An Innovative Non-Opioid Option for the Management of Postsurgical Pain
Disclosures

- The speaker has a consulting relationship with Pacira Pharmaceuticals, Inc.
- This program is sponsored and approved by Pacira Pharmaceuticals, Inc.
A Multimodal Approach Uses a Variety of Therapeutics to Minimize Opioid Use and ORAEs

- Simultaneous use of a combination of ≥2 analgesics that act at different sites within the central and peripheral nervous systems in an effort to
  - Reduce pain
  - Minimize opioid use and ORAEs

ORAE, opioid-related adverse event; NSAID, nonsteroidal anti-inflammatory drug; NMDA, N-methyl-D-aspartate; COX, cyclooxygenase.

Role of Local Anesthetics

Act as Membrane Stabilizers

- ↓ rate of depolarization and repolarization of excitable membranes, including nociceptors
- Inhibit sodium influx through sodium-specific ion channels in the neuronal cell membrane
  - Thus, an action potential cannot arise, and signal conduction is inhibited

Techniques for Administering Local Anesthetics

- Surgical site infiltration\(^1\)
  - Single injection
  - Catheters
- Peripheral nerve blocks\(^2\)
  - Single injection
  - Catheters
- Epidural

Use of Local Analgesics for Postsurgical Pain

• Target pain at the source
  – Postsurgical pain is mostly nociceptive pain caused by stimulation of peripheral receptors responding to the surgical insult\(^1\)

• Infiltrating the surgical site is a simple, effective means of providing analgesia in a variety of surgical procedures\(^1\)

• Not typically associated with severe side effects\(^1\)
  – Local toxicity, wound infection, and wound healing

• When delivered in single doses, the duration of traditional local anesthetics can be a limiting factor\(^2\)

EXPAREL: Indicated for Single-Dose Administration Into the Surgical Site to Produce Postsurgical Analgesia

- Provides long acting pain control with a reduced reliance on opioids
  - 30% reduction in cumulative pain scores and a 45% reduction in opioid consumption
- No need for catheters or pumps
- The clinical benefit of the attendant decrease in opioid consumption was not demonstrated
- EXPAREL is contraindicated in obstetrical paracervical block anesthesia
- In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting
EXPAREL Uses DepoFoam® to Release Bupivacaine Over Time

• By utilizing the DepoFoam product delivery platform, EXPAREL delivers therapeutic levels of bupivacaine over time

• DepoFoam is a multivesicular liposomal product delivery technology that encapsulates drugs without altering their molecular structure and then releases them over a desired period of time

• DepoFoam utilizes membrane components that are based on natural and well tolerated sources and are cleared by normal metabolic pathways

• DepoFoam is <3% lipid, biodegradable, and biocompatible

Pharmacokinetics Demonstrate Plasma Levels of Bupivacaine That Can Persist for 96 Hours

- Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL
- Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy
- 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
- The blood plasma level for central nervous system effects is 2000 ng/mL
- The blood plasma level for cardiac effects is 4000 ng/mL

Clinical Program for FDA Approval

- Evidence of efficacy and safety with EXPAREL is available from two pivotal Phase 3 trials (one soft tissue and one orthopedic model)
- The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures including:
  - Hemorrhoidectomy
  - Bunionectomy
  - Inguinal hernia repair
  - Breast augmentation
  - Total knee arthroplasty
Safety Evaluated in Broad Clinical Development Program

- 21 clinical studies, 1307 patients received EXPAREL
- 10 wound infiltration studies: 823 patients
  - Various surgical procedures; EXPAREL doses ranged from 66 mg to 532 mg
    - The maximum dose of EXPAREL should not exceed 266 mg (one 20 mL vial)
    - The most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting

Cardiac Safety

- No QTc prolongation
  - Even at supratherapeutic doses
- No signal of any clinically important cardiac events from development program

Additional Safety Findings

- No events of chondrolysis
- No hepatic dosing adjustment for mild to moderate disease
- No abnormal findings reflecting improper wound healing

Clinical Experience to Date With EXPAREL

- The safety and efficacy of EXPAREL have only been demonstrated in bunionectomy and hemorrhoidectomy.
- Broad label indication: Used in more than 1,000,000 patients since its launch in April 2012.
- Soft tissue:
  - Bariatric procedures
  - Anorectal procedures
  - Ventral and inguinal herniorrhaphy
  - Open and laparoscopic colorectal procedures
  - Ileostomy reversal
  - Cosmetic plastic surgery: breast augmentation, breast reduction, abdominoplasty
  - Plastic reconstructive surgery
  - Transversus abdominis plane (TAP) infiltration
- Orthopedic:
  - Total knee arthroplasty
  - Total hip arthroplasty
  - Laminectomy
  - Thoracotomy
• EXPAREL is available as 266 mg, 1.3%/20 mL single-use vials

• Recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area
  – Dosing is not weight based

• Maximum dose of EXPAREL should not exceed 266 mg (one 20 mL vial)
Administration

- EXPAREL should be injected slowly into the soft tissues of the surgical site with frequent aspiration to check for blood and minimize the risk of intravascular injection.

- Administer with a 25-gauge or larger needle.

- Following withdrawal from the vial, EXPAREL may be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration.

**Soft Tissue Infiltration**

**TAP Infiltration**

EO=External oblique
IO=Internal oblique
TA=Transversus abdominis
LA=Local anesthetic

Adapted from: *Journal of New York School of Regional Anesthesia*
Expanding the Volume

• The volume of EXPAREL can be expanded as necessary to accommodate administration into a larger surgical site without impacting efficacy
  – EXPAREL can be expanded up to a total volume of 300 mL with normal (0.9%) saline for injection or lactated Ringer’s solution

• Volumes used in clinical practice range from 20 to 300 mL depending on the size of the surgical site
Administration Technique Is Important

- EXPAREL does not diffuse throughout tissues in the same manner as bupivacaine
- Meticulous infiltration technique is important to ensure best results

Note: graphic is for illustrative purposes only.
Administration Precautions

- Wait 20 minutes after administering lidocaine or other non-bupivacaine-based local anesthetics before administering EXPAREL into the same surgical site.
- Allow topical antiseptics to dry before administering EXPAREL into the same surgical site.
- When using bupivacaine HCl before EXPAREL, the dose of bupivacaine HCl should be ≤50% of the dose of EXPAREL. As a reference:
  - One 20 mL vial of EXPAREL contains 266 mg of free base bupivacaine; 266 mg of free base bupivacaine is equivalent to 300 mg of bupivacaine HCl.
  - One 30 mL vial of 0.5% bupivacaine HCl contains 150 mg bupivacaine HCl.
  - Toxic effects of these drugs are additive and their administration should be used with caution, including monitoring for neurological and cardiovascular effects related to toxicity.
Compatibility With Medications and Implantable Materials Commonly Used During Surgery

- No significant interaction with the following materials:
  - Stainless steel
  - Titanium
  - Polypropylene
  - Silicone

- Liposomal bupivacaine should not be admixed with other compounds

- In vivo compatibility studies have not been conducted, but when the following classes of compounds were tested in vitro with EXPAREL they did not cause excessive release of bupivacaine from the liposomal formulation:
  - NSAIDs
  - Opioids
  - Epinephrine
  - Tranexamic acid
  - Corticosteroids
  - Antibiotics

Cardiovascular and Central Nervous System Risks Associated With Local Anesthetics

- As with other local anesthetic products, monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL.

- The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient.
One Dose of EXPAREL Provides Significant Pain Control With Reduced Opioid Consumption

- Indicated for administration into the surgical site for postsurgical analgesia
- Requires no catheter or additional device
- Supplied in a ready-to-use aqueous suspension or the volume can be expanded to accommodate larger surgical sites
- Administered using a single-dose deep tissue infiltration technique
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. Other formulations of bupivacaine 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 ≥10%) following EXPAREL administration were nausea, constipation, and vomiting