Bupivacaine Liposome Injectable Suspension (EXPAREL®) National Drug Monograph June 2013

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Description

- Bupivacaine liposomal injectable suspension (Exparel®) is an amide-type local anesthetic in an encapsulated liposomal formulation developed with the goal of providing a longer duration of anesthesia compared with its non-liposomal counterpart, bupivacaine hydrochloride or other local anesthetics.
- The product utilizes the DepoFoam® drug delivery system consisting of an aqueous suspension of multivesicular liposomes containing bupivacaine in a honeycomb-like structure that allows for a more gradual release.
- The FDA approved bupivacaine liposomal in October 2011 for single-dose infiltration into the surgical site for postoperative analgesia.

Efficacy

- To date, there have been a limited number of published clinical trials evaluating the safety and efficacy of liposomal bupivacaine.
- Three phase 3 pivotal trials were reviewed by the FDA for final approval, two of them comparing liposomal bupivacaine to placebo and one comparing liposomal bupivacaine to unencapsulated bupivacaine HCl/epinephrine (unpublished). In each of the trials, the primary endpoint was pain intensity and duration using the numeric pain rating score through a predetermined period of time postoperatively (24, 72 and 96 hrs). In the placebo-controlled trials (1-bunionectomy[4], 1-hemorrhoidectomy[5]), liposomal bupivacaine was associated with statistically less intense pain through the stated time period compared to placebo. In addition, opioid consumption was statistically less in favor of liposomal bupivacaine versus placebo, but the clinical significance of the difference is unknown (Golf-3.8 vs. 4.7 tabs of oxycodone 5 mg/APAP 325 mg tablets at 24 hrs, p=0.008 and Gorfine-22.3 mg vs. 29.1 mg morphine equivalents at 72 hrs, p=0.0006). In an unpublished study, liposomal bupivacaine was not statistically different from unencapsulated bupivacaine HCl/epinephrine in reducing pain intensity through the specified time points or other secondary outcome measures in patients following hemorrhoidectomy.
- The FDA reviewer highlighted some important points regarding the results of these three trials as follows:

- In the two pivotal, placebo controlled trials, liposomal bupivacaine provided postoperative analgesia for up to 24 hours in patients having bunionectorny or hemorrhoidectomy surgery. In these studies, pain intensity was significantly reduced in patients receiving liposomal bupivacaine compared to placebo for the initial 12 hours after infiltration, but diminished over the subsequent 12 hours resulting in no clinical meaningful difference in pain between groups beyond 24 hrs.
- Unpublished, active comparison: Based upon the results, investigators failed to show any statistically or clinically meaningful advantage of liposomal bupivacaine over bupivacaine HCl when used after hemorrhoidectomy, despite examining over 60 different efficacy endpoints. Both agents were equally well tolerated.
- The manufacturer did request a priority review. However, that request was denied since the manufacturer was unable to demonstrate that use of liposomal bupivacaine reduced the use of opioids or their associated adverse events or a relevant benefit in reduced time to discharge or return to usual activities.

- Since different doses and manner of administration were used in the two types of surgery, extrapolation of dosing and effectiveness to other surgical interventions is not possible. Additional studies are needed to answer the question of appropriate dose and manner of administration for use in other surgeries.
- Original recommendation was for the labeling to specifically include postoperative use following bunionectomy or hemorrhoidectomy. The final labeling was less specific.
- Labeling should contain a strong caution against use of liposomal bupivacaine by other administration routes (other than single-dose, postoperative wound infiltration) that are commonly used with other local anesthetics in clinical practice but may be unsafe for this product.

- There have been two published phase 2 trials (1-hemorrhoidectomy[9], 1-total knee arthroplasty[10]) and two published phase 3 trials (1-total knee arthroplasty[11], 1-breast augmentation[18]) comparing the cumulative pain scores between liposomal bupivacaine and unencapsulated bupivacaine HCl (0.25% with epinephrine 1:200,000).
- In the phase-2 studies, the primary endpoint of cumulative pain intensity was met in favor of the liposomal product[9,10] but not in the phase-3 studies[11,18]. However, since the analysis of pain intensity was determined over the entire planned study length (through 72 hrs or 4 days), the differences at the various time points were not entirely consistent between studies making it difficult to determine the actual length of time the differences between groups existed or if the differences were clinically important. For example in the pivotal trials, the primary endpoint was reportedly met through 72 hrs but when the FDA reviewer reported their findings, the statistical difference from placebo was present only through 24 hours, but not beyond.
- In each of the studies, sample sizes were small, multiple comparisons between groups at a number of time points were made with some showing statistical benefit of the liposomal product and others not, and post-hoc changes were made to the analysis of one of the studies, thereby limiting the strength of the evidence.[9]
- In three of the studies[9,10,11], there was no statistical or clinically important difference in total consumption of opioids, discharge readiness, proportion of patients who were opioid free or who were able to return to work or resume normal daily activities between groups.

Safety

- Liposomal bupivacaine was well tolerated and adverse events were not significantly different than bupivacaine HCl/epinephrine or placebo when administered as a single-dose infiltrated into the surgical site after bunionectomy or hemorrhoidectomy.
- The most common adverse events reported with bupivacaine liposomal injectable suspension were constipation, nausea, and vomiting.
- Similar to other local anesthetics, there is a potential for neurologic or cardiovascular adverse events and is related to the total dose administered. However, other factors may increase the incidence of these adverse events and include the specific anesthetic used, the route of administration and the patient's health status. Early signs of central nervous system toxicity include restlessness, anxiety, incoherent speech, lightheadedness, numbness, tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, twitching, tremors, depression, or drowsiness.
- There are no known long-term safety issues that have been identified to date.
- Since liposomal bupivacaine has not been studied or data are limited in patients undergoing other types of surgery (other than bunionectomy or hemorrhoidectomy), the safety, efficacy and appropriate doses of liposomal bupivacaine are not known and therefore, use is not recommended.
- Furthermore, other routes of administration or types of analgesia have not been studied and therefore, are not recommended (e.g., epidural, intrathecal, regional nerve block or intravascular or intra-articular use).

Conclusion

- Although liposomal bupivacaine statistically reduced pain intensity in patients undergoing bunionectomy or hemorrhoidectomy when compared to placebo, there was no difference in the primary outcome or secondary outcomes when compared to traditional unencapsulated

bupivacaine HCl in an unpublished phase 3 pivotal trial in patients undergoing hemorrhoidectomy.

- In two phase 2, dose-ranging studies, liposomal bupivacaine was associated with improved cumulative pain scores compared to bupivacaine HCl but differences in total consumption of opioids, readiness for discharge, proportion of patients who were opioid free or who were able to return to work or resume normal activities were not different.
- Since the safety and efficacy of liposomal bupivacaine has been evaluated primarily in patients undergoing hemorrhoidectomy or bunionectomy (using a single-dose infiltrated into the surgical site), the safety and efficacy when used after other surgeries; by other routes of administration; or use for other types of analgesia are unknown and therefore, use after other surgeries is not recommended.
- Based on the existing evidence, there are no clear or substantive advantages of the liposomal bupivacaine product over bupivacaine HCl.
- There are no clinical trials comparing liposomal bupivacaine to other local anesthetic agents so any advantage or disadvantage of liposomal bupivacaine over other local anesthetics is unknown.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating bupivacaine liposome injectable suspension for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Bupivacaine liposomal injectable suspension is an amide-type local anesthetic in an encapsulated liposomal formulation developed to provide a longer duration of anesthesia compared with its non-liposomal counterpart, bupivacaine hydrochloride or other local anesthetics. Anesthesia occurs by reversibly binding to sodium channels on the neuronal cell wall, preventing the influx of sodium, and increasing the nerve's electrical excitation threshold. Action potential firing is reduced and the nerve's impulse generation and conduction are blocked. Small unmyelinated C-fibers are blocked first, which mediate pain, followed by small myelinated Aδ-fibers which mediate pain and temperature sensation, and lastly large myelinated fibers including Aγ-, Aβ-, and Aα- fibers which mediate touch, pressure, muscle and postural sensations.

Bupivacaine liposomal injectable suspension utilizes the DepoFoam® drug delivery system, an aqueous suspension of multivesicular liposomes containing bupivacaine, for gradual systemic release. The multivesicular liposome particles are made up of a honeycomb like structure consisting of many nonconcentric compartments containing bupivacaine. In vivo, DepoFoam particles release drug over an extended period of time by erosion of the exterior surface and reorganization of the particles' lipid membranes. Bupivacaine liposomal injectable suspension follows a two-compartment model. Initially, first order short-term release followed by zero-order release over an extended period of time. When bupivacaine liposomal injectable suspension is administered, free bupivacaine in the solution is immediately available to anesthetize the surgical site, while the bupivacaine enclosed in the DepoFoam is released more gradually over an extended period of time.

Once Bupivacaine liposomal injectable suspension is released from the liposome, distribution, metabolism, and excretion follows the same kinetics as bupivacaine HCl. Of note, bupivacaine liposomal injectable suspension can have elevated systemic plasma levels for up to 96 hours, but the systemic plasma levels do not correlate with local efficacy. Duration of local analgesia properties is ~24 hours. Different formulations of bupivacaine are not bioequivalent and it is not possible to convert dosing from one formulation to another.[1]

Table 1. PK Parameters of Bupivacaine Liposomal Injectable Suspension[1]

Parameters	Bunionectomy 106 mg (8 mL) (N=26)	Hemorrhoidectomy 266 mg (20 mL) (N=25)
Mean Cmax (ng/mL)	166(92.7)	867 (353)
Median Tmax (h)	2	0.5
Mean $AUC_{(0-t)}$ (h*ng/mL)	5864 (2038)	16,867 (7868)
Mean $AUC_{(inf)}$ (h*ng/mL)	7105 (2283)	18,289 (7569)
Mean t 1/2 (h)	34.1 (17.0)	23.8 (39.4)

Table adapted from product information

Table 2. PK parameters of bupivacaine liposomal injectable suspension and bupivacaine HCl[2,3]

PK Parameter	EXPAREL	Bupivacaine HCl
Metabolism	Hepatic conjugation with glucuronic acid; inactive metabolite pipecoloxylidine (PPX)	Hepatic conjugation with glucuronic acid; inactive metabolite pipecoloxylidine (PPX)
Elimination	Urine (6% unchanged)	Urine (6% unchanged)
Half-life	24-34 h	2.7 h
Protein binding	95%	95%
Local onset	2 minutes	1-17 minutes
Duration	Local: 24 h Systemic: 96 h *(does not correlate with local efficacy)*	2-9 h (route and dose dependent)
Time to peak	Bunionectomy: 2 h Hemorrhoidectomy: 0.5 h Inguinal hernia: 12 h Total Knee Arthroplasty: 36 h	0.5 hours-0.75 h

Bupivacaine liposomal injectable suspension is not associated with major motor blockade at doses up to 266 mg. When motor block did occur, the maximum duration was 4 hours instead of 12 hours as seen with unencapsulated bupivacaine.[17]

FDA Approved Indication(s)[1]

Bupivacaine liposomal injectable suspension is indicated for single-dose infiltration into the surgical site to produce anesthesia after surgery. The U.S. Food and Drug Administration approved it on October 28, 2011. Of note, the pivotal trials providing the basis for FDA approval consisted of patients having bunionectomy or hemorroidectomy.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence- based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Bupivacaine liposomal injectable suspension has been studied for use in postoperative local analgesia in adults having hernia repair, breast augmentation, and total knee arthroplasty. There are also several phase 4 trials currently recruiting patients. Investigators for these trials will examine bupivacaine liposomal injectable suspension in comparison to morphine or other opioids for pain associated with colectomy, ileostomy reversal and robotic assisted laparoscopic prostatectomy.[20-22] Most of these trials are designed as health-economic trials. There is one planned trial to examine femoral nerve block with liposomal bupivacaine in patients having total knee arthroplasty. **At this time, evidence is lacking to support the efficacy and safety of liposomal bupivacaine for post-operative local anesthesia in surgeries other than bunionectomy or hemorroidectomy, and therefore use in other surgeries cannot be recommended. Furthermore, evidence is lacking for use of other types of analgesia or routes of administration for liposomal bupivacaine (e.g., epidural, intrathecal, regional nerve blocks, etc.) and therefore should not be used outside of its approved dosage and administration.**

Current VA National Formulary Alternatives

Current VA National Formulary Injectable local anesthetics (VA Class CN204) include: bupivacaine HCl*, chloroprocaine HCL, prilocaine, lidocaine HCl, mepivacaine HCl, ropivacaine HCl, and tetracaine HCl. Lidocaine, bupivacaine and prilocaine combined with epinephrine are also on the VANF.

*It is important to note that when using non-liposomal bupivacaine, there are multiple formulations with and without preservative. Bupivacaine multi-dose vials with methylparaben as a preservative can only be used for peripheral nerve block. The preservative free versions (also referred to as methylparaben free) are required for caudal or epidural anesthesia. For spinal anesthesia, bupivacaine spinal, which also contains dextrose, is the only bupivacaine product indicated.

Dosage and Administration[1]

Bunionectomy (Adult): Inject 106 mg by infiltrating 7 mL into surrounding tissue of the osteotomy and 1 mL into the subcutaneous tissue. Bupivacaine liposomal is intended for single-dose infiltration only and the maximum dose should not exceed 266 mg. The recommended dose is based on surgical site and volume needed to cover the surgical area.

Hemorrhoidectomy (Adult): Dilute 20 mL vial of bupivacaine liposome with 10 mL of normal saline for a total of 30 mL. Inject 266 mg via infiltration by dividing the 30 mL mixture into six 5-mL aliquots. Visualize the anal sphincter as a clock face and perform anal block by slowly infiltrating one aliquot to each of the even numbers. Liposomal bupivacaine is intended for single-dose infiltration only and maximum dose should not exceed 266 mg.

Safety and efficacy of bupivacaine liposome have not been established in patients less than 18 years of age. Bupivacaine liposomal injectable suspension should be used with caution in patients with hepatic and renal impairment (Refer to section on Special Populations for additional information).

Administration: Bupivacaine liposomal injectable suspension is indicated for single-dose infiltration only.

- A 25-gauge or larger bore needle should be used to administer bupivacaine liposomal. Do not filter or heat before use. Invert vials several times to re-suspend particles immediately before withdrawing drug from vial.
- Do not administer if vial has been frozen (as reflected by the temperature indicator) or exposed to high temperatures (40°C or 104°F) for an extended period of time. Freeze indicator turns from green to white if product has been exposed to freezing temperatures.
- Inspect product for discoloration, do not administer if product is discolored.
- Bupivacaine liposomal should be injected into the surrounding soft tissue of the surgical site. Frequent aspiration should be done to check for blood and to reduce the risk of intravascular administration. The maximum dose is 266 mg and should not be exceeded.

- Bupivacaine liposomal can be administered diluted up to 0.89 mg/ml (i.e., 1:14 dilution by volume) with preservative free normal sterile saline (0.9%) for injection or undiluted.
- Non-bupivacaine based local anesthetics may cause immediate release of bupivacaine from bupivacaine liposomal injectable suspension if administered together locally. Administration of bupivacaine liposomal injectable suspension may follow the administration of lidocaine after at least 20 minutes. Other formulations of bupivacaine should not be used within 96 hours due to risk of toxicity.
- When a topical antiseptic (povidone iodine) is applied to site, the site should be allowed to dry before liposomal bupivacaine is administered since topical antiseptics should not come into contact with liposomal bupivacaine.

Storage: Store refrigerated between 2°C to 8°C. Unopened vials may be kept at room temperature (20 to 25°C) for up to 30 days. Record the date when a vial is removed from refrigeration. Unopened vials should not be re-refrigerated. After withdrawal from vial, the suspension may be stored up to 4 hours at room temperature. Diluted suspensions should be used within 4 hours.

Dose conversion: Bupivacaine liposomal injectable suspension is not bioequivalent with other formulations of bupivacaine, even if the milligram strength is the same. Therefore, dosage conversion between bupivacaine liposomal and other forms of bupivacaine, and vice versa, is not possible.

Efficacy

For this review, all published studies examining the efficacy and/or safety of bupivacaine liposomal injectable suspension for producing post-surgical, local anesthesia in humans were included.

Efficacy Measures

Primary Outcome Measure:

- Pain Intensity-Assessed by the cumulative pain score using the numeric rating scale (NRS) area under the curve (AUC) through a designated period of time (e.g., 0-24 hrs, 0-72 hrs, etc.). At designated time points, patients rate their pain intensity at rest or with activity on an 11-point scale (0=no pain, 10=worst pain possible). The pain assessment ratings are then summed during the time points and the NRS-AUC for the period of time is obtained.

Secondary Outcome Measures:

- Proportion of patients receiving no supplemental opioids
- Total milligrams of opioid rescue medications
- Time to first post-surgical use of opioid rescue medications
- Brief pain inventory (BIP)-Measures the severity of pain and its impact on daily function
- Patient rating of satisfaction with pain control after surgery
- Caregiver assessment of wound healing
- Adverse effects, including those commonly associated with opioid use

Summary of Efficacy Findings[4-5, 28]

As part of the FDA review process, the manufacturer submitted three clinical trials examining the safety and efficacy of liposomal bupivacaine. Two of the trials were published and involved a comparison of liposomal bupivacaine to placebo in patients undergoing bunionectomy (n=193 patients)[4] or hemorrhoidectomy (n=189 patients)[5]. The third, unpublished trial involved a comparison of liposomal bupivacaine with bupivacaine HCl in patients having hemorrhoidectomy[28]. In each of the three trials, the primary endpoint was the intensity and duration of pain as reported using the area under the curve (AUC) of the numeric rating scale (NRS) through 24-72 hrs after surgery between treatments. The three trials are summarized below in Table 3.

Table 3. Clinical Efficacy Trials (Pivotal, Phase 3 Clinical Trials Used for FDA Submission)

Clinical Trial	Exclusion/Intervention	Outcome Measures	Results	Adverse Events/Comments
Golf[4] Phase 3, R, MC, PC, DB N=193 Inclusion: Adult patients undergoing primary unilateral first metatarsal osteotomy without hammertoe. Able to have Mayo block for intraoperative local analgesia and propofol and/or midazolam for sedation. *Sponsored by Pacira Pharma	Exclusion: pregnancy, nursing or planning to become pregnant, chronic users of analgesics either opioids or non-opioids, any analgesic within 24 hrs to 3 days prior to surgery, peripheral neuropathy, hx of hepatitis, addiction to drugs or etoh past 2 yrs, peripheral ischemic disease, diabetes, acute or chronic medical or psychiatric disease, malignancy in last 2 yrs, sensitivity to amide local anesthetics or opioids, etc. Intervention: LBup 8 mL (120 mg) or Placebo Rescue meds: 1-2 oxy 5 mg/APAP 325 mg every 4-6 hrs prn. (Max 12/d). If pain couldn't be rescued by oxy/APAP, a single dose of ketorolac 15-30 mg was allowed. If pain still not controlled, pt removed from efficacy portion of study. No other analgesics were allowed for first 72 hrs.	Primary: AUC-NRS score through 24 hrs (Measured at 2, 4, 8, 12, 24, 26, 48, 60 and 72 hrs post-op) Secondary: *AUC-NRS through 36, 48, 60 and 72 hrs * Proportion of patients pain free at 24 hrs and other time points. * Proportion of pts receiving no rescue pain med * Total oxy/APAP mg through 24, 36, 48, 60 and 72 hrs. * Time to first rescue Patients were d/c after 24 hrs and staff called patients to get assessments beyond 24 hrs.	N=193 randomized, 97 to LBup, 96 to placebo. 4 pts from each group withdrew or violated study protocol. Mean age: 42 years Primary: AUC-NRS_{0-24}: LBup 124.9 vs. 146.4 (p=0.0005, LSM difference: -22.297, 95% CI for difference: -34.8 to -9.8) Secondary: Adjusted mean AUC-$NRS_{0-36 \text{ and } 0-48:}$ LBup 0-36 hr: 196.9 vs. 220.3 placebo (p=0.0229) and LBup 0-48 hr: 268.9 vs. 290.5 placebo (p=0.1316) (NS) Pts pain free: Statistical difference in favor of LBup for 2, 4, 8 and 48 hrs but not other time points. (No diff at 12, 36 or 60 hrs) Pts receiving no opioids: Statistical difference in favor of LBup through 24 hrs, after that, no diff. Time to first opioid: LBup: 7.2 hrs vs. 4.3 hrs placebo (p<0.0001) Total use of rescue opioids (tabs) through 24 hrs: LBup: 3.8 tabs vs. 4.7 tabs placebo (p=0.008)	Most ADEs were mild-moderate. Systemic ADEs were higher with LBup vs placebo (9.3% vs. 5.2%, respectively), including somnolence. Incidence of severe ADEs was also higher with LBup than placebo (11.3% vs. 5.2%, respectively), these severe ADEs were not detailed. Moderate ADEs were higher in the placebo group (20.8%) vs. LBup (12.4%). Vomiting was reported more often in the LBup vs. placebo (27.8% vs. 17.7%, respectively). Reports of constipation were also numerically higher with LBup vs. placebo (2.1% vs. 1%, respectively) Comments/Limitations: *No active control, only placebo controlled *Patients left study site after 24 hrs and were contacted via telephone for follow up pain assessments. *Authors cautioned against extrapolation of their results to other surgical populations, those with multiple medical problems or those taking other medications and the controlled conditions of the study. They also state that interpretation of their results is limited due to the inherent subjectivity and intra-patient variability of patient-rated pain evaluations. FDA reviewer comments: *Severe vomiting reported by 9% of LBup vs. 2% placebo. *When taking into account individual NRS scores for entire study period, the analgesic effect of LBup is greatest during the first 12 hours and after that differences become less apparent between groups. At 8 hrs, both groups have NRS scores indicating at least moderate pain. By 16 h hrs, the pain intensity is as if no treatment was received and rescue pain meds are necessary. Post-hoc Changes to protocol: Addition of % of patients receiving no rescue meds through 8, 12,16 and 20 hrs was added. And, "pain free: was originally defined as a NRS score of 0 but changed to a NSR score of 0, 1 or 2. FDA Reviewer Conclusion: Superior to placebo when used with oxycodone, acetaminophen and

				ketorolac for up to 12 hrs and no more than 24 hrs after surgery. Little risk for ADEs when used at this dose in this surgical setting.
Gorfine[5] Phase 3, R MC, PC, DB N=189 Inclusion: Adult men and women undergoing 2 or 3 column excisional hemorrhoidectomy under general anesthesia. Patients had ASA physical exam status of 1, 2 or 3. *Sponsored by Pacira Pharma	Exclusion: medical conditions believed to interfere with study including hepatitis, etoh/substance abuse, uncontrolled psychiatric disorders, know allergy or contraindication to amide type local anesthetics, opioids or propofol. Also, those with body weight of <50 kg, participation in other study within 30 days, or taking NSAIDs, APAP, opioids, antidepressants or glucocorticoids within 3 days of surgery. Intervention: LBup 300 mg/30 mL or placebo. Infiltrated into 6 sites of the perianal tissues (surrounding external sphincter), each injection was 5 mL. Fentanyl was permitted during surgery but intraoperative use of other analgesics was not permitted unless to treat and ADE. Rescue meds: MS 10 mg IM every 4-6 hrs prn for 72 hrs post-op. Patients were allowed antiemetic meds or low dose aspirin for CV protection or platelet inhibition. The use of any topical rectal meds was prohibited for 72 hrs. Stool softeners and laxatives were given prn and sitz baths were at the discretion of the surgeon.	Primary: AUC-NRS score through 72 hrs (Measured at the end of anesthesia, before first dose of MS (if applicable) and at 1, 2, 4, 8, 12, 24, 36, 48, 60 and 72 hrs post-op) Secondary: * Proportion of pts receiving no rescue opioid pain med * Total opioid dose (mg) through 24, 36, 48, 60 and 72 hrs. * Time to first rescue dose *BPI assessment at 24 and 72 hrs and 30 days post-op *Patient's rating of satisfaction with post-op analgesia. *ADEs *Caregiver satisfaction with wound healing. Patients remained at study site for 72 hrs.	N=189 randomized, 187 analyzed, 186 completed study. LBup: 94, Placebo: 93 (ASA 3 status: 2.1% and 3.2% placebo) Mean age in both groups: 48 years Primary: AUC-NRS 0-72 hr (LSM): 141.8 LBup vs. 202.5 placebo (p<0.0001) Secondary: *Proportion of pts receiving no rescue opioids: Significant difference favoring LBup beginning at 12 hrs through 72 hrs (p<0.0008). At 72 hrs: 28% LBup vs. 10% for placebo (p=0.0007) *Total opioid dose: Lower total dose at each time point through 72 hrs in favor of LBup vs. placebo (p<0.0001 through 48 hrs, p<0.0003 at 60 hrs and p<0.0006 at 72 hrs). Total dose of opioid (MS) consumed by 72hrs: LBup 22.3 mg vs. 29.1 mg Placebo (p=0.0006). *Median time to first opioid rescue: LBup: 14 hr and 20 min vs. 1 hr and 10 min placebo (p<0.0001) *BPI: At 24 hrs, LBup pts reported less pain and pain-interference with general activities vs. placebo (no numbers provided or statistical significance values). At 72 hrs, LBup pts reported less pain-interference with general activities vs. placebo. At 30 days, no difference. *Patient Satisfaction with post-op analgesia: LBup: 89/94 (94.7%) were satisfied or extremely satisfied vs. 68/93 (73.1%) were satisfied or extremely satisfied with placebo. (p=0.0007) *Caregiver satisfaction with wound healing: No difference	No difference in overall number of ADEs between groups. Most were mild in severity. Anal hemorrhage and painful defecation were the most common ADEs reported. Anal hemorrhage, painful defecation, vomting and rectal discharged trended towards a higher percentage of patients in the placebo group. Comments/Limitations: *No active control, only placebo controlled *Relatively young, healthy population of patients. Authors cautioned against extrapolation of their results to settings where other modes of administration are used (e.g., nerve block, epidural, etc.) or to broader patient populations. FDA reviewer comments: After 24 hrs, there is no difference between placebo and LBup with regard to the primary endpoint. Changes to protocol Post-hoc: an exploratory analysis was added, the NRS pain intensity scores were summarized using a wWOCF+ LOCF imputation at each specified time point. FDA reviewer Conclusion: LBup is effective at reducing post-op pain following hemorrhoidectomy at the dose and method of administration used. Clinical and statistical differences were observed only during the initial 24 hrs. The dose used could result in plasma concentrations of bupivacaine that have been reported to lead to neurotoxic ADEs. Post-hoc, an exploratory analysis was added: The NRS pain intensity scores were summarized using a wWOCF+LOCF imputation at each specified time point.
Unpublished[28] Phase 3, R, MC, DB N=198 Inclusion: Adult men and women undergoing 2 or 3	Exclusion: pregnancy, significant medical conditions believed to interfere with study results, etoh/substance abuse within past 2 yrs, uncontrolled psychiatric disorders, know allergy or	Primary Endpoint: AUC-NRS through 96 hrs. Secondary: *Total post-op use of	N=198 randomized, LBup=99 pts, Bupivacaine HCl/epi=99 pts Primary endpoint: AUC-NRS (mean): LBup: 393 vs. Bupivacaine HCl/epi: 359	ADEs were similar between groups. In the LBUP group, flatulence, abdominal pain, pyrexia, pruritis, and urinary retention were reported in ≥5% vs. only headache was the only ADE with an incidence ≥5%.

column excisional hemorrhoidectomy under general or spinal anesthesia. Hemorrhoids were either internal or internal/external. Patients had ASA physical exam status of 1, 2, 3 or 4. *Sponsored by Pacira Pharma	contraindication to amide type local anesthetics, opioids or propofol or other pain meds planned for post-op use. Use of long-acting opioids within 3 days of surgery or any opioid within 24 hrs of surgery. Contraindication to epinephrine, monoamine oxidase inhibitors or antidepressants of tryptyline or imipramine types or conditions where the production or exacerbation of tachycardia could prove fatal or any condition that can be aggravated by epi. Also, those with body weight of <50 kg and participation in other study within 30 days, etc. Intervention: LBup 300 mg/30 mL or bupivacaine HCl 100 mg/epi as a single dose. The dose was infiltrated into 6 sites of the perianal tissues (surrounding external sphincter), each injection was 5 mL. Ketorolac IV or alternative was given at the end of surgery. Rescue meds: No specific details on rescue opioid protocol. APAP was given as 1000 mg three times a day for 4 days as soon as oral meds were tolerated.	opioids through 12, 24, 36, 48, 60, 72 and 96 hrs * Proportion of pts receiving no supplemental opioids through same time periods. *Pain intensity at each time point assessed. *Pain with first BM. *Time to first post-op use of opioid. *Quality of life questionnaire. *Time to first occurrence of PONV. *PONV free through 96 hrs. *Discharge readiness. *Subject's overall satisfaction with post-op analgesia. *Blinded care providers satisfaction with post-op analgesia. *Time to return to work or normal daily activities. ADEs were monitored through day 8 and deaths through 30 d. Unclear length of stay at study site.	No significant difference through 96 hrs (p=0.15). Secondary measures: (Over 60 secondary endpoints). *Not all summarized in FDA review, only the following points were made:* *Only two time points differed between groups and in both periods, differences favored Bupivacaine HCl over LBup. (Page 137, FDA reviewer report). *Study failed to show a difference between LBup and bupivacaine HCl/epi. This failure to show a difference was not only in the primary endpoint but also in nearly all secondary endpoints examined.	Comments/Limitations: Unpublished FDA reviewer comments: "The study failed to show any statistically or clinically meaningful advantage of LBup over bupivacaine HCl when used after hemorrhoidectomy despite examining over 60 different efficacy endpoints. Both drugs were tolerated equally well." Changes to protocol Post-hoc: Prior to unbinding, those sites that enrolled <10 patients were pooled. Only one site used spinal anesthesia so that mode of anesthesia was not used in the model. FDA reviewer Conclusion: "The study failed to show any statistically or clinically meaningful advantage of LBup over bupivacaine HCl when used after hemorrhoidectomy despite examining over 60 different efficacy endpoints. Both drugs were tolerated equally well."

ADE-adverse drug event, ASA=American Society of Anesthesiologists (1=normal, health, 2=mild systemic disease, 3=severe systemic disease, 4=severe systemic disease that is a constant threat to life), BM=bowel movement, BPI=brief pain inventory, CV=cardiovascular, DB=double-blind, IM=intramuscular, LBup=liposomal bupivacaine, LSM=least squares mean, MC-multicenter, NS=not significant Oxy/APAP=oxycodone/acetaminophen, PC-placebo-controlled, PONV=post-op nausea and vomiting, PRN=as needed, R=randomized, wWOCF+LOCF=windowed worst observation carried forward+last observation carried forward.

Additional Information from FDA Reviewer [28]

- In the two pivotal, placebo controlled trials, liposomal bupivacaine provided postoperative analgesia for up to 24 hours in patients having bunionectormy or hemorrhoidectomy surgery. In these studies, pain intensity was significantly reduced in patients receiving liposomal bupivacaine compared to placebo for the initial 12 hours after infiltration, but diminished over the subsequent 12 hours resulting in no clinical meaningful difference in pain between groups beyond 24 hrs.
- Liposomal bupivacaine was compared to the existing formulation of bupivacaine HCl after hemorrhoidectomy in a third pivotal, unpublished study. In their review, the FDA medical officer concluded that based upon the results, investigators failed to show any statistically or clinically meaningful advantage of liposomal bupivacaine over bupivacaine HCl when used after hemorrhoidectomy, despite examining over 60 different efficacy endpoints. Both agents were equally well tolerated.
- The manufacturer did request a priority review. However, that request was denied since the manufacturer was unable to demonstrate that the use of liposomal bupivacaine reduces the use of opioids or their associated adverse events or has shown relevant benefit in reduced time to discharge or return to usual activities.
- Since different doses and manner of administration were used in the two studies, extrapolation of dosing and effectiveness to other surgical interventions is not possible. Additional studies are needed to answer the question of appropriate dose and manner of administration for use in other surgeries.
- Original recommendation was for the labeling to specifically include postoperative use following bunionectomy or hemorrhoidectomy. The final labeling was less specific.
- Labeling should contain a strong caution against use of liposomal bupivacaine by other administration routes (other than single-dose, postoperative wound infiltration) that are commonly used with other local anesthetics in clinical practice but may be unsafe for this product.
- Post-marketing studies are recommended in pediatric patients.

In the phase 3 clinical trials submitted to gain FDA approval, liposomal bupivacaine reduced pain intensity versus placebo for the first 24 hours in patients following bunionectomy or hemorrhoidectomy. In addition, opioid use was reduced in favor of liposomal bupivacaine vs. placebo but the clinical relevance of the difference is unknown (Golf-3.8 vs. 4.7 tabs of oxycodone 5 mg/APAP 325 mg tablets, p=0.008 and Gorfine-22.3 mg vs. 29.1 mg morphine equivalents, p=0.0006). However, liposomal bupivacaine was not statistically different from unencapsulated bupivacaine HCl in reducing pain intensity or other secondary outcome measures in patients following hemorrhoidectomy.

Other published clinical trials

There have been two published phase 2 trials (1-hemorrhoidectomy[9], 1-total knee arthroplasty[10]) and two published phase 3 trials (1-total knee arthroplasty[11], 1-breast augmentation[18]) comparing the cumulative pain scores between liposomal bupivacaine and unencapsulated bupivacaine HCl (0.25% with epinephrine 1:200,000). In the phase-2 studies, the primary endpoint of cumulative pain intensity was met in favor of the liposomal product[9,10] but not in the phase-3 studies[11,18]. However, since the analysis of pain intensity was determined over the entire planned study length (through 72 hrs or 4 days), the differences at the various time points were not entirely consistent between studies to determine actually how long the differences between groups existed or if the differences were clinically important. For example in the pivotal trials,[4-5,28] the primary endpoint was reportedly met through 72 hrs but when the FDA reviewer reported their findings, the statistical difference from placebo was present only through 24 hours, but not beyond. In each of the studies, sample sizes were small, multiple comparisons between groups at a number of time points were made with some showing statistical benefit of the liposomal product and others not, and post-hoc changes were made to the analysis of one of the studies, thereby limiting the strength of the evidence.[9] In three of the studies, there was no statistical or clinically important difference in total consumption of opioids, discharge readiness, proportion of patients who were opioid free or who were able to return to work or resume normal daily activities. (Details below)

- In a phase 2, dose-ranging study, 100 patients were randomized to receive liposomal bupivacaine 66 mg, 199 mg, 266 mg or unencapsulated bupivacaine HCl 75 mg (0.25% with 1:200,000 epinephrine) via local infiltration after hemorrhoidectomy. The primary endpoint was cumulative pain intensity using the numeric rating scale at rest over 72 hrs (AUC-NRS-R_{0-72}) after surgery. Pain intensity was reported to be significantly less in the 199 mg and 266 mg liposomal bupivacaine groups vs. bupivacaine HCl at 72 hrs (p=0.001, p<0.001, respectively). A number of post-hoc changes were made including the decision to make multiple comparisons (study not powered to do so) between groups so a Bonferroni correction was made so that statistical significance was achieved only if a p-value of ≤0.017 was achieved. In addition, differences between groups in incidence of opioid-related adverse events were determined, post-hoc. Pain intensity scores with first bowel movement (NRS-BM) were higher in the bupivacaine HCl vs. the liposomal bupivacaine 199 mg and 266 mg groups (p=0.003), but the mean NRS-BM scores did not differ between groups. Time to first BM was not different between groups and ranged from 55-64 hours. No significant between-group differences were reported for use of rescue opioids or proportion of patients who were opioid free through 72 hours. Time to first rescue opioid was statistically different between bupivacaine HCl and favored only the 266 mg liposomal bupivacaine group (p=0.005). Post-hoc, no difference in opioid consumption was observed in the first 12 hours but between 12 and 72 hours after dosing, there was a difference in favor of the 266 mg group vs. bupivacaine HCl (3.7 mg vs. 10.2 mg, respectively, p=0.019). Authors noted since the analysis was done post-hoc, they did not apply to Bonferroni adjustment; otherwise the difference would not have been significant. Finally, no differences were observed in numbers of patients meeting criteria for discharge at 1, 2 or 3 hours after surgery or in the proportion of patients that were able to return to work or resume normal activities.[9]

- In another phase 2, dose-ranging study, 138 adults undergoing total knee arthroplasty (TKA) were randomly assigned to received liposomal bupivacaine 133 mg, 266 mg or 150 mg of bupivacaine HCl (0.25% with epinephrine 1:200,000) postoperatively, via local infiltration. Investigators planned three consecutive cohorts with gradually increasing doses of liposomal bupivacaine to identify a therapeutic dose for use in patients having TKA and further examine its safety and pharmacokinetics. Cohort 1 involved the doses listed above randomized 1:1:1; Cohort 2 added a 399 mg dose of liposomal bupivacaine randomized 2:2:5:2; and Cohort 3 added a 532 mg dose of the liposomal product vs. bupivacaine HCl 150 mg, randomized 5:2. At the end of the surgery, patients were given a single intravenous dose of ketorolac, ketoprofen or diclofenac. If oral medications were tolerated, 1000 mg of acetaminophen was given three times a day through 96 hours post-op. The primary outcome measure was the cumulative pain score with activity through the fourth post-op day (NRS-A AUC). Mean NRS-A AUC through four days after surgery were all stated to be statistically different than bupivacaine HCl but the cumulative NRS-A score was numerically lower in the bupivacaine HCl 150 mg vs. liposomal bupivacaine 133 mg group and differed by only 0.9 vs. liposomal bupivacaine 266 mg. *Although the authors state a significant difference in the primary endpoint in favor of the liposomal product (results section), presentation of the results is misleading since they later comment in the conclusion section that a statistical difference was not attained in the primary endpoint.* A number of assessment time periods were favorable for liposomal bupivacaine vs. bupivacaine HCl. However, the mean NRS score with activity (NRS-A), total consumption of rescue opioids and time to resuming work or normal activities was not different between groups.[10]

- Bupivacaine liposomal injectable suspension 532 mg and bupivacaine HCl 200 mg were compared in a phase 3 study in a primarily female population having total knee arthroplasty. The investigators found that both groups had similar pain intensity during activity. Total opioid consumption after surgery and quality of life scores were comparable between groups as well as time to physical recovery and return to daily activities.[11]

- In a phase 3 study conducted in patients undergoing breast augmentation, 136 patients were randomly assigned to bupivacaine liposomal injectable suspension 300 mg in each breast or bupivacaine HCl 100 mg in each breast. The primary endpoint was the cumulative pain intensity with activity (NRS-A) through 72 hours post-op. The investigators found that there was no difference in NRS-A AUC_{0-72} between groups (liposomal bupivacaine 441.5 vs. bupivacaine HCl 468.2, p=0.3999). Total opioid consumption was lower through 24 hours (p=0.0211) and just reached

statistical significance at 48 hours (p=0.0459) in favor of the liposomal product. The authors note that the study was underpowered due to early termination, resulting from administrative reasons unrelated to safety.[18]

- A manufacturer sponsored analysis of pooled data from nine placebo or active controlled trials (several trials are published only as abstracts; some are already detailed above) showed a mean cumulative pain score through 72 hours that was significantly lower with liposomal bupivacaine vs. bupivacaine HCl (283 vs. 329, respectively, p=0.039); a median time to first opioid rescue that was prolonged in the liposomal group (10 vs. 3 hours, p<0.0001) and significantly less opioid consumed (12 mg vs. 19 mg, p<0.0001) during the study period vs. non-liposomal bupivacaine. As already mentioned in the text above, some of these endpoints were reviewed post-hoc and alterations to the study were made during the course of the earlier phase studies. No difference in discharge readiness, time resuming work or normal activities were reported.[30]

For further details on the efficacy results of the phase 2 and off-label clinical trials, refer to Appendix: Clinical Trials

Adverse Events (Safety Data)

Safety and effectiveness of liposomal bupivacaine are dependent upon appropriate dose, administration technique, taking sufficient precautions and readiness to respond to emergency situations if one arises.

Deaths and Other Serious Adverse Events (Sentinel Events)

No deaths have been reported that are attributable to administration of liposomal bupivacaine.

Common Adverse Events

The most common adverse reactions in wound filtration clinical trials were nausea, constipation, and vomiting. Overall incidence of these common adverse events with bupivacaine liposomal injectable suspension and bupivacaine HCl was similar (62% vs. 75%). Severity and frequency were also similar.

Other common adverse reactions, defined as incidence between 2 to 10%, include pyrexia (2%), dizziness (6%), peripheral edema (2-10%), hemorrhagic anemia (2-10%), hypotension (2-10%), pruritus (3%), tachycardia (4%), headache (4%), insomnia (2-10%), muscle spasms (2-10%), back pain (2-10%), somnolence (2-5%), and procedural pain (<2%).

Table 4. Adverse events from pivotal trial data[1,4-5]

	Bupivacaine liposomal injectable suspension (8 mL)[4]	**Placebo**	**Bupivacaine liposomal injectable suspension (30 mL)**[5]	**Placebo**
Gastrointestinal Disorders	42.3%	39.6%	7.4%	13.8%
Nausea	40.2%	37.5%	2.1%	1.1%
Vomiting	27.8%	17.7%	2.1%	4.3%
Constipation	2.1%	1%	2.1%	2.1%
Nervous System Disorders	20.6%	31.3%	0	0
Dizziness	11.3%	26%	0	0
Headache	5.2%	8.3%	0	0
Somnolence	5.2%	1%	0	0

Skin Disorders	8.2%	7.3%	0	0
Pruitus	3.1%	1%	0	0
Other	5.2%	3.1%	--	--
Increased Alanine Aminotransferase	3.1%	3.1%	1.1%	0
Increased Aspartate Aminotransferase	3.1%	2.1%	0	0
Serum Creatinine Increased	2.1%	0%	0	0
Feeling Hot	2.1%	0%	0	0
Post Procedural Swelling	2.1%	0%	0	0

Adverse events derived from 2 pivotal studies. Table adapted from product information[1]
Study 1: Bunionectomy[4]
Study 2: Hemorrhoiddectomy[5]

Other Adverse Events[1,29]

Less common adverse events defined as an incidence of less than 2% were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, procedural hypertension, procedural hypotension, muscular weakness, neck pain, pruritus generalized, rash pruritus, hyperhidrosis, cold sweat, palpitations, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, anxiety, confusion, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory failure, body temperature increase, oxygen saturation decreased, urinary retention, urinary incontinence, blurry vision, tinnitus, and hypersensitivity.

Tolerability

Bupivacaine liposomal injectable suspension is generally well tolerated. Common adverse events were mostly assessed as mild or moderate severity[2,29]. When compared directly to unencapsulated bupivacaine HCl, liposomal bupivacaine was equally well tolerated.

For further details on safety results of the clinical trials, refer to *Appendix: Clinical Trials*.

Contraindications

Use of Bupivacaine liposomal injectable suspension is contraindicated in the setting of obstetrical paracervical block anesthesia. Bupivacaine liposomal injectable suspension has not been tested using this technique; however, administration of bupivacaine HCl with this technique has resulted in fetal bradycardia and death[1].

Warnings and Precautions

Potential life-threatening adverse effects: Bupivacaine liposomal injectable suspension should be administered in a setting where trained personnel and equipment are available to promptly treat patients displaying evidence of neurological or cardiac toxicity. Cardiovascular, respiratory, and neurological status, as well as vital signs should be monitored during and after administration.

Central Nervous System Reactions: The occurrence of neurologic adverse events with local anesthetics is related to the total dose administered. However, other factors may increase the incidence and include the specific anesthetic used, the route of administration and the patient's health status. Early signs of central

nervous system toxicity include restlessness, anxiety, incoherent speech, lightheadedness, numbness, tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, twitching, tremors, depression, or drowsiness. Symptoms may proceed to convulsion, followed by unconsciousness and respiratory arrest. Incidence of convulsions is associated with total dose administered and varies with procedure. Local anesthetics have been associated with localized neurological toxicity, which encompasses numbness, weakness, and paralysis, and may be slow to resolve or be partially or completely irreversible.

From the clinical trials involving wound infiltration with liposomal bupivacaine, the following neurologic adverse events were reported with an incidence of at least 1%: dizziness (6.2%), headache (3.8%), somnolence (2.1%) and lethargy (1.3%)[1].

Cardiovascular System Reactions: Toxic blood concentrations depress cardiac conductivity and excitability leading to atrioventricular block, ventricular arrhythmias, cardiac arrest, and fatalities. Myocardial contractility is depressed and peripheral vasodilation, decreased cardiac output, and decreased arterial blood pressure can result.

An analysis, involving a number of clinical trials, was conducted to determine if wound infiltration with liposomal bupivacaine led to clinically important electrocardiogram (ECG) changes or cardiac related adverse events. In the analysis, no cardiac safety issues were identified[22]. In all the wound infiltration studies involving liposomal bupivacaine, adverse cardiac events reported with an incidence of at least 1% were as follows: tachycardia (3.9%) and bradycardia (1.6%)[1].

Cardiovascular disease: Use with caution in patients with cardiovascular disease including patients with hypotension or heart block since they may be less capable of compensating for functional changes associated with prolongation of AV conduction.

Hepatic impairment: Use with caution in hepatic impairment since bupivacaine is hepatically metabolized. Patients with severe hepatic impairment are at a greater risk of developing toxic plasma concentrations.

Multiple doses: Injections of multiple doses of bupivacaine liposomal injectable suspension may cause significant increases in plasma concentration due to slow accumulation or slow metabolic degradation.

Hypersensitivity: Systemic hypersensitivity reactions have been reported. These reactions are rare, and may include urticaria, pruritus, angioneurotic edema, tachycardia, sneezing, and possibly anaphylactoid-like symptoms.
Accidental intravascular injection: Avoid accidental intravascular injection. Convulsions and cardiac arrest have been reported with intravascular injection of bupivacaine.

Other local anesthetics: Wait 96 hours after administration of bupivacaine liposomal injectable suspension before administering other bupivacaine products. Use of bupivacaine liposomal injectable suspension and other bupivacaine containing products has not been studied. Wait at least 20 minutes after administration of local lidocaine to administer bupivacaine liposomal injectable suspension

Pre-incisional or pre-procedural anesthetic techniques: Bupivacaine liposomal injectable suspension is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

Administration: Epidural, intrathecal, regional nerve block and intravascular or intra-articular routes of administration or types of analgesia have not been evaluated for liposomal bupivacaine and therefore are not recommended.

Chondrolysis: Intra-articular infusions of local anesthetics have been described in post marketing reports, and have resulted in chondrolysis. There have been case reports of chondrolysis from local, single-dose use of bupivacaine dating back to 1979 due to intra-articular administration. Intra-articular use of liposomal bupivacaine has not been evaluated and is not recommended.

Special Populations

Safety and effectiveness of liposomal bupivacaine has not been evaluated in patients below the age of 18 years old, pregnant patients, or patients who are nursing[1].

Pregnancy: Category C. Bupivacaine liposomal injectable suspension has not been studied in adequate, well-controlled studies in pregnant women of the effect on the developing fetus. Only consider bupivacaine liposomal injectable suspension during pregnancy if potential benefits justify the risk to the fetus.

Bupivacaine HCl was administered subcutaneously to rats during fetal organogenesis and no embryo-fetal effects were observed in rats at high doses. Administration during pregnancy and lactation resulted in decreased offspring survival. Studies in rabbits showed an increase in embryo-fetal deaths at high doses in the absence of maternal toxicity[1-3].

Nursing mothers: Bupivacaine is excreted to some extent during lactation. A theoretical potential exists for a nursing infant to be exposed to the drug and is therefore, not recommended.

Pediatric: Bupivacaine liposomal injectable suspension safety and effectiveness has not been established in patients below the age of 18 years old.

Geriatric: In the bupivacaine liposomal injectable suspension wound infiltration clinical studies, no overall difference was found for safety or effectiveness between patients greater than 65 years of age and younger patients. A total number of 171 patients of 823 (20.8%) were greater than 65 years old. Although clinical experience has not identified differences between these populations, greater sensitivity in some older individuals cannot be ruled out. Bupivacaine liposomal injectable suspension is excreted by the kidneys; elderly patients are more likely to be at risk of toxicities as they are more likely to have decreased renal function[1].

Hepatic Impairment: Bupivacaine liposomal injectable suspension is metabolized by the liver and should be used with caution in patients with hepatic impairment. Patients with severe hepatic disease are at greater risk of toxic plasma concentrations. In patients with moderate hepatic impairment, mean plasma concentrations were higher than in healthy control volunteers with approximately 1.5 and 1.6 fold increases in mean C_{max} and AUC, respectively. However, there are no dosage adjustments for hepatic impairment provided in the manufacturer's labeling.

Table 6. Role of hepatic function on bupivacaine pharmacokinetics after bupivacaine liposomal injectable suspension administration[2]

Mean (Standard Deviation)	Moderate hepatic impairment (n=9)	Normal hepatic function (n=9)
C_{max} (ng/mL)	149.1 (42.6)	102.8 (37.7)
T_{max} (h)	42.7 (28.2)	54.7 (28.8)
$AUC_{l0\text{-}last)}$ (h • ng/mL)	17,177.8 (2349.3)	10,682.7 (4392.6)
$AUC_{l0\text{-}\infty)}$ (h • ng/mL)	17,975.5 (2447.0)	11,050.7 (4498.8)
Half-life (h)	46.5 (26.3)	37.6 (9.8)
Cl/F (L/h)	17.0 (2.2)	31.2 (11.5)
Vd/F (L)	1131.6 (624.4)	1742.1 (861.9)

Renal Impairment: Bupivacaine liposomal injectable suspension is excreted by the kidneys. Caution should be used in patients with impaired renal function due to the potential risk of toxic concentrations. No dosage adjustment is provided in the manufacturer's labeling for patients with renal impairment. However, the manufacturer indicates that care should be taken in proper dose selection in these patients. There are no studies examining the use of bupivacaine liposomal injectable suspension in patients on dialysis.

Sentinel Events

There are no sentinel events that have been reported in association with bupivacaine liposomal injectable suspension.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of the Joint Commission standards, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name bupivacaine liposome injectable suspension[2]:

- Mepivacaine
- Ropivacaine
- Non-liposomal bupivacaine (bupivacaine HCl)
- Buprenorphine
- Benzocaine

Bupivacaine liposomal may be confused with propofol due to similar white, milky appearance. Of note: This is on the ISMP high alert list of drug classes which have a heightened risk of causing significant patient harm when used in error.[31]

Accidental administration of Bupivacaine liposomal injectable suspension intravenously may result in atrioventricular block, ventricular arrhythmias, and cardiac arrest. No errors had been reported to the FDA by the manufacturer as of March 2012, however, it is recommended that prepared syringes be properly labeled, vials separated, and directions for managing bupivacaine toxicity be available[3].

LA/SA for trade name Exparel®

- Eldepryl
- Extavia
- Enalapril
- Estriol
- Enbrel
- Exterol
- Isuprel

Drug Interactions

Drug-Drug Interactions

- If diluting, only dilute using sterile, preservative-free normal (0.9%) saline for injection. DO NOT dilute with water or other hypotonic agents as these may disrupt the liposomal structure.
- Do not mix with other drugs prior to administration due to possible free drug rapid release from liposomes with direct contact.
- Do not admix bupivacaine liposomal injectable suspension with any other product in the same syringe.
- If concurrently using with locally administered drugs or antiseptics, allow site to dry completely before administration.

Lidocaine and Other Non-Bupivacaine-Based Local Anesthetics

If administered together locally, non-bupivacaine based local anesthetics (i.e. lidocaine, ropivacaine, mepivacaine) may cause an immediate displacement of the bupivacaine from the multivesicular liposomes, potentially affecting the efficacy and safety of the product. This displacement is the result of increased affinity of non-bupivacaine based local anesthetics to the liposomes.

Local administration of bupivacaine liposomal injectable suspension and lidocaine should be separated by at least 20 minutes to negate any displacement and avoid an interaction. Bupivacaine liposomal injectable suspension can be administered in the same area at least 20 minutes after local administration of lidocaine. If the time between lidocaine and bupivacaine liposomal injectable suspension is 5 minutes, 10 minutes, 20 minutes; then the plasma bupivacaine C_{max} increases by 100%, 67%, or 0%, respectively.

Bupivacaine HCl
Other formulations of bupivacaine should not be administered within 96 hours following administration of bupivacaine liposomal.

Topical Antiseptics
Because of the surfactant properties of topical antiseptics (e.g., povidone iodine or chlorhexidine), skin surface should be allowed to dry completely prior to administration of bupivacaine liposomal injectable suspension.

Coadministration[2]
The following medications have shown minor to no interaction with Bupivacaine liposomal injectable suspension and can be co-administered at the same infiltration area: corticosteroids, gentamicin, bacitracin, cefazolin, ketorolac, and opioids.

Acquisition Cost

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

There are a number of trials that are planned or underway to determine the economic advantage of bupivacaine liposomal and can be viewed on the clinicaltrials.gov website. However, there is one published economic trial in adult patients having open colectomy. This trial is a single-center, open-label, nonrandomized trial in 39 patients. Patients were sequentially assigned to the first cohort of patient controlled analgesia (PCA) with opioids until the patient was discharged or able to tolerate oral medication (then received oxycodone alone or combined with acetaminophen) (n=18). The second cohort was enrolled once the first cohort was fully enrolled. In the second cohort, patients received “multimodal therapy” which included receipt of a single dose of liposomal bupivacaine 266 mg administered into the surgical site prior to wound closure (n=21). This cohort also received ketorolac 30 mg (or other NSAID) at the end of surgery followed by 1000 mg of acetaminophen and ibuprofen 600 mg every 6 hours for 72 hours after surgery; starting once patients were able to take oral medications. Both groups were offered rescue analgesia with IV opioids or oxycodone 5 mg/acetaminophen 325 mg every 6 hours if needed until discharge. There were three primary outcome measures including total mg amount of morphine equivalents post surgery through discharge; total hospitalization cost; and length of hospital stay. Although there was a difference in total mg amount of opioid consumed (57 mg vs. 115 mg) in favor of liposomal bupivacaine (Cohort 2), there were too many variables since the groups did not receive the same standard baseline pain regimen post-op. Cohort 1 received an opioid-based PCA as their analgesic regimen while Cohort 2 received IV ketorolac 30 mg post-op and scheduled dosing of maximum daily doses of acetaminophen and ibuprofen as their analgesic regimen. The study design does not allow for concluding that the difference in mg amount of opioid was due to use of liposomal bupivacaine. Costs and length of stay were also different in favor of liposomal bupivacaine but since the post-op analgesia regimens were not matched, and Cohort 1 involved the use of PCA, the cost difference of using a PCA pump vs. oral medications could account for the difference. There were no differences in hospital readmission, unplanned visits or contact to medical provider, or health problems after discharge. The primary limitation of the study was in its design. It was a single-center, open-label, nonrandomized study with a small sample size and included too many variables to draw any conclusions about the findings[27].

Conclusions

Bupivacaine liposomal injectable suspension (Exparel®) is an amide-type local anesthetic in an encapsulated liposomal formulation developed with the goal of providing a longer duration of anesthesia compared with its non-liposomal counterpart, bupivacaine hydrochloride or other local anesthetics. The product utilizes the DepoFoam® drug delivery system consisting of an aqueous suspension of multivesicular liposomes containing bupivacaine in a honeycomb-like structure that allows for a more gradual release. The FDA approved it in October 2011 for single-dose infiltration into the surgical site for postoperative analgesia.

To date, there have been a limited number of published clinical trials evaluating the safety and efficacy of liposomal bupivacaine. Three were phase 3 pivotal trials reviewed by the FDA for final approval, two of them comparing liposomal bupivacaine to placebo and one comparing liposomal bupivacaine to unencapsulated bupivacaine HCl/epinephrine (unpublished). In each of the trials, the primary endpoint was pain intensity and duration using the numeric pain rating score through a predetermined period of time postoperatively (24, 72 and 96 hrs). In the placebo-controlled trials (1-bunionectomy, 1-hemorrhoidectomy) liposomal bupivacaine was associated with statistically less intense pain through the stated time period compared to placebo. In addition, opioid consumption was statistically less in favor of liposomal bupivacaine versus placebo, but the clinical relevance of the difference is unknown (Golf-3.8 vs. 4.7 tabs of oxycodone 5 mg/APAP 325 mg tablets at 24 hrs, p=0.008 and Gorfine-22.3 mg vs. 29.1 mg morphine equivalents at 72 hrs, p=0.0006). In an unpublished study, liposomal bupivacaine was not statistically different from unencapsulated bupivacaine HCl/epinephrine in reducing pain intensity through the specified time points or other secondary outcome measures in patients following hemorrhoidectomy. The FDA reviewer highlighted some important points regarding the results of these three trials as follows:

- In the two pivotal, placebo controlled trials, liposomal bupivacaine provided postoperative analgesia for up to 24 hours in patients having bunionectormy or hemorrhoidectomy surgery. In these studies, pain intensity was significantly reduced in patients receiving liposomal bupivacaine compared to placebo for the initial 12 hours after infiltration, but diminished over the subsequent 12 hours resulting in no clinical meaningful difference in pain between groups beyond 24 hrs.
- Unpublished, active comparison: Based upon the results, investigators failed to show any statistically or clinically meaningful advantage of liposomal bupivacaine over bupivacaine HCl when used after hemorrhoidectomy, despite examining over 60 different efficacy endpoints. Both agents were equally well tolerated.
- The manufacturer did request a priority review. However, that request was denied since the manufacturer was unable to demonstrate that the use of liposomal bupivacaine reduces the use of opioids or their associated adverse events or has shown relevant benefit in reduced time to discharge or return to usual activities.
- Since different doses and manner of administration were used in the two studies, extrapolation of dosing and effectiveness to other surgical interventions is not possible. Additional studies are needed to answer the question of appropriate dose and manner of administration for use in other surgeries.
- Original recommendation was for the labeling to specifically include postoperative use following bunionectomy or hemorrhoidectomy. The final labeling was less specific.
- Labeling should contain a strong caution against use of liposomal bupivacaine by other administration routes (other than single-dose, postoperative wound infiltration) that are commonly used with other local anesthetics in clinical practice but may be unsafe for this product.

As for other studies, there have been two published phase 2 trials (1-hemorrhoidectomy[9], 1-total knee arthroplasty[10]) and two phase 3 trials (1-total knee arthroplasty[11], 1-breast augmentation[18]) comparing the cumulative pain scores between liposomal bupivacaine and unencapsulated bupivacaine HCl (0.25% with epinephrine 1:200,000). In the phase-2 studies, the primary endpoint of cumulative pain intensity was met in favor of the liposomal product[9,10] but not in the phase-3 studies[18]. However, since the analysis of pain intensity was determined over the entire planned study length (through 72 hrs or 4 days), the differences at the various time points were not entirely consistent between studies to determine the actual length of time the differences between groups existed or if the differences were clinically important. For example in the pivotal trials, the primary endpoint was reportedly met through 72 hrs but when the FDA reviewer reported their findings, the statistical difference from placebo was present only through 24 hours, but not beyond. In each of the studies, sample sizes were small, multiple comparisons between groups at a number of time points were made with some showing statistical benefit of the liposomal product and others not, and post-hoc changes were made to the analysis of one of the studies, thereby limiting the strength of the evidence[9]. In

three of the studies, there was no statistical or clinically important difference in total consumption of opioids, discharge readiness, proportion of patients who were opioid free or who were able to return to work or resume normal daily activities.

With regard to safety, liposomal bupivacaine was well tolerated and adverse events were not significantly different than bupivacaine HCl/epinephrine or placebo when administered as a single-dose infiltrated into the surgical site after bunionectomy or hemorrhoidectomy. The most common adverse events reported with bupivacaine liposomal injectable suspension were constipation, nausea, and vomiting. Similar to other local anesthetics, there is a potential for neurologic or cardiovascular adverse events and is related to the total dose administered. However, other factors may increase the incidence and include the specific anesthetic used, the route of administration and the patient's health status. Early signs of central nervous system toxicity include restlessness, anxiety, incoherent speech, lightheadedness, numbness, tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, twitching, tremors, depression, or drowsiness.

Since liposomal bupivacaine has not been studied or data are limited in patients undergoing other types of surgery (aside from bunionectomy or hemorrhoidectomy), the safety, efficacy and appropriate doses of liposomal bupivacaine are not known and therefore, use after other surgeries is not recommended. Furthermore, other routes of administration or types of analgesia have not been studied and therefore, use is not recommended (e.g., epidural, intrathecal, regional nerve block or intravascular or intra-articular use).

Although liposomal bupivacaine statistically reduced pain intensity in patients undergoing bunionectomy or hemorrhoidectomy when compared to placebo, there was no difference in the primary outcome or secondary outcomes when compared to traditional unencapsulated bupivacaine HCl in an unpublished phase 3 pivotal trial in patients undergoing hemorrhoidectomy. In two phase 2, dose-ranging studies, liposomal bupivacaine was associated with improved cumulative pain scores compared to bupivacaine HCl but differences in total consumption of opioids, readiness for discharge, proportion of patients who were opioid free or who were able to return to work or resume normal activities were not different between the two bupivacaine products. Since the safety and efficacy of liposomal bupivacaine has been evaluated primarily in patients undergoing hemorrhoidectomy or bunionectomy (using a single-dose infiltrated into the surgical site), the safety and efficacy when used after other surgeries; by other routes of administration; or use for other types of analgesia are unknown and therefore, use is not recommended in these settings. Based on the existing evidence, there are no clear or substantive advantages of the liposomal bupivacaine product over bupivacaine HCl. To date, there are no clinical trials comparing liposomal bupivacaine to other local anesthetic agents and therefore any clinically important advantages or disadvantages of the liposomal product are unknown.

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31.

Exparel Alert PDF.pdf

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Appendix 1.

A literature search using PubMed/Medline and Google Scholar was conducted using the following search terms: "bupivacaine", "sustained release encapsulate bupivacaine", "liposome bupivacaine," "bupivacaine liposomal injectable suspension," "post-surgical analgesia", "local anesthetic and pain relief", "liposome anesthetic" and "Exparel". Reference lists of selected articles related to bupivacaine and the product dossier were also used to identify additional sources of data. Published clinical trials examining the efficacy and/or safety of bupivacaine in humans and for approved indications were included. Included studies were limited to English language. All randomized controlled trials were published in the manufacturer's New Drug Application to the FDA.

Clinical Trials (Phase-2 and Off-Label) Evidence Summary Table

Ref. and Evidence	Drug	N	Time	Demographics	Design*	End Points/Results/Comments
Bupivacaine ER Liposome Injection Exhibits a Favorable Cardiac Safety Profile. Bergese SD, et al.[22]	A. Exparel® 532 mg SC B. Exparel® 655 mg SC	16	---	---	· R · OL · Seq	· No change from baseline in QtcI of >60 msec with any dose of EXPAREL
High-Dose Bupivacaine Remotely Loaded into Multivesicular Liposomes Demonstrates Slow Drug Release Without Systemic Toxic Plasma Concentrations After Subcutaneous Administration in Humans. Davidson EM, et al.[23]	A. Exparel® 400 mg B. Bupivacaine HCl 200 mg	8	8 days	· Adults (age 18-45 years) · Within 20% of IBW · No medications in past week	· OL · CO	· Peak plasma bupivacaine concentrations were similar in the two groups, despite a 4-fold increase in total bupivacaine dose administered with the novel liposomal preparation · Administration of 0.5%, 1%, & 2% LMVV bupivacaine provided 19, 38, & 48 hours of analgesia, respectively, compared to 1 hour for the standard 0.5% bupivacaine control
The Pharmacokinetics and Pharmacodynamics of Liposome Bupivacaine Administered via a Single Epidural Injection. Viscusi ER, et al.[34]	A. Exparel® 89 mg B. Exparel® 155 mg C. Exparel® 266 mg D. Bupivacaine HCl 50 mg	30	96 hours	· Adults (age 18-49 years) · BMI <35 kg/m^2 · 100% male · 100% white	· R · DB · AC · Seq	· All doses of Exparel® exhibited significantly greater AUC_{0}-t_{last} and $AUC_{0\text{-}[infinity]}$ than bupivacaine HCl and a longer T_{max} · P<0.001 · Mean C_{max} values in the Exparel® 89 mg & 155 mg groups were statistically significantly lower than the C_{max} values for bupivacaine HCl · P<0.001 · Mean C_{max} after administration of Exparel® 266 mg was not statistically significantly different from bupivacaine HCl 50 mg · Half-life was similar across the Exparel® groups (14.0-19.3 hours) & ~3x longer than bupivacaine HCl (5.7 hours)
A 2 Year Observational Study Assessing the Safety of DepoFoam Bupivacaine after Augmentation	Study 1: A. Exparel® 133 mg or 266 mg in	94	Mean 15-21 months	· Adults (mean age 31.5 y)	· MC · O	· Long-term safety follow-up: Most (>90%) subjects had no change in breast size or shape or changes in skin or nipple. When noted, such changes were most commonly attributed to scar contracture.

Mammoplasty. Minkowitz H, et al.[7]	one breast pocket B. Bupivacaine HCl 75 mg in the contralateral side <u>Study 2:</u> A. Exparel® 266 mg in each side (total dose 532 mg) B. Bupivacaine HCl 100 mg in each side (total dose 200 mg)			· Underwent bilateral cosmetic, submuscular breast augmentation · Participated in previous studies (Smoot 2012, Minkowitz 2012) · 87.2% white		· In study 1, the incidence of uneven appearance of breasts was low (16.1% for EXPAREL and 6.3% for bupivacaine HCl; mean time to appearance 7.18 and 14.19 months, respectively), and the difference between the groups was not likely to be clinically significant. · In study 2, one bupivacaine HCl recipient had uneven appearance of breasts at approximately 12 months. There were no reports of palpable hard knots or swelling, and one report of signs of irritation or implant leakage. There was no clear evidence that either EXPAREL or bupivacaine HCl was associated with changes in sensation or any other abnormal finding.
A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Sustained-Release Encapsulated Bupivacaine Administered as a Nerve Block in the Management of Postoperative Pain in Subjects Undergoing Bunionectomy. Pacira Pharmaceuticals, Inc: Data on File[8]	A. Exparel® 155 mg B. Exparel® 200 mg C. Exparel® 244 mg D. Exparel® 279 mg E. Exparel® 310 mg F. Bupivacaine HCl 125 mg	58	96 hours	· Adults (mean age 52-59 years) · Undergoing a unilateral first metatarsal bunionectomy repair · Under general Anesthesia · >90% white · 57-92% female	· MC · R · DB · PG · AC	· Primary: Median time to first use of supplemental postsurgical pain medication (opioid or nonopioid) significantly longer for bupivacaine HCl vs EXPAREL 200 mg (9.42 vs 1.24 h); no significant difference vs EXPAREL 155 mg (1.94 h) and 310 mg (2.43 h) · P<0.001; P>0.05 · Secondary: Median time to first supplemental postsurgical opioid medication was 96 hours for all treatment groups except EXPAREL 200 mg (7.3 h) · P>0.05 · Secondary: 33.3% to 64.3% of EXPAREL recipients and 55% of bupivacaine HCl recipients did not take supplemental opioid medication · P>0.05 · Secondary: The quantity of supplemental opioid medication used postsurgically was similar for EXPAREL 310 mg vs bupivacaine HCl, with an adjusted mean ratio of 0.86 (95% CI 0.25, 3.00). Adjusted mean ratios for EXPAREL 155 mg and 200 mg vs bupivacaine HCl were 1.37 (95% CI 0.37, 5.37) and 2.56 (95% CI 0.69, 9.49), respectively. · Secondary: VAS-A and VAS-R scores higher in all EXPAREL groups vs bupivacaine HCl for the first 12 h, but generally lower with EXPAREL 310 mg vs bupivacaine HCl from 24 to 96 h · P>0.05 · Secondary: Integrated assessment of VAS scores and total opioid usage showed a lower effect for EXPAREL 155 mg and 200 mg vs bupivacaine HCl throughout the 96-h assessment period, and a better effect for EXPAREL 310 mg vs bupivacaine HCl after 12 h; integrated assessment AUC0-96 for EXPAREL 310 mg was better (> 4-fold greater) than bupivacaine HCl at rest and slightly worse (25% lower AUC) with activity, but no significant differences between the 2 treatment groups at any time point. · P>0.05

A Double-Blind Randomized, Active Controlled Study for Post-Hemorrhoidectomy pain Management with DepoFoam Bupivacaine, a Liposomal Local Analgesic. Haas E, et al.[9]	A. Exparel® 67 mg B. Exparel® 200 mg C. Exparel® 266 mg D. Bupivacaine HCl 75 mg	100	96 hours	· Adults (mean age 43 y) · Undergoing hemorrhoidectomy · Under general anesthesia · 94% white	· MC · R · DB · PG · AC	· Primary endpoint: EXPAREL 266 mg contained greatest number of subjects receiving no supplemental opioid pain medication · P>0.05 · Secondary: Significantly less opioid pain medication consumed by subjects in the EXPAREL 266 mg at 24, 36, 48, 72, 84, and 96 h · P≤0.035 · Secondary: AUC of NRS-R scores significantly reduced in all EXPAREL treatment groups compared with bupivacaine HCl through 12, 24, 36 (75 mg group was not significant), 48 (75 mg group was not significant), 60 (75 mg group was not significant), 72, 84, and 96 h · P<0.05 · Secondary: Significant improvements in integrated analysis of AUC NRS-R scores and supplemental opioid pain medication usage observed in the EXPAREL 200 mg and 266 mg groups over 12, 24, 36, 48, 60, 84 and 96 h, and in the EXPAREL 75-mg group over 72 and 96 h vs bupivacaine HCl · P<0.05 · Secondary: Significant improvements in subject QOL (VAS score) observed at 48 h in the 266 mg EXPAREL treatment group, at 72 h in the 67, 200, and 266 mg EXPAREL treatment groups, and at 96 h in the 266 mg EXPAREL treatment group, compared with bupivacaine HCl group · P≤0.029 · Secondary: Over the first 3 postsurgical days, EXPAREL 266 mg significantly reduced pain intensity by 47%, opioid use by 66%, and opioid-related side effects by 89%, relative to bupivacaine HCl 75 mg · P<0.05 for all
A Randomized, Double-Blind, Dose-Ranging Study Comparing Wound Infiltration of DepoFoam Bupivacaine to Bupivacaine HCl for Postsurgical Analgesia in Total Knee Arthroplasty. Bramlett KW, et al.[10]	A. Exparel® 133 mg B. Exparel® 266 mg C. Exparel® 399 mg D. Exparel® 532 mg E. Bupivacaine HCl 150 mg	138	5 days	· Adults (mean age 62 y) · Undergoing TKA · Under general anesthesia · 62% female · 92% white	· MC · R · DB · PG · AC	· Primary: Comparable pain intensity during activity (NRS-A AUC0-4d) in each group · P>0.05 · Secondary: Comparable proportion of subjects in each group required no supplemental opioid medication post-surgically, and the total postsurgical opioid consumption did not differ between groups · P>0.05 · Secondary: Significantly lower cumulative pain intensity at rest (AUC NRS-R) with EXPAREL 532 mg vs bupivacaine HCl through Day 2, 3, 4 and 5 · P≤0.015 · Secondary: Bupivacaine HCl more effective than EXPAREL 133 mg in integrated analysis of cumulative pain intensity during activity or rest + supplemental opioid use · P<0.05 · Secondary: EXPAREL 266 mg or 399 mg significantly delayed time to first opioid medication vs bupivacaine HCl · P≤0.005

						· Secondary: EXPAREL 266 mg or 399 mg significantly delayed time to first occurrence of PONV vs bupivacaine HCl · P<0.05
The Efficacy and Safety of DepoFoam Bupivacaine in Patients Undergoing Bilateral, Cosmetic, Submuscular Augmentation Mammoplasty. Smoot JD, et al.[18]	A. Exparel® 266 mg in each side (total dose 532 mg) B. Bupivacaine HCl 100 mg in each side (total dose 200 mg)	136	96 hours	· Adults (mean age 31 y) · **U**ndergoing bilateral cosmetic, submuscular breast augmentation · Under general anesthesia	· MC · R · DB · PG · AC	· Primary: NRS-A AUC0-72 similar (441.0 for EXPAREL and 467.2 with bupivacaine HCl); study terminated early so not powered to detect a difference in primary endpoint · P>0.05 · Secondary: NRS-A and NRS-R AUCs similar among treatment groups at all post-dose assessments (12, 24, 36, 48, 60, 72, 84, 96 h) · P>0.05 · Secondary: NRS-A scores significantly lower for EXPAREL vs bupivacaine HCl at 8 h and 12 h, and NRSR significantly lower at 8 h · P<0.05 · Secondary: Postsurgical opioid consumption significantly lower for EXPAREL vs bupivacaine HCl at 24 h (9.73 vs 13.68 mg morphine equivalents) and 48 h (18.44 vs 55.69 mg) · P<0.05 · Secondary: No significant difference in median time to first opioid analgesia (2.9 vs 2.5 h for EXPAREL vs bupivacaine HCl) · P>0.05 · Secondary: Integrated assessment of NRS-A scores and opioid usage significantly favored EXPAREL at 12 and 48 h, as did integrated assessment of NRS-A AUC and opioid usage between 12 and 72 h and at 96 h · P<0.05 · Secondary: Integrated assessment of NRS-R scores and opioid usage significantly favored EXPAREL at 12, 48, and 60 h, as did integrated assessment of NRS-R AUC and opioid usage assessment at 72 and 96 h · P<0.05
Efficacy Profile of Liposome Bupivacaine, a Novel Formulation of Bupivacaine for Postsurgical Analgesia. Bergese S, et al.[26]	A. Exparel® 532 mg B. Bupivacaine HCl 200 mg	218	96 hours	· Adults (mean 66 y) · Undergoing TKA · **U**nder general or spinal anesthesia, · 64% female · 84% white	· MC · R · DB · PG	· Primary: Comparable pain intensity during activity (NRS-A AUC0-96) in each group · P=0.1266 · Secondary: Higher mean NRS-A score with EXPAREL vs bupivacaine HCl at 48 h · P=0.363 · Secondary: Comparable total postsurgical opioid consumption in both groups · P>0.05 · Secondary: Comparable pain scores (NRS-1 or NRS-R) at all time points and AUCs of pain scores in both groups · P>0.05 · Secondary: Comparable QOL scores (EQ-5D) in both groups

						· P>0.05 · Secondary: Comparable time to physical recovery and return to daily activities in both groups · P>0.05
Bupivacaine ER Liposome Injection does not Prolong QTc Interval in a Thorough QT/QTc Study in Healthy Volunteers. Naseem A, et al.[25]	A. Exparel® 300 mg B. Exparel® 450 mg C. Exparel® 600 mg D. Exparel® 750 mg E. Moxifloxacin 400 mg	Part 1: 49 Part 2: 16	96 hours	· Adults (mean age 26 years) · No history of CV disease · No abnormal ECGs · Nonsmoking	<u>Part 1:</u> · R · DB · AC · CO <u>Part 2:</u> · OL · Seq	· The 300 mg & 450 mg Exparel® produced mean QTc shortening of −2.24 ms & −2.45 ms, respectively · Upper limit of 2-sided 95% CI <10 ms · Mean QTc prolongation of −3.6 ms (600 mg) & −7.67 ms (750 mg) was identified · Upper limit of 2-sided 95% CI <10 ms · All four doses of Exparel® produced a slight shortening of the QTc interval, but only in the 600 mg dose was statistical significance not reached · Findings suggest that all tested doses of Exparel® do not have any clinically significant effect on QTc
Extended pain relief trial utilizing infiltration of Exparel®, a long-acting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy Cohen SM.[27]	A. Exparel® 266mg + IV NSAIDs followed by PO NSAIDs B. PCA with IV morphine or hydromorphone	39	10 days	· Adults (mean age 54 years) · Undergoing colectomy procedure · No history of alcohol/drug abuse	· OL · Seq · AC	· Both treatment arms were offered rescue analgesia with IV opioids and/or oxycodone/APAP 5/325mg q 6h prn until discharge · Exparel® group was associated with a 50%reduction in average amount of opioids used s/p surgery, a 59% shorter hospital stay, and 26% lower total average hospital costs compared with the opioid based regimen. · p= 0.025, p= 0.004, p= 0.027, respectively · Mean QTc prolongation of −3.6 ms (600 mg) & −7.67 ms (750 mg) was identified · Upper limit of 2-sided 95% CI <10 ms · Open-label study design weakens generalizability of results and increase risk for bias. Small sample size and use of rescue opioids in both groups also weakens the study.
MC=multicenter; R=randomized; DB=double-blind; PC=placebo-controlled; AC=active-controlled, PG=parallel group; CO =crossover; NRS-R=pain intensity score at rest; NRS-A=pain intensity score during activity; NRS AUC=cumulative pain intensity score; QOL=quality of life; Seq=sequential; VAS=visual analog scale; h=hours.						