - Full Clinical Guideline

Reference no.:CG-CLIN/4245/23

1. Introduction

Managing post-operative pain is an important role of the anaesthetist. Regional anaesthetic blocks are used as part of opioid-sparing and multi-modal analgesic plans. Bupivacaine is the commonly used local anaesthetic for such post-operative analgesia, which lasts for approximately 8 hours. Because the pain of many surgical procedures extends beyond the duration of analgesia provided with a single administration, it can be administered as an infusion via a nerve catheter and an elastomeric pump to prolong its effect. Inserting a nerve catheter is a specialist skill that not every anaesthetist is capable of performing, and extra resources (i.e. time, equipment, monetary) are required for the placement and maintenance of nerve catheters. We propose that a regional block with the addition of liposomal bupivacaine can be used as an alternative to the placement of a nerve catheter, which requires no additional skill or resources.

Liposomal bupivacaine consists of bupivacaine encapsulated in a multivesicular liposomal drug delivery system. The liposome slowly releases the local anaesthetic, providing analgesic effects that can last up to 96 hours.

Liposomal bupivacaine has been studied in clinical trials in adults for several different surgical procedures, and shown to be effective in controlling post-operative pain vs placebo or bupivacaine.

2. Aim and Purpose

This document aims to provide guidance on the use of liposomal bupivacaine in popliteal blocks in cases where we would previously have used a popliteal catheter (i.e. below knee amputations and complex ankle and foot surgery).

3. Definitions, Keywords

EXPAREL: the brand name of bupivacaine liposomal injectable solution

Popliteal block: a regional nerve block that targets the sciatic nerve in the popliteal fossa

4. Guidelines for the use of EXPAREL liposomal bupivacaine

4.1 Indications

Perineural infiltration for the management of post-operative pain in adults, currently **ONLY** to be used for popliteal blocks and saphenous / adductor canal blocks in patients who would otherwise have a of popliteal catheter sited for major foot/ankle surgery and below knee amputations. This is NOT currently approved for use in patients who would normally receive a single shot block of standard (levo)bupivacaine without a nerve catheter. Whilst approved by the FDA, the use of EXPAREL in popliteal blocks is currently off licence in the UK.

4.2 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Hypersensitivity to amide type local anaesthetics
- Intra-vascular administration
- Intra-articular administration
- Epidural or intrathecal injection

4.3 Cautions

Pregnancy: Not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding: Very little plasma bupivacaine is transferred into breast milk and bupivacaine does not accumulate in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue EXPAREL taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.4 Presentation

EXPAREL liposomal prolonged-release dispersion for injection.

White to off-white aqueous liposomal dispersion.

Vials come in two sizes, each mL contains 13.3 mg bupivacaine

- **133 mg/10 mL** (equivalent to 150 mg of bupivacaine HCl)
- **266 mg/20 mL** (equivalent to 300 mg of bupivacaine HCl)

4.5 Storage

Store unopened vials in a refrigerator (2°C to 8°C). Do not freeze. Once removed from the refrigerator, vials have a shelf-life of 30 days. Vials should not be re-refrigerated.

4.6 Dose

The manufacturer recommends a maximum dose of **266 mg** (20 mL undiluted product) for adults >17 years. As EXPAREL is a slow release product, the plasma levels of bupivacaine remain below well below toxicity thresholds, and there is no peak as such. When calculating the maximum dose of local anaesthetic for a patient, the EXPAREL component for practical purposes can be omitted.

4.7 Preparation and administration

It is recommended that EXPAREL is **ALWAYS** admixed with levobupivacaine or bupivacaine. On its own, EXPAREL has a very slow onset time and has minimal intra-operative or immediate post-operative benefit.

NEVER mix with any other amide local anaesthetic (e.g. lidocaine, ropivacaine, mepivacaine) because this can displace bupivacaine from the liposome.

- Remove vial from refrigerator and allow to come up to room temperature before use
- Gently invert the vial multiple times to re-suspend the particles in the suspension immediately prior to withdrawal from the vial
- Draw up using a non-filter needle, minimum 25G
- Do not use needles smaller than 25G for injection

4.8 Suggested recipe

20ml EXPAREL + 20ml 0.5% (levo)bupivacaine

- **20-25 mL at bifurcation of sciatic nerve**
- **10-15 mL saphenous nerve in adductor canal**

Bupivacaine hydrochloride (immediate release formulations) and EXPAREL may be administered simultaneously in the same syringe as long as the ratio of the milligram dose of bupivacaine solution to EXPAREL does not exceed 1:2 (i.e. 75mg bupivacaine to 133mg EXPAREL or 100mg bupivacaine to 266mg EXPAREL).

If preparing admixture, the total amount of bupivacaine used (EXPAREL + Bupivacaine HCl) should not exceed 400mg equivalents of Bupivacaine HCl in adults.

In patients with **body weight of 50kg or less a ceiling dose of 4mg/kg** Exparel should be used. For ease of use weight can be rounded down to the nearest 5kg and the following volumes used:

Patient Weight	Exparel Volume
50 kg	15 ml
45 kg	13.5 ml
40 kg	12 ml
35 kg	10.5 ml
30 kg	9 ml

The accompanying ceiling dose of levobupivacaine can be calculated separately using the standard ceiling dose of 2mg/kg.

4.9 Common side effects (>5%)

- Dysgeusia
- Oral hypoaesthesia

4.10 Serious adverse reactions

Central Nervous System (CNS) Reactions: There have been reports of adverse neurologic reactions with the use of local anaesthetics. These include persistent anaesthesia and paraesthesia. 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 (e.g. anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anaesthetic or to other formulation ingredients.

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

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

See Appendix 1 for the management of local anaesthetic toxicity.

4.11 Follow up and audit

All patients receiving liposomal bupivacaine should be referred to the acute pain team for follow up. The acute pain team will audit all EXPAREL popliteal blocks performed to assess the efficacy of this technique for future service development. The audit form should be started by the anaesthetist in theatre and placed in the patient's notes for the acute pain team to complete. See appendix 2.

5. References

- Pacira Biosciences (2023) EXPAREL liposomal 266 mg/20 mL prolonged-release dispersion for injection SmPC
- https://www.exparel.com/hcp/about-exparel/exparel-liposomal-bupivacaine
- Malik O, Kaye AD, Kaye A, Belani K, Urman RD. Emerging roles of liposomal bupivacaine in anesthesia practice. Journal of Anaesthesiology, Clinical Pharmacology. 2017 33(2):151-156
- Ilfield BM, Eisenach JC and Gabriel RA. Clinical effectiveness of liposomal bupivacaine administered by infiltration or peripheral nerve block to treat postoperative pain: a narrative review. Anaesthesiology. 2021 134: 283–344

6. Documentation Controls

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<tr><td>1.1</td><td>Jan 24</td><td>Stefan Valdinger</td><td>Correction to drug ampoule (should not be shaken) and dosing guidance for low body weight patients.</td></tr>
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7. Appendices

7.1 Appendix 1 – Local anaesthetic toxicity QRH

3-10 Local anaesthetic toxicity v.1

Signs of severe toxicity:
- Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions.
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur.
- Local anaesthetic toxicity may occur some time after an initial injection.

START

1. Stop injecting the local anaesthetic (remember infusion pumps).
2. Call for help and inform immediate clinical team of problem.
3. Call for cardiac arrest trolley and lipid rescue pack.
4. Give 100% oxygen and ensure adequate lung ventilation:
   - Maintain the airway and if necessary secure it with a tracheal tube.
   - Hyperventilation may help reduce acidosis.
5. Confirm or establish intravenous access.
6. **If circulatory arrest:**
   - Start continuous CPR using standard protocols.
   - **Give** intravenous lipid emulsion (Box A).
   - Recovery may take >1 hour.
   - Consider the use of cardiopulmonary bypass if available.

   If no circulatory arrest:
   - Conventional therapies to treat hypotension, brady- and tachyarrhythmia.
   - **Consider** intravenous lipid emulsion (Box A).
7. Control seizures with small incremental dose of benzodiazepine, thiopental or propofol.

Box A: LIPID EMULSION REGIME

USE 20% Intralipid® (propofol is not a suitable substitute)

Immediately
- Give an initial i.v. bolus of lipid emulsion 1.5 $ml.kg^{-1}$ over 1 min (~100 ml for a 70 kg adult)
- Start an i.v. infusion of lipid emulsion at 15 $ml.kg^{-1}.h^{-1}$ (17.5 $ml.min^{-1}$ for a 70 kg adult)

At 5 and 10 minutes:
- Give a repeat bolus (same dose) if:
  - cardiovascular stability has not been restored or
  - an adequate circulation deteriorates

At any time after 5 minutes:
- Double the rate to 30 $ml.kg^{-1}.h^{-1}$ if:
  - cardiovascular stability has not been restored or
  - an adequate circulation deteriorates

Do not exceed maximum cumulative dose 12 $ml.kg^{-1}$ (70 kg: 840 ml)

Box B: CRITICAL CHANGES

If cardiac arrest, continue lipid emulsion and → **2-1**

Box C: AFTER THE EVENT

Arrange safe transfer to appropriate clinical area
Exclude pancreatitis: regular clinical review, daily amylase or lipase
Report cases to MHRA: https://yellowcard.mhra.gov.uk/

7.2 Appendix 2 – Data collection and audit form

Liposomal bupivacaine audit

Patient sticker

Date of surgery:

Operation:

Location of operation:

Analgesics taken regularly/prn prior to surgery:

Surgeon: **Anaesthetist:**

Anaesthetic technique (circle all that apply): GA / RA / sedation

Local anaesthetic in popliteal block:

(Levo)bupivacaine: 0.25% / 0.5% ____ml
EXPAREL liposomal bupivacaine ____ml
Giving a total mixed volume of ____ml

Volume of mix administered to the popliteal fossa: ____ml
Volume of mix administered to the adductor canal / saphenous nerve: ____ml

Anaesthetic concerns:

Any intraoperative issues (e.g. pain, nausea, neurological or cardiovascular disturbances):

Any immediate postoperative complications (e.g. pain/nausea):

Post-op day:	**Immediate post-op**	**1**	**2**	**3**
Pain scores (none/mild/mod/severe)				
Analgesics taken (drugs and dose)				
Nausea / Vomiting (none/mild/mod/severe)				
Sleep (good/fair/poor)	**X**			
Constipation (none/mild/mod/severe)	**X**			
Mobility (good/fair/poor)	**X**			
Residual foot numbness i.e. touch sensation (not pain) (present/absent)				

Overall patient satisfaction with post-operative analgesia: poor / fair / good / excellent

Date of discharge:

Analgesics on discharge: