

**Does liposomal bupivacaine improve postoperative pain control  
after one level posterior spinal fusion with instrumentation?**

Christopher Alcala-Marquez, MD

Principal Investigator

Manuel R. Pinto, MD

Co-Investigator

Twin Cities Spine Surgeons and Allina Health

**Study Synopsis**

This study will describe postoperative pain management for spine surgery patients receiving Exparel® (liposomal bupivacaine) compared to patients not receiving the drug. It is a prospective, randomized Phase 4 (post-market) clinical trial with two cohorts: Group A: standard of care (SOC) *plus* Exparel (n=30) and Group B: SOC (n=30). All subjects will undergo open single-level posterior decompression and instrumented fusion for degenerative spondylolisthesis. The surgery is not an experimental procedure. Prior to closing the surgical wound, Exparel will be administered to Group A. The administration of the drug is a study procedure. Postoperatively, subjects will be assessed for pain and opioid consumption. The study is funded by the John H. Moe Research Fund of Twin Cities Spine Center. Study procedures occur at Twin Cities Spine Center and Allina Health facilities. Subjects incur no costs.

**Background**

*Postoperative Pain Management*

Good pain control after surgery is associated with higher satisfaction rates.<sup>1</sup> On the other hand, inadequate postoperative pain management is associated with patient dissatisfaction with medical care.<sup>2</sup> It has been shown that Patient Controlled Analgesia (PCA) reduces postoperative pain but the opioids delivered can provoke adverse effects such as respiratory depression leading to hypoxemia (decreased blood oxygen saturation). Such adverse effects may prolong hospitalization.<sup>3,4</sup> The Joint Commission recommends that surgical-site specific local anesthetic infiltration be considered for acute postoperative pain management for those procedures when

evidence indicates efficacy.<sup>5</sup> Locally-injected analgesic drugs can significantly reduce PCA, increase patient satisfaction, and decrease length of stay.<sup>1</sup>

### *Liposomal Bupivacaine for Postoperative Pain*

Liposomal bupivacaine (Exparel) may be injected locally to achieve postoperative pain control for 72-96 hours.<sup>6</sup> Exparel was first approved by the US FDA for analgesia following bunionectomy and hemorrhoidectomy. Subsequently, the drug has been approved more broadly for post-surgical pain. Table 1 outlines a number of clinical trials conducted on patients undergoing total knee arthroplasty and total hip arthroplasty. Overall, patients receiving liposomal bupivacaine experienced less postoperative pain, used less opioid, and had shorter hospital stays. These and other studies also demonstrated that common instrumentation materials are unaffected by the drug and none have an adverse effect on the drug.<sup>13</sup>

Investigator	Patient Population	Study Design	Outcome
Barrington <sup>7</sup>	Total Joint Arthroplasty (Knee and Hip)	Liposomal bupivacaine injection (LBUP) (n=1124) <i>versus</i> multimodal analgesia including periarticular injection (n=1124)	Pain scores were significantly lower in the LBUP group for both hip and knee procedures. There was an increased number of pain-free patients, a decreased LOS, trends toward decreased falls, and a decreased overall cost for the LBUP cohort.
Cheridan <sup>8</sup>	Total Hip Arthroplasty	Liposomal bupivacaine (LBUP) suspension (n=5267) <i>versus</i> standard analgesic regimens (n=54,604)	Length of stay for the LBUP cohort was shorter compared to no injection cohort. Numbers patients being discharged to home compared to a short-term nursing facility or a rehab facility were higher in the LBUP cohort.
Chughtai <sup>9</sup>	Total Knee Arthroplasty	Liposomal bupivacaine (LBUP) suspension (n=14,668) <i>versus</i> no injection (n=80,160)	Length of hospital stay was shorter for the LBUP cohort. Patients being discharged to home compared with short-term nursing facility or rehabilitation was higher in the LBUP cohort compared with the no injection cohort
Emerson <sup>10</sup>	Total Hip Arthroplasty	Routine wound infiltration (RWI) (n=36) <i>versus</i> liposomal bupivacaine	Pain scores were significantly higher for RWI patients overall and trended higher for each day after surgery up to day 5. The average number of opioid doses

		infiltration injection (LBUP) (n=36)	was 2.6x greater for the RWI group compared the LBUP group. The total opioid dosage consumed was greater in the RWI group.
Emerson <sup>11</sup>	Total Knee Arthroplasty	Continuous femoral nerve block (FNB) (n=36) <i>versus</i> liposomal bupivacaine infiltration injection (LBUP) (n=36)	The average number of narcotic doses and the total number of narcotics consumed was greater in the FNB group. Average visual analog scale pain scores trended higher for FNB patients overall and for each day postoperatively up to day 5, although the overall difference was not significant in this study sample.
Yu <sup>12</sup>	Total Hip Arthroplasty	Intraoperative liposomal bupivacaine injection (LBUP) (n=586) <i>versus</i> standard pain management protocol (n=686)	Pain scores were similar between cohorts; LBUP cohort had decreased total narcotic use up to postoperative day 2 and physical therapy milestones were better achieved. OR time and hospital cost were unaffected. LB cohort exhibited a decrease in length of stay by 0.31 days and improvement in discharge disposition to home.

#### *Liposomal Bupivacaine for Postoperative Pain in Spine Patients*

Kim et al. compared lidocaine HCL to saline control in patients undergoing one-level lumbar laminectomy and discectomy.<sup>14</sup> The investigators intravenously administered lidocaine HCl preoperatively and throughout the spine surgery. Lydocaine HCL significantly reduced PCA consumption and decreased length of stay compared to the control. Because lydocaine HCL typically has an elimination half-life of 1.5 to 2 hours,<sup>15</sup> it must be administered repeatedly or continuously for post-surgical pain management. In contrast, liposomal bupivacaine is formulated for delayed release and has an effective duration of up to 96 hours. For this reason, liposomal bupivacaine is now being tested for postoperative pain management in patients who have undergone spine surgery (Table 2). While the results are encouraging, medical evidence is presently insufficient to recommend adopting the routine the use of Exparel in spine surgery patients. There have been no published prospective randomized control (Level I evidence) clinical trials to evaluate its efficacy and potential complications in spine surgery.

Investigator	Patient Population	Study Design	Outcome
Grieff <sup>16</sup>	Posterior cervical de-compression and fusion or lumbar fusion for spondylolisthesis and/or stenosis	Consecutive prospective case series (n=52 cervical and n=64 lumbar), bupivacaine HCL (Marcaine™) (n=65) <i>versus</i> liposomal bupivacaine (n=51)	A trend toward decreased PCA use with liposomal bupivacaine in comparison with bupivacaine hydrochloride was observed. The study suffered from low statistical power.
Kim <sup>17</sup>	Transforaminal Lumbar Interbody Fusion (TLIF)	Liposomal bupivacaine (n=38) <i>versus</i> non-liposomal local anesthetic (n=38)	Significantly lower pain scores, significantly fewer narcotic equivalents consumed, and significantly shorter lengths of stay for the LBUP group compared to the control group.
Puffer <sup>18</sup>	Single-level microdiscectomy	Prospective case series (n=40) versus historical control (n=40)	Significant decrease in length of time for narcotic pain medication for study group compared to control. No significant differences between cohorts in VAS pain in the postoperative period, in total injectable morphine equivalent doses, or in 30-day emergency room visits for pain
Tomov <sup>19</sup>	Single-level TLIF	Retrospective case-control series (n=16 intervention cohort, n=14 control cohort)	Significantly less morphine equivalents of intravenous narcotic use postoperatively in the intervention cohort from day of surgery to postoperative day 3 compared to control.
Wang <sup>20</sup>	Endoscopic single-level MIS TLIF without general anesthesia	Consecutive retrospective case series (n=10)	Length of hospital stay was reduced from typical 2 days to 1 day; Functional scores were statistically improved from preoperative values.

## Objectives

Opioids have demonstrated efficacy and often are drugs of choice for postoperative pain management. However, they are also associated with adverse effects including vomiting, pruritus, dizziness, somnolence, nausea, and constipation.<sup>21</sup> There are additional severe risks such as respiratory depression, bradycardia, and hypotension.<sup>22</sup> Long term adverse effects include iatrogenic addiction and opioid-induced hyperalgesia. Such complications have been shown to increase length of stay, costs, and mortality.<sup>23,24</sup> Prescribing liposomal bupivacaine for

postoperative pain management may reduce a patient's need for opioids and thereby decrease his or her pain scores and reduce his or her risk of adverse events; costs to ANW Hospital will be potentially reduced as the incidence of adverse events would be less.

### **Study Design**

This is a prospective randomized clinical trial with two cohorts: one experimental and one control. Our hypothesis for statistical analysis is that there will be a 30% decrease in pain medication requirement for the experimental group (Group A: Exparel) *versus* the control group (Group B: No Exparel). Based upon the data of others,<sup>14</sup> this would be a large effect (Cohen's  $d=1.4$ , Effect size ( $r$ ) = 0.6). For this anticipated effect size, a power level of 90% and a probability level of 5%, the minimum sample size per group is 9 for a one-tailed hypothesis. This study is designed for 30 subjects per cohort. We expect drop out to be low, so we also expect 30 per group to be sufficient.

The power analysis was based on a two-sample t-test. In the absence of data on the primary outcome variable (area under the curve (AUC) of the VAS pain intensity scores) to perform a power analysis, the decrease in analgesic use for the experimental group was used as a surrogate variable. Information on this substitute variable was gleaned from Grieff 2016, Yu 2016, and Chughtai 2016 (references cited in the protocol). We note that the proposed sample size is similar to that of other published studies cited in the protocol.

### **Test Article**

#### *Name*

Exparel® (liposomal bupivacaine).

#### *Dosage*

Exparel® (bupivacaine liposome injectable suspension) 20 mL single use vial, 1.3% (13.3 mg/mL), Maximum dose of 266 mg (20 mL).

#### *Method/route of administration*

Inject Exparel® slowly into soft tissue via infiltration.

*Mechanism of action*

Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

*Known Drug Interactions*

Exparel® should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics, Exparel® may be administered after at least 20 minutes or more have elapsed following local administration of lidocaine, Bupivacaine HCl, when injected immediately before or admixed with Exparel®, may impact the pharmacokinetic and/or physicochemical properties of the drugs.

*Known side effects*

Adverse reactions reported with an incidence greater than or equal to 10% following Exparel® administration were nausea, constipation, and vomiting.

*Manufacturer/Sponsor*

Pacira Pharmaceuticals, Inc.

*Name of Supplier*

Pacira Pharmaceuticals, Inc.

*Location of Supply*

Abbott Northwestern Hospital Pharmacy, United Hospital Pharmacy.

*IND Exemption*

The test drug is liposomal bupivacaine (Exparel®). Per the “Guidance for Clinical Investigators, Sponsors, and IRBs Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND,” clinical investigation of a

marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

- The drug product is lawfully marketed in the United States.  
This drug is lawfully marketed in the US.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.  
This drug will be used according to its current indications for use; there is no intent to use it to support a change in labeling.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.  
This study is an investigator-initiated study; the investigators have no relationship – financial or otherwise – with the manufacturer.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).  
This drug will be administered in a manner consistent with its current instructions for use.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).  
The Allina Health IRB is reviewing this study and its informed consent aspects.
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).  
This investigation is not intended to promote or commercialize the drug.

Therefore, the test drug does not require an IND.

## **Subject Selection**

### *Inclusion Criteria*

To be a participant, a patient must have both of the following:

1. Have a primary diagnosis of single-level lumbar stenosis, disc herniation, and/or spondylolisthesis excluding degenerative disc disease
2. Receive open, one-level posterior spinal fusion

### *Exclusion Criteria*

Excluded patients meet one or more of the following:

1. Are opioid-tolerant. Opioid tolerant patients are receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid.<sup>25</sup>
2. Experienced intraoperative complications (i.e., a dural tear or durotomy). Intra- and post-operative data will be excluded from the analysis for these patients.
3. Have severe liver disease. Bupivacaine is primarily metabolized in the liver via conjugation with glucuronic acid. Patients with liver disease, especially severe disease may be more susceptible to toxicity.
4. Have severe renal disease. Bupivacaine and the metabolite are primarily excreted by the kidneys. Excretion can be significantly changed by urinary perfusion, the presence of renal disease, factors affecting urinary pH, and renal blood flow
5. Are less than 18 years old.
6. Is pregnant.
7. Cannot read and speak English.

### **Study Procedures**

#### *Subject Consenting*

The PI or co-PI will identify a potential subject in clinic based upon his diagnosis and recommended surgical treatment. Either will explain the study to the patient and ask if he/she would be interested in participating. If the patient is interested in participating, the investigator or his clinic nurse will contact TCSC research staff to come to the clinic to consent the patient. TCSC will discuss the study with the patient in a private clinic examination room and consent the subject. The potential subject must not be pregnant as demonstrated by a pregnancy test (this is SOC) and must not have severe liver or renal disease as demonstrated by a complete metabolic plan

#### *Pain Assessments*

After written patient consent is obtained, subjects will be instructed on the use of the 100-mm Visual Analog Scale (VAS) for pain<sup>26</sup> and the Overall Benefit of Analgesia Score (OBAS).<sup>27</sup>

### Visual Analog Pain Scale (VAS) (Attachment 1)

Respondents indicate their pain by marking a position long a line between 0 (no pain) and 10 (intolerable pain) (Attachment, Page 1). Scores will be obtained when the patient is transferred to the hospital spine care unit from the Post-anesthesia Care Unit (PACU) (“Index”), once per day thereafter (every 24 hours), and at hospital discharge (“Discharge”). Subjects will be instructed to give responses in relation to their incision and drain sites only.

### Overall Benefit of Analgesia Score (OBAS) (Attachment 2)

Respondents complete seven questions, each with a score of 0 to 4 (Attachment, Page 2); the OBAS ranges between 0 (complete relief of pain) and 28 (no benefit). Scores will be obtained once per day (every 24 hours) after the patient is transferred from the PACU and at discharge from the hospital (“Discharge”). (Note: Time intervals are approximate to respect the comfort of the patient. It is not, for instance, intended to awaken the subject in the middle of the night.) Subjects will be instructed at the time of each assessment to give responses in relation to their incision and drain sites only.

### Assessment Schedule

Assessment	Transfer from PACU (“Index”)	Once per day (Every 24 hours)	Hospital Discharge (“Discharge”)
VAS	Yes	Yes	Yes
OBAS	No	Yes	Yes

### *Randomization*

Randomization will be performed prior to surgery using sealed envelopes. Sixty (60) envelopes will be sequentially numbered and 60 chits with either the letter “A” (SOC+Exparel group, n=30) or the letter “B” (SOC, n=30) will be prepared. Chits will be drawn at random and sequentially placed in the envelopes, which will be sealed. For each consented subject, when surgery is scheduled, an envelope will be opened and the surgery worksheet annotated, as appropriate.

### *Blinding*

This will be a semi-blinded trial. Investigators cannot be for the following reasons:

1. Exparel is a milky-white substance that will be recognizable; to use a placebo of similar appearance (such as neutral buffered sterile saline with colorant) would introduce an experimental substance.
2. Group A subjects will receive 140ml of Exparel plus saline plus free bupivacaine. The administration of the same volume of a placebo may itself cause pain.

Subjects will be blinded and will not be informed if they received the study drug or not.

#### *Intraoperative Administration of Exparel*

Intraoperatively at closing, for Group A patients, 140ml Exparel plus Bupivacaine plus saline will be injected under the skin and into the paraspinal muscles of the surgical wound and at the drain site. (Note: 140ml = 20ml Exparel 1.3% (266mg) + 50ml 0.25% Bupivacaine (150mg) + 70ml preservative-free 0.9% neutral saline. This volume will be equally divided between four 20cc syringes with 20-21 gauge spinal needles for deep injections and three 20cc syringes with 20-21g 1½" long needles for subdermal and drain site injections.) Cardiovascular status, neurological status, and vital signs will be routinely monitored during and after injections. Group B patients will receive SOC.

#### *Postoperative pain control*

Post-operative pain will be managed per patient needs *versus* a set protocol. Dilaudid or Morphine Sulfate is sometimes administered post-operatively for pain via Patient-Controlled Analgesia (PCA). The PCA system is typically programmed to administer incremental doses of 0.2 mg Dilaudid or 1 mg Morphine Sulfate at intervals of not less than 10 minutes and not more than 6 mg Dilaudid or 30mg Morphine Sulfate in a 4 hour period. Typically, the PCA will be discontinued after 24 hours (unless prevented by patient need). Subjects should not receive additional bupivacaine for pain during their hospitalization.

#### **Risk/Safety Information**

In ten prior clinical studies cited by the drug manufacturer (Pacira Pharmaceuticals, Inc.), the most common adverse reactions with incidence greater than or equal to 10% were nausea, constipation, and vomiting. Adverse reactions with incidence greater than or equal to 2% to less than 10% were fever, dizziness, swelling of the legs, feet, ankles, arms, or hands, lowered ability of the blood to carry oxygen, low blood pressure, severe itching of the skin, abnormally rapid

heart rate, headache, insomnia, anemia, postoperative muscle spasms, anemia resulting directly from loss of blood, back pain, drowsiness or sleepiness, and procedural pain. Other less common side effects have been reported (each occurring in less than 2% of patients): chills, superficial reddening of the skin, abnormally slow heart rate, anxiety, urinary retention, pain, watery fluid collection in the cavities or tissues of the body, tremor, postural dizziness, abnormal skin sensation (such as tingling), fainting, incision site reddening, procedural high blood pressure, procedural low blood pressure, procedural nausea, muscular weakness, neck pain, generalized itching, itching rash, sweating, cold sweat, hives, palpitations, abnormal heartbeat, abnormally fast heartbeat, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, abnormally low level of oxygen in the blood, uncontrolled/involuntary muscular contraction of the vocal chords, suspension of breathing, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, ringing in the ears, drug hypersensitivity, and hypersensitivity.

The drug manufacturer has previously trained research and ANW spine OR, and spine floor staff, 21-22 August 2017. New in-training will be provided to ANW floor staff and to United spine floor and OR staff by the Principal Investigator and TCSC Research Staff. Training will occur at a staff meeting, before or after shift change prior to the start of subject enrollment. Training will include a short didactic presentation (10 minutes) followed by time for questions. In addition to an overview of the study, the drug manufacturer's "Patient Fact Sheet" and "Nurse Information Sheet" (see Attachments) will be provided as educational material. We will provide examples of the patient assessments (VAS and OBAS) as well. Pharmacy, Anesthesia, and PACU are already familiar with the study drug at ANW and United hospitals.

### **Monitoring/Reporting of AE/SAE**

The Principal Investigator (PI) will monitor for Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO) including Adverse Events (AE) and Serious Adverse Events. (Definitions of these are detailed in the Allina Health Human Research Protection Program and Institutional Review Board (HRPP/IRB) Standard Operating Procedures.) Per the SOP, the PI will report a death, a Serious Adverse Event, or an Unanticipated Problem to the IRB within 7 days. The Allina Health IRB "Event Report" will be used.

## **Safety Monitoring Plan**

Safety will be monitored by experts who are knowledgeable about the disease and treatment under study, who will be able to interpret the data to ensure patient safety, and who have no direct involvement with the study. Experts include Joseph H. Perra, MD, Twin Cities Spine Center staff surgeon (fellowship trained and board certified), Matthew R Monsein, MD (board-certified in chronic pain management), and Stan Skinner, MD (board-certified in neurology). Each will sign a Conflict of Interest Statement which includes any relationship that could be perceived as a conflict of interest including commercial or non-commercial interests pertinent to study objectives. The PI will provide a report of safety (Serious Adverse Events and Unanticipated Problems, UPIRTSO) to them twice a year. The report will also include updates on study progress, procedures for maintaining the confidentiality of data, the quality of data collection, and UPIRTSO. They will conduct an *ad hoc* safety review within 30 days of receipt. They will make a recommendation to continue, terminate or modify the study based on observed benefit or harm. If individuals given the investigational intervention (Exparel) are found to be at higher risk for UPIRTSO including AEs and SAEs than those not receiving the drug, the Board may consider recommending early termination on safety grounds. The Board may also consider recommending early termination if external reports raise serious, unexpected safety concerns.

## **Study Oversight**

Study data will be made available for monitoring, auditing, IRB review and regulatory inspection by providing direct access to study related source data. The study may be prematurely closed for administrative reasons by the Principal Investigator (for examples, lack of enrollment, lack of adequate research staffing, lack of adequate funding). The study may be prematurely closed by the safety monitors based on study progress or UPIRTSO.

## **Data Management**

### *Data Collection – Primary Outcome*

The primary outcome is the area under the curve (AUC) of the VAS pain intensity scores from when the patient is transferred to the hospital spine care unit from the PACU (“Index”) until hospital discharge (“Discharge”). This will be calculated using the trapezoidal rule. The AUC will be adjusted for differences in length of hospital stay. Discharge criteria include ability to

self-ambulate or self-care, no signs of wound problems, absence of infectious signs or increased infectious parameters, and pain controlled by oral analgesics.

#### *Data Collection – Secondary Outcomes*

1. Proportion of subjects who are pain free (VAS pain intensity score of  $\leq 1.5$  and no prior rescue medication), Index until Discharge in 24 hour intervals
2. OBAS, Index until Discharge, in 24 hour intervals
3. Total postsurgical opioid consumption (morphine equivalents), Index until Discharge
4. Percentage of opioid-free subjects, Index until Discharge
5. Time to first opioid rescue, Index until Discharge
6. Opioid-related adverse events, Index until Discharge: respiratory depression, hypoventilation, hypoxia, dry mouth, nausea, vomiting, constipation, altered mental status, pruritus, urinary retention, and postoperative ileus
7. Costs (e.g., hospital room, drugs, laboratory, physical therapy, and respiratory therapy), until discharge.
8. Length of stay from Index until Discharge

#### *Data Collection – Tertiary Outcomes*

Collected patient information will include sex, age, height, weight, ASA physical status, smoking status, worker's compensation claim status, and co-morbidities (diabetes, chronic kidney disease, coronary artery disease, and chronic obstructive pulmonary disease). Perioperative data to be documented includes duration of anesthesia, intraoperative complications, duration of surgery (from skin incision to end of closure), and time in PACU.

#### *Data Analyses*

Research staff members will be abstracting data. They will be trained by the Lead Study Coordinator to collect data in the same manner. Results will be analyzed by descriptive and inferential statistics. We will look for difference between cohorts using t-tests; if the data are robust, then a regression analysis will be considered. Assumptions for statistical tests will be tested and alternate tests used if necessary. Missing data will be assessed and reported; it will not be imputed.

### **IRB Review/Ethics/Informed Consent**

The protocol, informed consent document and relevant supporting information will be submitted to the IRB for review and must be approved before the study is initiated. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study will be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56 [add 312 for IND studies or 812 for device studies], applicable laws and the IRB requirements. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the IRB is notified within 10 working days.

It will be the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB-approved informed consent document, including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent will be obtained prior to performing any study-related procedures, including screening and changes in medications including any washout of medications. A copy of the signed informed consent will be given to the study subject.

### **Confidentiality**

Data will be stored on TCSC computers, which are linked by Allina Health servers. No data will be physically removed from TCSC. The United States Food and Drug Administration may inspect all records related to the study. The IRB and/or other regulatory authorities (for example, the United States Food and Drug Administration) will have access to study-related medical records. Study-related records identifying the subject will be kept confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available. If any results of the study are published, the subject's identity will remain confidential.

### **Intended Use of the Data**

The study investigators may publish the results of the study in medical journals and society meetings. The study investigators may use the results to modify the Standard of Care.

## Study Funding

This study is funded through the Twin Cities Spine John H. Moe Research Fund. No funds from the drug manufacturer are being used to pay for this study. None of the study investigators or staff are receiving support of any kind from the manufacturer. Study procedures will occur at Twin Cities Spine Center and Allina Health facilities. Subjects incur no costs.

## References

1. Vaishya R, Wani AM, Vijay V. Local Infiltration Analgesia reduces pain and hospital stay after primary TKA: randomized controlled double blind trial. *Acta Orthop Belg.* 2015 Dec;81(4):720-9.
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg.* 2003 Aug;97(2):534-40.
3. Dias AS, Rinaldi T, Barbosa LG. The impact of patients controlled analgesia undergoing orthopedic surgery. *Braz J Anesthesiol.* 2016 May-Jun;66(3):265-71. Epub 2015 Apr 17.
4. McBeath DM, Shah J, Sebastian L, Sledzinski K. The effect of patient controlled analgesia and continuous epidural infusion on length of hospital stay after total knee or total hip replacement. *CRNA.* 1995 Feb;6(1):31-6.
5. Gordon DB. American Pain Society Acute Postoperative Pain Guidelines. *JCR Webinar*, Sept 2015. Available at <http://www.jcrinc.com/acute-postoperative-pain-guidelines>. Accessed on 25 May 2018.
6. Chahar P, Cummings KC. Liposomal bupivacaine: a review of a new bupivacaine formulation. *J Pain Res.* 2012; 5: 257–264. Published online 2012.
7. Barrington JW, Olugbode O, Lovald S, Ong K, Watson H, Emerson RH Jr. Liposomal bupivacaine: A comparative study of more than 1000 total joint arthroplasty cases. *Orthop Clin North Am* 2015 Oct; 46 (4): 469-77.
8. Cherian JJ, Barrington J, Elmallah RK, Chughtai M, Mistry JB, Mont MA. Liposomal Bupivacaine Suspension Can Reduce Length of Stay and Improve Discharge Status of Patients Undergoing Total Hip Arthroplasty. *Surg Technol Int.* 2015 Nov;27:235
9. Chughtai M, Cherian JJ, Mistry JB, Elmallah RD, Bennett A, Mont MA. Liposomal bupivacaine suspension can reduce lengths of stay and improve discharge status of patients undergoing total knee arthroplasty. *J Knee Surg* 2016 Feb 2.

10. Emerson RH, Barrington JW, Olugbode O, Lovald S, Watson H, Ong K. Comparison of Local Infiltration Analgesia to Bupivacaine Wound Infiltration as Part of a Multimodal Pain Program in Total Hip Replacement. *J Surg Orthop Adv.* 2015 Winter;24(4):235-41.
11. Emerson RH, Barrington JW, Olugbode O, Lovald S, Watson H, Ong K. Femoral Nerve Block Versus Long-Acting Wound Infiltration in Total Knee Arthroplasty. *Orthopedics.* 2016 May 1;39(3):e449-55. Epub 2016 Mar 29.
12. Yu SW, Szulc AL, Walton SL, Davidovitch RI, Bosco JA, Iorio R. Liposomal bupivacaine as an adjunct to postoperative pain control in total hip arthroplasty. *J Arthroplasty* 2016 Jan 21
13. United States Food and Drug Administration. Supplemental Approval, NDA 022496/S-019, Reference ID: 3860081. 14 December 2015. Available at [http://media.corporate-ir.net/media\\_files/IROL/22/220759/The\\_New\\_Label\\_with\\_Approval\\_Cover\\_Letter.pdf](http://media.corporate-ir.net/media_files/IROL/22/220759/The_New_Label_with_Approval_Cover_Letter.pdf). Accessed 25 May 2018.
14. Kim KT, Cho DC, Sung JK, Kim YB, Kang H, Song KS, Choi GJ. Intraoperative systemic infusion of lidocaine reduces postoperative pain after lumbar surgery: a double-blinded, randomized, placebo-controlled clinical trial. *Spine J.* 2014 Aug 1;14(8):1559-66. Epub 2013 Nov 8.
15. MedLibrary.Org. Xylocaine MPF. Available at <https://medlibrary.org/lib/rx/meds/xylocaine-mpf-4/>. Accessed 14 June 2016.
16. Grieff AN, Ghobrial GM, Jallo J. Use of liposomal bupivacaine in the postoperative management of posterior spinal decompression. *J Neurosurg Spine* 2016 Mar 4:1-6.
17. Kim J, Burke SM, Kryzanski JT, Roberts RJ, Roguski M, Qu E, Hwang SW, Liu PP, Desilier A, Riesenburger RI. The role of liposomal bupivacaine in reduction of post-operative pain after Transforaminal Lumbar Interbody Fusion (TLIF): A clinical study. *World Neurosurg.* 2016 Apr 22.
18. Puffer RC, Tou K, Winkel RE, Bydon M, Currier B, Freedman BA. Liposomal bupivacaine incisional injection in single-level lumbar spine surgery. *Spine J.* 2016 Nov;16(11):1305-1308. Epub 2016 Jun 24.
19. Tomov M, Tou K, Winkel R, Puffer R, Bydon M, Nassr A, Huddleston P, Yaszemski M, Currier B, Freedman B. Does subcutaneous infiltration of liposomal bupivacaine following single-level transforaminal lumbar interbody fusion surgery improve immediate postoperative pain control? *Asian Spine J.* 2018 Feb;12(1):85-93Epub 2018 Feb 7.

20. Wang MY, Grossman J. Endoscopic minimally invasive transforaminal interbody fusion without general anesthesia: initial clinical experience with 1-year follow up. *Neurosurg Focus* 2016 Feb; 40(2): E13.
21. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372-380. *Pain Physician*. 2008 Mar;11(2 Suppl):S105-20.
22. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. *Pain Physician*. 2008 Mar;11(2 Suppl):S105-20.
23. Oderda GM, Evans RS, Lloyd J, Lipman A, Chen C, Ashburn M, Burke J, Samore M. Cost of opioid-related adverse drug events in surgical patients. *J Pain Symptom Manage*. 2003 Mar;25(3):276-83.
24. Oderda GM, Gan TJ, Johnson BH, Robinson SB. Effect of opioid-related adverse events on outcomes in selected surgical patients. *J Pain Palliat Care Pharmacother*. 2013 Mar;27(1):62-70. Epub 2013 Jan 9.
25. Food and Drug Administration. FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014.
26. Million R, Hall W, Nilsen KH, Baker RD, Jayson MI. Assessment of the progress of the back-pain patient 1981 Volvo Award in Clinical Science. *Spine*. 1982 May-Jun;7(3):204-12.
27. Lehmann N, Joshi GP, Dirkmann D, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *British Journal of Anaesthesia* 2010; 105(4):511–18.

Attachment – Patient Assessments (Page 1)

**Visual Analog Pain Scale**Attach Patient  
Sticker Here

Instructions:

- a. Attach patient sticker or complete information below
- b. Ask the subject to complete the two statements below. Score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks
- c. Record when the assessment was made and by whom

Patient Name (Last, First MI) \_\_\_\_\_, \_\_\_\_\_

Date of Birth (DD/MM/YYYY) \_\_\_\_ / \_\_\_\_ / \_\_\_\_

MRN \_\_\_\_\_

1. How severe is your pain at the place where you were operated on (your incision site)?

No \_\_\_\_\_ Intolerable  
Pain \_\_\_\_\_ Pain

Score: \_\_\_\_\_

2. How severe is your pain at the place where your surgeon placed a drain?

No \_\_\_\_\_ Intolerable  
Pain \_\_\_\_\_ Pain

Score: \_\_\_\_\_

Assessment:

Index  Post-Op  Day 1  Day 2  Day 3  Day 4  Day \_\_\_\_  Discharge Time (HH:MM DD/MM/YYYY) \_\_\_\_ : \_\_\_\_ AM/PM \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
(Circle)

Assessor Name (Last, First MI) \_\_\_\_\_, \_\_\_\_\_

Attachment – Patient Assessments (Page 2)

**Overall Benefit of Analgesia Score (OBAS)**Attach Patient  
Sticker Here

Instructions:

- a. Attach patient sticker or complete information below
- b. Ask the subject to complete the seven statements below. Record responses in the rating column. The score is the sum of items 1 – 6 and “4-score in item 7.”
- c. Record when the assessment was made and by whom

Patient Name (Last, First MI) \_\_\_\_\_, \_\_\_\_\_

Date of Birth (DD/MM/YYYY) \_\_\_\_ / \_\_\_\_ / \_\_\_\_

MRN \_\_\_\_\_

With respect to the place where the place where you were operated on (your incision site) and the place where your surgeon placed a drain:

1. Please rate your current pain at rest on a scale between 0=minimal pain and 4=maximum imaginable pain	_____
2. Please grade any distress and bother from vomiting in the past 24 hours (0=not at all to 4=very much)	_____
3. Please grade any distress and bother from itching in the past 24 hours (0=not at all to 4=very much)	_____
4. Please grade any distress and bother from sweating in the past 24 hours (0=not at all to 4=very much)	_____
5. Please grade any distress and bother from freezing in the past 24 hours (0=not at all to 4=very much)	_____
6. Please grade any distress and bother from dizziness in the past 24 hours (0=not at all to 4=very much)	_____
7. How satisfied are you with your pain treatment during the past 24 hours (0=not at all to 4= very much)	4 - _____ = _____
Overall Benefit of Analgesia Score	_____

Assessment:

Index  Post-Op  Day 1  Day 2  Day 3  Day 4  Day \_\_\_\_  Discharge Time (HH:MM DD/MM/YYYY) \_\_\_\_ : \_\_\_\_ AM/PM \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
(Circle)

Assessor Name (Last, First MI) \_\_\_\_\_, \_\_\_\_\_

## Attachment: Educational Materials (Page 1)

## The Role of EXPAREL® (bupivacaine liposome injectable suspension) in Postoperative Patient Care: **WHAT NURSES NEED TO KNOW**

**EXPAREL® (bupivacaine liposome injectable suspension) is part of a multimodal analgesic strategy that reduces opioid requirements and may help patients experience a smoother recovery.**

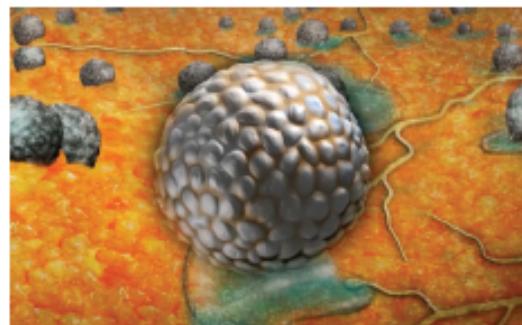
### **INDICATION:**

EXPAREL is indicated for administration into the surgical site to produce postsurgical analgesia. EXPAREL has not been studied for use in patients younger than 18 years of age<sup>1</sup>

### **FORMULATION:**

EXPAREL consists of DepoFoam® encapsulated bupivacaine suspended in saline<sup>2,3</sup>

- DepoFoam is a liposomal drug delivery technology composed of synthetic lipids that can be cleared by normal metabolic pathways from the body
- Upon administration of EXPAREL, liposomes break down to allow for gradual release of bupivacaine, which may be detected in the serum for up to 96 hours, depending on the surgical site



### **DOSING AND ADMINISTRATION:**

EXPAREL is packaged as 266 mg of bupivacaine (13.3 mg/mL) in a 20 mL vial<sup>1</sup>

- The maximum dose should not exceed 266 mg (20 mL)
- EXPAREL should be injected slowly into the soft tissues and with a meticulous technique that covers the entire surgical site
- A single 20 mL vial can be administered undiluted or expanded to a total volume up to 300 mL with normal saline for injection or Lactated Ringer's solution without changing efficacy
- Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL
- Some providers choose to utilize a short-acting local anesthetic with EXPAREL
  - Bupivacaine HCl may be administered in the same syringe with EXPAREL, as long as the ratio of bupivacaine HCl to EXPAREL does not exceed a ratio of 1:2
  - Non-bupivacaine local anesthetics must be administered  $\geq$ 20 minutes prior to administration of EXPAREL into the same site

### **MECHANISM OF ACTION:**

- Upon release from the liposomes, the bupivacaine in EXPAREL has the same mechanism of action as other available bupivacaine formulations<sup>1</sup>
- Onset of action will vary
- Patients receiving EXPAREL may not require as much opioid medication for pain management postoperatively<sup>1</sup>
- Several studies support the use of EXPAREL as part of a multimodal regimen to control postsurgical pain<sup>4,5</sup>

### **DURATION:**

EXPAREL will slowly wear off over a period of days<sup>1</sup>

- The patient may experience pain at the surgical site as EXPAREL wears off
  - The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site<sup>1</sup>
- EXPAREL should be used as part of a multimodal regimen that includes scheduled round-the-clock non-opioid medications in order to control postsurgical pain<sup>6</sup>
- It is important to educate patients about managing pain after hospital discharge and to set appropriate expectations for recovery
- Patients should continue to take prescribed medication in order to maintain adequate pain control as the effects of EXPAREL wear off<sup>6</sup>

**EXPAREL®**  
(bupivacaine liposome injectable suspension)

## Attachment: Educational Materials (Page 2)

**ASSESSMENT AND EVALUATION:**

The patient may have decreased sensation where the EXPAREL was administered<sup>1</sup>

- If a patient reports that he or she is in pain, conduct a thorough pain assessment
- Thorough pain assessments should include asking the patient about the EXACT location of pain being experienced<sup>1</sup>
  - Because EXPAREL is technique dependent, informing the administrator of the pain assessment will provide valuable feedback for subsequent patients

**TOLERABILITY:**

- In clinical trials, the most common adverse reactions (incidence  $\geq 10\%$ ) following EXPAREL administration were nausea, constipation, and vomiting

**OTHER CONSIDERATIONS:**

- Manifestations of local anesthetic toxicity typically appear 1 to 5 minutes after the injection, but onset may range from 30 seconds to as long as 60 minutes<sup>2</sup>

Patients with local anesthetic toxicity may experience the following symptoms<sup>2,3</sup>:

- **Central nervous system symptoms:** circumoral and/or tongue numbness, metallic taste, lightheadedness, dizziness, visual and auditory disturbances (difficulty focusing and tinnitus), disorientation, drowsiness, muscle twitching, convulsions, unconsciousness, coma, respiratory depression and arrest, and cardiovascular depression and collapse
- **Cardiac symptoms:** chest pain, shortness of breath, palpitations, lightheadedness, diaphoresis, hypotension, and syncope

Follow your institution's policies regarding monitoring of cardiovascular and neurological status, as well as vital signs, after injection of local anesthetic products.

See [www.exparel.com](http://www.exparel.com) for more information and FULL PRESCRIBING INFORMATION.

For questions or to report a suspected adverse event, call 1-855-RX-EXPAREL.

**IMPORTANT SAFETY INFORMATION**

- EXPAREL is contraindicated in obstetrical paracervical block anesthesia
- EXPAREL has not been studied for use in patients younger than 18 years of age
- Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL
- Monitoring of cardiovascular and neurological status as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations
- In clinical trials, the most common adverse reactions (incidence  $\geq 10\%$ ) following EXPAREL administration were nausea, constipation, and vomiting

**References:** 1. EXPAREL® (bupivacaine liposome injectable suspension) prescribing information. Parsippany, NJ: Pacira Pharmaceuticals, Inc; December 2015. 2. Lambert WJ, Los K. DopoFoam® multivesicular liposomes for the sustained release of macromolecules. In: Rathbone MJ, Hadgraft J, Roberts MS, Lane ME, eds. Modified Release Drug Delivery Technology. 2nd ed. New York: Informa Healthcare; 2008:207-214. 3. Angst MS, Droyer DR. Pharmacology of drugs formulated with DopoFoam: a sustained release drug delivery system for parenteral administration using multivesicular liposome technology. *Clin Pharmacokinet*. 2006;45(12):1153-1176. 4. Cohen SM, Vogel JD, Marcel JE, Candiotti KA. Liposome bupivacaine for improvement in economic outcomes and opioid burden in GI surgery: IMPROVE study pooled analysis. *J Pain Res*. 2014;7:359-366. 5. Balldorf NJ, Lemarie V, Lovely JK, et al. Enhanced recovery after surgery in microvascular breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2015;68(3):395-402. 6. Scuderi G. The challenges of perioperative pain management in total joint arthroplasty. *Am J Orthop (Belle Mead NJ)*. 2015;44(10, suppl):S2-S4. 7. The National Initiative on Pain Control™. Pain Assessment Scales. [https://www.painedu.org/downloads/NIPC/pain\\_assessment\\_scales.pdf](https://www.painedu.org/downloads/NIPC/pain_assessment_scales.pdf). Accessed November 9, 2015. 8. Kapitanyan R, Su M. Local anesthetic toxicity. January 20, 2015. <http://emedicine.medscape.com/article/1844551-overview>. Accessed March 18, 2016. 9. Neal JM, Mulroy MF, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. *Reg Anesth Pain Med*. 2012;37(1):16-18.



©2016 Pacira Pharmaceuticals, Inc. Parsippany, NJ 07054 PP-EX-US-1542 05/2016

