Long-acting bupivacaine products side-by-side comparison

June 2023

About this document

This abbreviated side-by-side comparison reviews liposomal bupivacaine (Exparel) and bupivacaine and meloxicam solution (Zynrelef). Bupivacaine solution (Posimir) and bupivacaine implant (Xaracoll) are not included in this review given their narrow indications and distinct methods of administration. Liposomal bupivacaine and bupivacaine and meloxicam solution share several possible indications based on broader FDA-approved labeling. Efficacy for each of these agents is not reviewed in this document. For a detailed review of the evidence for liposomal bupivacaine and bupivacaine and meloxicam solution, please refer to the 2023 Vizient expert panel white paper on long-acting bupivacaine products.

Long-acting bupivacaine product side-by-side comparison

	Generic name (brand name)	
	Liposomal bupivacaine (Exparel)[a]	**Bupivacaine and meloxicam solution (Zynrelef)[b]**
Manufacturer	Pacira Pharmaceuticals	Heron Therapeutics
Approval date	October 28, 2011	May 12, 2021
FDA-approved indications		
Pediatric use	Yes	No
Adult use	Yes	Yes
Indications	• For use in patients ≥ 6 y of age for single-dose infiltration to produce postsurgical analgesia. • For use in adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.	For use in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 h after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.
Limitations of use	Safety and efficacy have not been established in other nerve blocks.	Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.
Pharmacology		
Mechanism of action	**Bupivacaine:** Local anesthetics block the generation and conduction of nerve impulses by increasing the threshold of electrical excitation, slowing nerve impulse propagation, and reducing the rate of rise of the action potential.	
	--	**Meloxicam:** The mechanism of action for NSAIDs is not completely understood, but involves inhibition of COX-1 and COX-2, which leads to the inhibition of prostaglandin synthesis. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain. Prostaglandins are also mediators of inflammation. Meloxicam in bupivacaine and meloxicam solution is specifically included to reduce local inflammation and normalize pH, which is purported to provide synergistic effect by enhancing the uptake of bupivacaine.[c,d]
Pharmacodynamics	**Bupivacaine:** Systemic absorption of local anesthetics can produce effects on the cardiovascular and CNS. With normal therapeutic doses, manifestations of CNS stimulation or depression or cardiovascular effects are minimal. Clinical reports and animal research suggest cardiovascular changes are more likely following unintended IV injection of bupivacaine.	
	--	**Meloxicam:** Phase 2 studies evaluated the contribution of each active ingredient in bupivacaine and meloxicam solution using the Zynrelef polymer vehicle. Meloxicam alone demonstrated negligible local analgesia. Bupivacaine and meloxicam together produced greater and longer-lasting analgesia through 24, 48, and 72 h compared with bupivacaine alone.

<table>
<tr><th></th><th colspan="2">Generic name (brand name)</th></tr>
<tr><th></th><th>Liposomal bupivacaine (Exparel)[a]</th><th>Bupivacaine and meloxicam solution (Zynrelef)[b]</th></tr>
<tr><td>Pharmacokinetics (adults)</td><td>
Bupivacaine
<table>
<tr><th>Parameter*</th><th>Bunionectomy (106 mg) via infiltration</th><th>Hemorrhoidectomy (266 mg) via infiltration</th><th>Total shoulder arthroplasty (133 mg) via interscalene brachial plexus block</th></tr>
<tr><td>Cmax (ng/mL)</td><td>166 (93)</td><td>867 (353)</td><td>207 (137)</td></tr>
<tr><td>Tmax (h)</td><td>2 (0.5, 24)</td><td>0.5 (0.25, 36)</td><td>48 (3, 74)</td></tr>
<tr><td>AUC (h x ng/mL)</td><td>0-72h: 5,864 (2,038)</td><td>0-72h: 16,867 (7,868)</td><td>0-120h: 11,484 (8,615)</td></tr>
<tr><td>Half-life (h)</td><td>34 (17)</td><td>24 (39)</td><td>11 (5)</td></tr>
</table>
*Results are presented as arithmetic mean (SD) except Tmax where it is median (minimum, maximum)
</td><td>
Bupivacaine
<table>
<tr><th>Parameter*</th><th>Bunionectomy (60 mg/1.8 mg) via instillation</th><th>Herniorrhaphy (300 mg/9 mg) via instillation</th><th>TKA (400 mg/12 mg) via instillation</th></tr>
<tr><td>Cmax (ng/mL)</td><td>54 (33)</td><td>271 (147)</td><td>695 (411)</td></tr>
<tr><td>Tmax (h)</td><td>3 (1.6, 24)</td><td>18 (3, 30)</td><td>21 (4, 59)</td></tr>
<tr><td>AUC (h x ng/mL)</td><td>0-120h: 1,681 (1,154)</td><td>0-120h: 15,174 (8,545)</td><td>0-144h: 35,890 (28,400)</td></tr>
<tr><td>Half-life (h)</td><td>15 (8)</td><td>16 (9)</td><td>17 (7)</td></tr>
</table>
*Results are presented as arithmetic mean (SD) except Tmax where it is median (minimum, maximum)

Meloxicam
<table>
<tr><th>Parameter*</th><th>Bunionectomy (60 mg/1.8 mg) via instillation</th><th>Herniorrhaphy (300 mg/9 mg) via instillation</th><th>TKA (400 mg/12 mg) via instillation</th></tr>
<tr><td>Cmax (ng/mL)</td><td>26 (14)</td><td>225 (96)</td><td>275 (134)**</td></tr>
<tr><td>Tmax (h)</td><td>18 (8, 60)</td><td>54 (24, 96)</td><td>36 (12, 72)</td></tr>
<tr><td>AUC (h x ng/mL)</td><td>0-120h: 1,621 (927)</td><td>0-120h: 18,721 (7,923)</td><td>0-144h: 19,525 (12,259)</td></tr>
<tr><td>Half-life (h)</td><td>33 (36)</td><td>Not reported</td><td>42 (37)</td></tr>
</table>
*Results are presented as arithmetic mean (SD) except Tmax where it is median (minimum, maximum)
** For reference: Cmax following single 15 mg of oral meloxicam is approximately 10-fold, or greater, with a concentration of 2,300 to 3,200 ng/mL.[e]
</td></tr>
<tr><td>Long-acting delivery system</td><td>Multivesicular liposomes</td><td>Biochronomer polymer[d]</td></tr>
<tr><td colspan="3">Dosage and administration</td></tr>
<tr><td>Preparation and handling</td><td>
• Inspect vials for particulate matter and discoloration prior to use.
• Invert vials to re-suspend particles immediately prior to withdrawal from vial; multiple inversions may be necessary if vial contents have settled.
</td><td>
• Inspect vials for particulate matter and discoloration prior to use.
• Supplied as a kit consisting of single-dose vial, vented vial spike, Luer Lock syringe, Luer Lock applicator, and syringe tip cap. Only prepare and administer product with components from kit.
</td></tr>
</table>

	Generic name (brand name)	
	Liposomal bupivacaine (Exparel)[a]	**Bupivacaine and meloxicam solution (Zynrelef)[b]**
	• Do not filter. • Following removal from vial, product may be stored for up to 4 h at room temperature between 20 to 25˚C. • May be diluted to increase volume up to a final concentration of 0.89 mg/mL (ie, 1:14 dilution by volume) with normal saline or lactate Ringer's solution.	• Prepare vial for filling of syringes by attaching vented vial spike. Prepare syringe by filling with air and attaching to vented vial spike. • Invert to allow product to fill the vial neck and push air into vial. Withdraw dose of bupivacaine and meloxicam solution into the syringe. Repeat as needed to prepare more than 1 syringe. Refer to product labeling for additional information. • Prepare product immediately prior to use and apply syringe cap until product is administered. • Do not dilute or mix with other products. Bupivacaine and meloxicam solution is nonaqueous; mixing with other products will cause the product to become more viscous and difficult to administer.

Dosage	Adults
	• **Injection site infiltration:** The recommended dose is based on the size of the surgical site, volume required to cover the area, and individual patient factors. The following general guidance is provided in product labeling:
	  ○ *Bunionectomy:* Patients received 106 mg (8 mL) of liposomal bupivacaine in clinical studies
	  ○ *Hemorrhoidectomy*: Patients received 266 mg (20 mL) of liposomal bupivacaine in clinical studies
	  ○ Maximum recommended dose is 266 mg
	• **Interscalene brachial plexus block**: The recommended dose is 133 mg (10 mL) based on studies evaluating total shoulder arthroplasty or rotator cuff repair.
	
	Pediatric
	• **Injection-site infiltration:** The recommend dose is 4 mg/kg (up to a maximum of 266 mg) based on clinical studies evaluating spine and cardiac surgery.
		Injection-site instillation: The recommended dose will vary based on surgical site. The following general guidance is provided in product labeling:
		• *Foot and ankle surgical procedures:* Use up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam
		• *Small-to-medium abdominal surgical procedures:* Use up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam
		• *Lower extremity total joint arthroplasty:* Use up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam

Administration	**Injection-site infiltration** • Administer undiluted or diluted to increase volume up to a final concentration of 0.89 mg/mL (ie, 1:14 dilution by volume) with normal saline or lactate Ringer's solution. • Inject slowly (generally as 1 to 2 mL per injection) with frequent aspiration to check for blood and minimize risk of inadvertent intravascular injection.	• Remove syringe tip cap and attach Luer Lock applicator to the syringe. • See product labeling for recommended sites of administration based on surgery type. • Apply to surgical site without a needle following final irrigation and suctioning, and prior to suturing of each layer when multiple tissue layers are involved. Only apply to tissue layers below the skin

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	• Administer with a 25 gauge or larger bore needle.	incision and not directly onto the subdermal layer of the skin. Minimize administration near the incision line. • Wipe off excess product from skin prior to or during closure of the wound.
Ability to mix with standard bupivacaine	**Yes**, standard bupivacaine (but not other local anesthetics) may be admixed with liposomal bupivacaine as long as the ratio does not exceed 1:2.	**No*** **Cannot mix. However, local anesthetics, including ropivacaine and lidocaine, have been administered separately before, during, or after application of bupivacaine and meloxicam solution without evidence of local anesthetic toxicity (see drug-drug interactions for more information).*
Safety		
Boxed warning	None	Risk of serious cardiovascular and gastrointestinal events* **Standard box warning for NSAIDs included in product labeling due to inclusion of meloxicam in this product.*
Contraindications (*as reported in product labeling*)	Obstetrical paracervical block anesthesia.	
	--	• Known hypersensitivity to any local anesthetic agent of the amide-type, NSAID, or any other component in product. • Patients with history of asthma, urticaria, or other allergic-type reaction following aspirin or other NSAIDs. • Patients undergoing coronary artery bypass graft surgery.
Precautions	• **Impaired cardiovascular function:** Patients with impaired cardiovascular function may be less able to compensate for functional changes associated with prolongation of atrioventricular node conduction produced by anesthetics. • **Hepatotoxicity:** Amide-type local anesthetics are metabolized in the liver; use cautiously in patients with hepatic disease. • **Dose-related toxicity:** The toxic effects of local anesthetics are additive; avoid additional local anesthetic administration within 96 h. If additional anesthetic cannot be avoided, monitor for cardiovascular and CNS effects. • **Methemoglobinemia:** Cases of methemoglobinemia have been reported in association with local anesthetic use. • **Chondrolysis:** Intra-articular infusions of local anesthetics following arthroscopic or other surgical procedures is an unapproved use. Limit exposure to articular cartilage due to potential risk of chondrolysis.	
	• **Allergic reactions:** Allergic reactions may rarely occur as a result of hypersensitivity to local anesthetic or other formulation ingredients.	• **Type of analgesia/route of administration:** Not intended for epidural use, intrathecal use, regional nerve blocks, intravascular or intra-articular use, or for pre-incisional or preprocedural locoregional anesthetic techniques.

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	• **IV administration:** Avoid accidental IV injection of liposomal bupivacaine. • **Type of analgesia/route of administration:** Liposomal bupivacaine has not been evaluated in and is not recommended for epidural use, intrathecal use, regional nerve blocks other than interscalene brachial plexus block, intravascular or intra-articular use. • **Populations:** Liposomal bupivacaine has not been evaluated in and is not recommended for use in patients < 6 y of age, patients <18 y of age for interscalene brachial plexus block, and pregnant patients. • **Sensory or motor loss:** Temporary sensory and motor loss varies in degree and duration; may last for up to 5 d as seen in clinical trials.	NSAID-specific* • **Cardiovascular thrombotic events with NSAID use:** NSAIDs may increase risk of serious cardiovascular thrombotic events. • **Gastrointestinal bleeding, ulceration, and perforation with NSAID use:** NSAIDs may cause serious gastrointestinal events. • **Elevation of liver function tests:** NSAIDs have been associated with elevations of ALT or AST ≥ 3 times the upper limit of normal in 1% of patients and < 3 times the upper limit of normal in 15% of patients. • **Hypertension:** NSAIDs can lead to new or worsening pre-existing hypertension. • **Heart failure or edema:** NSAID use may increase risk of MI, hospitalization for heart failure, and death. • **Renal toxicity and hyperkalemia:** Renal effects of meloxicam may hasten progression of renal dysfunction in patients with pre-existing renal disease. Renal toxicity has been observed in patients in whom renal prostaglandins have a compensatory role in maintaining renal perfusion (eg, dehydration, hypovolemic, impaired renal function. heart failure, liver dysfunction, taking diuretics or ACE/ARB, and elderly). • **Anaphylactic reactions:** Anaphylactic reactions have been reported with NSAID use, including meloxicam. • **Hematologic toxicity:** Anemia may occur in patients receiving NSAIDs. • **Masking of inflammation and fever:** NSAIDs may reduce inflammation and fever which may diminish utility of diagnostic signs in detecting infections. • **Exacerbation of asthma related to aspirin sensitivity:** A subpopulation of patients with asthma may have aspirin-sensitive asthma; cross reactivity with NSAIDs and aspirin is possible; therefore NSAIDs are contraindicated in these patients. • **Serious skin reactions:** NSAIDs can cause serious skin reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. • **Drug reaction with eosinophilia and systemic symptoms (DRESS):** DRESS has been reported in patients taking NSAIDs.

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		• **Fetal toxicity:** Avoid NSAIDs in pregnant women at ≥ 30 wks gestation due to risk of premature closure of fetal ductus arteriosus. Use of NSAIDs at ≥ 20 wks gestation may cause fetal renal dysfunction. *These are *standard precautions for NSAIDs included in product labeling due to inclusion of meloxicam in this product. Applicability to single-dose administration with bupivacaine and meloxicam solution is unclear.*
Adverse reactions	• **Via infiltration (adults):** most common (incidence ≥ 10%) adverse reactions are nausea, constipation, and vomiting • **Via infiltration (pediatric):** most common (incidence ≥ 10%) adverse reactions are nausea, vomiting, constipation, hypotension, anemia, muscle twitching, vision blurred, pruritus, and tachycardia • **Via nerve block:** most common (incidence ≥ 10%) adverse reactions are nausea, pyrexia, and constipation	**Via instillation:** most common (incidence ≥ 10%) adverse reactions are constipation, vomiting, and headache
Drug-drug interactions (*as reported in product labeling*)	**Bupivacaine** • *Standard bupivacaine:* May be mixed together with liposomal bupivacaine in the same syringe or injection immediately before liposomal bupivacaine as long as the ratio does not exceed 1:2. • *Non-bupivacaine local anesthetics:* Do not mix liposomal bupivacaine with local anesthetics other than bupivacaine, as this may cause an immediate release of bupivacaine. Liposomal bupivacaine may be administered following a delay of ≥ 20 min after lidocaine administration. Data for use with other local anesthetics are not available. • *Water and hypotonic agents:* Do not dilute liposomal bupivacaine with water or other hypotonic agents as this will disrupt the liposomal particles. • Toxic effects of local anesthetics are additive. Avoid use of local anesthetics within 96 h following administration of liposomal bupivacaine. If co-administration cannot be avoided, monitor for cardiovascular and CNS effects. • Patients administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed with certain medications. Refer to product labeling for listing of these medications.	**Bupivacaine** • Local anesthetics, including ropivacaine and lidocaine, have been administered separately before, during, or after application of bupivacaine and meloxicam solution without evidence of local anesthetic toxicity. Administration with other formulations, such as liposomal bupivacaine, has not been evaluated. • Toxic effects of local anesthetics are additive. Avoid use of local anesthetics within 96 h following administration of bupivacaine and meloxicam solution. If co-administration cannot be avoided, monitor for cardiovascular and CNS effects. • Patients administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed with certain medications. Refer to product labeling for listing of these medications. **Meloxicam** • Refer to product labeling for listing of drug-drug interactions* for meloxicam. **Note: These drug interactions are the standard interactions listed in product labeling for NSAIDs and are primarily derived from studies looking at systemic NSAID exposure.*

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Special populations		
Pregnancy and lactation	No data are available on use of liposomal bupivacaine in pregnancy or lactation in humans. Refer to product labeling for general considerations related to the use of bupivacaine in pregnancy and lactation.	No data are available on use of bupivacaine and meloxicam solution in pregnancy or lactation in humans. Refer to product labeling for general considerations related to the use of bupivacaine or NSAIDS in pregnancy and lactation.
Pediatric population	Approved for use via single-dose infiltration in patients ≥ 6 y of age. Safety and effectiveness of this product in patients < 6 y of age have not been established. Safety and effectiveness for use as an interscalene brachial plexus block has not been established in patients < 18 y of age.	Safety and effectiveness not established in pediatric patients.
Geriatric population	No differences in safety or efficacy were observed between younger and older (≥ 65 y) patients in clinical trials; however, greater sensitivity of some older individuals may be possible.	
Renal impairment	Bupivacaine is substantially excreted by the kidney; risk of toxic reactions may be greater in patients with impaired renal function.	Bupivacaine, meloxicam, and their metabolites are excreted by the kidney; risk of toxic reactions may be greater in patients with impaired renal function.
Hepatic impairment	Amide-type local anesthetics are metabolized in the liver; use cautiously in patients with hepatic disease.	
How supplied		
Product description	White to off-white milky aqueous suspension	Clear, pale-yellow to yellow viscous liquid
Supplied as	Single-dose vial • 20 mL vial: 266 mg • 10 mL vial: 133 mg	Supplied as kit including single-dose vial (14 mL or 7 mL), vented vial spike, Luer Lock syringe, Luer Lock applicator, and syringe tip cap. Volume of Luer Lock syringe and number of Luer Lock applicators and syringe caps vary based by kit. Bupivacaine/meloxicam kits: • **400 mg/12 mg (14 mL)**, 1 vented vial spike, two 12 mL Luer Lock syringes, 2 Luer Lock applicators, and 2 syringe tip caps • **300 mg/9 mg (10.5 mL)**, 1 vented vial spike, one 12 mL Luer Lock syringe, 1 Luer Lock applicator, and 1 syringe tip cap • **200 mg/6 mg (7 mL)**, 1 vented vial spike, one 12 mL Luer Lock syringe, 1 Luer Lock applicator, and 1 syringe tip cap • **60 mg/1.8 mg (2.3 mL)**, 1 vented vial spike, one 3 mL Luer Lock syringe, 1 Luer Lock applicator, and 1 syringe tip cap

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Storage	Store vials refrigerated between 2 to 8˚C. May be stored at room temperature between 20 to 25˚C for up to 30 d (do not re-refrigerate vials). Do not freeze.	Store kit at room temperature between 20 to 25˚C. Protect vials from light during storage if removed from kit.
Cost information		
WAC[f]	• 20 mL vial: $365 • 10 mL vial: $215	• 14 mL vial-based kit: $281 • 7 mL vial-based kit: $142
Brand manufacturer participates in 340B Drug Pricing Program[g-i]	Yes	Yes
Vizient contract	No	Yes
Reimbursement information[g,j,k]		
Inpatient	Not reimbursed separately; bundled with MS-DRG payment	
ASC	Reimbursed at ASP + 6%	
HOPD	Not separately reimbursed* ** May become eligible for reimbursement in HOPD setting in 2025 as part of the NOPAIN act.[l-n]*	Reimbursed at ASP + 6%; 3-y pass-through status effective April 1, 2022* **May be extended through 2027 as part of the NOPAIN act.[l,m,o]*
Generic availability	No	No
Anticipated LOE[p]	2041 *Note: ANDA filed by eVenus Pharmaceutical/Fresenius – on hold until March 24, 2024 due to patent litigation*	2035
Product training and education resources	• Connect with representative • Healthcare provider resources • Patient and practice resources	• Request meeting with representative by navigating to the yellow "Let's Connect" button on the right side on the Zynrelef website • Product resource center (includes videos on preparation and administration)
Efficacy	See 2023 Vizient expert panel whiter paper on long-acting bupivacaine products	

Abbreviations: ACE = angiotensin converting enzyme; ALT = alanine aminotransferase; ANDA = abbreviated new drug application; ARB = angiotensin receptor blocker; ASC = ambulatory surgery center; ASP = average selling price; AST = aspartate aminotransferase; AUC = area under the curve; Cmax = maximum concentration; CNS = central nervous system; HOPD = hospital outpatient department; IV = intravenous; LOE = loss of exclusivity; MI = myocardial infarction; MS-DRG = Medicare Severity Diagnosis-Related Group; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; TKA = total knee arthroplasty; Tmax = time to maximum concentration; WAC = wholesale acquisition cost

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Vizient, Inc.
290 E. John Carpenter Freeway
Irving, TX 75062-5146
(800) 842-5146

To learn more, please contact
Vizient Center for Pharmacy Practice Excellence, Evidence-Based Medicine Group at
pharmacyquestions@vizientinc.com.

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