CCHCS Pharmacy and Therapeutics Formulary Monograph

Physician Requesting Medication:	**Artee Gandhi, MD**	**Date Requested:**	**June 2019**
Generic Name:	**Liposomal bupivacaine 1.3%**	**Brand Name:**	**Exparel®**
Manufacturer:	**Pacira Pharmaceuticals, Inc.**	**NDC: 6525-133-04 (10 mL), 6525-266-04 (20 mL)**	
Cost:	**$21.01/ mL**	**Included on Medicaid Formulary?**	**No**

Therapeutic Class: Local anesthetic

Mechanism of Action: Blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

FDA approved indication: Infiltration for local anesthesia for bunionectomy or hemorrhoidectomy; Interscalene brachial plexus nerve block for total shoulder arthroplasty or rotator cuff repair

Other indications: N/A

Dosage Forms: Suspension for injection 1.3% (10 mL, 20 mL)

Dosing:
Bunionectomy: 7 mL of undiluted liposomal bupivacaine infiltrated into the tissues surrounding the osteotomy and 1 mL infiltrated into the subcutaneous tissue of the surgical site (total dose = 106 mg [8 mL])
Hemorrhoidectomy: 30 mL of diluted liposomal bupivacaine (20 mL diluted with 10 mL of NS) divided and infiltrated as 6 injections of 5 mL each around the anal sphincter (total dose = 266 mg [20 mL])
Interscalene brachial plus nerve block for total shoulder arthroplasty or rotator cuff repair: single dose of 10 mL (total dose = 133 mg [10 mL])

Administration: Administer undiluted or diluted with NS or LR. Inject slowly into the surgical site using a ≥ 25 gauge needle with frequent aspiration prior to and during administration. Do not administer epidurally, intrathecally, intravascularly, intra-articularly. Do not allow liposomal bupivacaine to come into contact with antiseptics (ex. povidone iodine) in solution. When a topical antiseptic is applied, allow site to dry prior to injection.

Monitoring: Cardiovascular and respiratory (adequacy of ventilation) vital signs, state of consciousness, signs of CNS toxicity, and pain relief

Bioavailability & Pharmacokinetics:
- Onset: rapid
- Time to peak effect: within 1 hour (initial peak); 12 to 26 hours (second peak)
- Duration: local up to 72 hours; systemic effects 96 hours (after local injection) and 120 hours (after interscalene brachial plexus nerve block)
- Protein binding: 95%
- Half-life: 13 – 34 hours
- Excretion: urine (~6% unchanged)
- Metabolism: hepatic via conjugation (major inactive metabolite: pipecoloxylidine [PPX])

Pharmaceutics: Store intact vials at 2°C to 8°C (36°F to 46°F); may also store at 20°C to 25°C (68°F to 77°F) for up to 30 days (do not re-refrigerate). Do not heat or autoclave vials before use.
Following withdrawal from the vial, store at 20°C to 25°C (68°F to 77°F) up to 4 hours prior to administration. Diluted suspensions must be used within 4 hours of preparation. Do not freeze or expose to high temperature (>40°C [104°F]) for an extended period of time.

SAFETY EVALUATION

- Central nervous system (CNS) toxicity can occur when using this medication, including convulsions, unconsciousness, and/ or respiratory depression. Patients CNS status should be monitored after receiving this medication.
- Cardiovascular toxicity can occur when using this medication, including decreased cardiac output, hypotension, and arrhythmias. Continuous electrocardiogram should be monitored after receiving this medication.

- Local anesthetics have been associated with rare occurrences of sudden respiratory arrest. Respiratory rate and oxygen saturations should be monitored.
- Allergic-type reactions and possible anaphylactoid-like symptoms have been reported, although these are rare. Cross-sensitivity among amide-type local anesthetics has also been reported.
- Other adverse reactions include: motor dysfunction (12-21%), nausea (<40%), vomiting (28%), constipation (2-22%), fever (2-23%), hypertension (<10%), hypotension (7%), headache (4-8%), insomnia (2-10%), urinary retention (8%), and dysgeusia (7%)

LITERATURE REVIEW

Cloyd C, Moffett BS, Bernhardt MB, Monico EM, Patel N, Hanson D. Efficacy of liposomal bupivacaine in pediatric patients undergoing spine surgery. Pediatric Anesthesia 2018;28:982-986.
Patient Population: A total of 141 pediatric patients (47 received liposomal bupivacaine, 94 received standard bupivacaine) undergoing posterior spinal fusion

Intervention(s): Liposomal bupivacaine compared to standard bupivacaine (study was unable to determine the dose of the medications administered)

Endpoint(s): To evaluate the efficacy of liposomal bupivacaine compared to standard bupivacaine in patients undergoing posterior spinal fusion. The primary objective was to determine the difference in the total amount of intravenous (IV) morphine equivalents (mg/kg) in the first 72 hours of the post-operative period. The secondary objectives were to evaluate the difference in the total amount of IV acetaminophen (mg/kg) and IV ketorolac (mg/kg) received.

Methods: Retrospective matched cohort between February 2011 and May 2016

Results: There was no statistically significant difference between liposomal bupivacaine and standard bupivacaine in regards to the total amount of IV morphine received in the first 72 hours of the post-operative period (liposomal: 2.02 ± 0.98 mg/kg vs. standard: 1.76 ± 0.82 mg/kg [p=0.14]). There was also no difference in the amount of IV acetaminophen received (liposomal: 58.6 ± 49.8 mg/kg vs. standard: 60.6 ± 54.8 mg/kg) or IV ketorolac (liposomal: 53.65 ± 2.8 mg/kg vs. standard: 3.3 ± 2.5 mg/kg).

Conclusion: Liposomal bupivacaine may not be beneficial for patients undergoing posterior spinal fusions, however further studies are needed to determine the efficacy in this patient population.

Day KM, Nair NM, Griner D, Sargent LA. Extended release liposomal bupivacaine injection (Exparal) for early postoperative pain control following pharyngoplasty. J Craniofac Surg 2018;29(3):726-730.
Patient Population: A total of 60 pediatric patients (30 received liposomal bupivacaine, 30 received lidocaine + epinephrine) undergoing pharyngoplasty

Intervention(s): Patients that were in the liposomal bupivacaine group received 0.5% bupivacaine and 1:200,000 epinephrine at the beginning of surgery, as well as 1.3% liposomal bupivacaine at the end of surgery as a palatal block and posterior pharyngeal circumferential submucosal field block. The dosage of liposomal bupivacaine was determined in reference to the conventional recommended dosage of standard bupivacaine (2.5 mg/kg). Patients in the lidocaine with epinephrine group received 0.5% lidocaine with 1:200,000 epinephrine.

Endpoint(s): To investigate the efficacy of liposomal bupivacaine compared to lidocaine with epinephrine in patients undergoing pharyngoplasty. The primary objective was to determine the difference in the total amount of opioid medications in hydrocodone equivalents (mg/kg) in the first 7 2hours of the post-operative period. The secondary outcomes were to determine the total non-opioid medications administered, and compare the pain score (FLACC), hospital length of stay, and oral intake, including the time to first intake and the total intake in the first 24 hours.

Methods: Retrospective case control between March 2010 and June 2016

Results: There was a statistically significant decrease in the total amount of opioid medications (hydrocodone equivalents [mg/kg]) used in the first 72 hours post-operatively between liposomal bupivacaine and lidocaine with epinephrine (liposomal: 15.5 ± 10.9 mg/kg vs. lidocaine + epinephrine: 27.5 ± 19.1 mg/kg [p=0.0041]). There was no difference in the amount of ibuprofen received between groups (liposomal: 0 ± 0 mg/kg vs. lidocaine + epinephrine: 60 ± 241.6 mg/kg [p=0.18]) or the amount of acetaminophen received (liposomal: 262.8 ± 419.1 mg/kg vs. lidocaine + epinephrine: 166.7 ± 450.8 mg/kg [p=0.4]). The initial pain score for patients receiving liposomal bupivacaine was less in the PACU (0.1 ± 0.56 vs 1.2 ± 2.1 [p=0.0075]), however there was no difference 12 hours post-operative (4.5 ± 1.9 vs 3.9 ± 2 [p=0.44]), 24 hours post-operative (4 ± 1.4 vs 3.6 ± 2.5 [p=0.32]), or 36 hours post-operative (4.1 ± 2.8 vs 3 ± 1.6 [p=0.35]). Patients that received liposomal bupivacaine demonstrated faster time to their first oral intake (0.21 ± 0.12 hours vs 0.48 ± 0.39 hours [p=0.00061]), as well as increased total intake during the first 24 hours post-operative period (402.2 ± 351.6 mL vs 173 ± 207.5 mL [p=0.0032]). Patients that received liposomal bupivacaine also demonstrated a decreased hospital length of stay compared to those that received lidocaine with epinephrine (1.8 ± 0.82 days vs 2.8 ± 1.3 [p=0.00072]).

Conclusion: Liposomal bupivacaine appears safe and is associated with decreased opioid use, increased and earlier oral intake, and a shorter hospital stay for patients undergoing pharyngoplasty.

Day KM, Nair NM, Griner D, Sargent LA. Extended release liposomal bupivacaine injection (Exparal) for early postoperative pain control following palatoplasty. J Craniofac Surg 2018;29(5):e525-e528.
Patient Population: A total of 27 pediatric patients undergoing palatoplasty

Intervention(s): Received 0.5% bupivacaine with 1:200,000 epinephrine at the beginning of the procedure and 1.3% liposomal bupivacaine at the end of the procedure as a greater palatal nerve block and submucosal surgical field blocks. The mean liposomal bupivacaine dose was 2.6 ± 1.9 mg/kg.

Endpoint(s): To investigate the efficacy of liposomal bupivacaine in patients undergoing palatoplasty. The primary objective was to describe the total amount of opioid medications (hydrocodone equivalents [mg/kg]) received in the first 72 hours post-operative period, describe the average pain score (FLACC), the total amount of non-opioid medications administered, total hospital length of stay, and oral intake, including the time to first intake and the total intake in the first 24 hours.

Methods: Retrospective case series between August 2014 and December 2015

Results: The mean total opioid amount administered was 8.5 ± 8.4 mg/kg (hydrocodone equivalents). The mean cumulative doses administered were: acetaminophen 270.5 ± 300.7 mg/kg, IV ketorolac 0.33 ± 1.7 mg/kg, and ibuprofen 17.7 ± 51.3 mg/kg. The mean pain scores (FLACC) were: PACU admission 2.1 ± 1.3, overall PACU average 2.4 ± 2.2, and overall inpatient average 3.8 ± 1.8. The mean time to first oral intake was 10.3 ± 11.5 hours, and the mean total intake during the first 24 hour post-operative period was 244.2 ± 215.3 mL. The mean length of hospital stay was 2.1 ± 1.3 days.

Conclusion: Liposomal bupivacaine appears safe and may decrease opioid use and increase oral intake in patients undergoing palatoplasty.

RECOMMENDATION

☐ **Add to Formulary** ☒ Add to Formulary Restricted to: _Anesthesia_____
☐ Add to formulary; conduct MUE in ___ months ☐ Do not add to formulary

References:

1. Exparel® [package insert]. Parsippany, NJ: Pacira Pharmaceuticals, Inc. 2018.
2. Cloyd C, Moffett BS, Bernhardt MB, Monico EM, Patel N, Hanson D. Efficacy of liposomal bupivacaine in pediatric patients undergoing spine surgery. Pediatric Anesthesia 2018;28:982-986.
3. Day KM, Nair NM, Griner D, Sargent LA. Extended release liposomal bupivacaine injection (Exparal) for early postoperative pain control following pharyngoplasty. J Craniofac Surg 2018;29(3):726-730.

4. Day KM, Nair NM, Griner D, Sargent LA. Extended release liposomal bupivacaine injection (Exparal) for early postoperative pain control following palatoplasty. J Craniofac Surg 2018;29(5):e525-e528.
5. Cohen B, Gloasser L, Saab R, Walters M, Salih A, Zafeer-Khan M, et al. Incidence of adverse events attributable to bupivacaine liposomal injectable suspension or plain bupivacaine for postoperative pain in pediatric surgical patients: a retrospective matched cohort analysis. Pediatric Anesthesia 2019;29:169-174.
6. Santago-Dieppa, et al. Poster Title: Pilot safety trial of extended release liposomal bupivacaine (Exparel®) for postoperative analgesia in the adult and pediatric neurosurgical population. Abstract 309. Presented at 2019 Annual Meeting of the American Association of Neurological Surgeons.