Pacira v. FDA: Summary of Key Points From Complaint Filed By Pacira Regarding Breadth of EXPAREL® Indication

Background

- On October 28, 2011, the FDA Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) approved EXPAREL
- The final, FDA-approved indication states that EXPAREL is indicated “for single-dose administration into the surgical site to produce postsurgical analgesia”
- The **Indications and Usage** section does not include any limitations on the surgical site, but does include a limitation against use in pediatric patients

The Broad Indication for EXPAREL is Evidenced by:

1. **FDA Labeling Regulations** related to the various sections of a product label (package insert [PI])
2. **Scientific Considerations** regarding the study of pain that have led to FDA's preference for extrapolating to broad indications
3. **FDA Application** of Pediatric Equity Research Act (PREA) to EXPAREL

1. The EXPAREL Broad Indication is Evidenced by FDA's Labeling Regulations

FDA Approval of Drug Labeling (the Package Insert [PI])

- Through the FDCA, as amended, FDA is empowered by Congress to regulate, among other things, the development, approval, and promotion of pharmaceuticals in the United States
- FDA regulations governing the Package Insert (PI) are embodied in the Code of Federal Regulations (CFR)

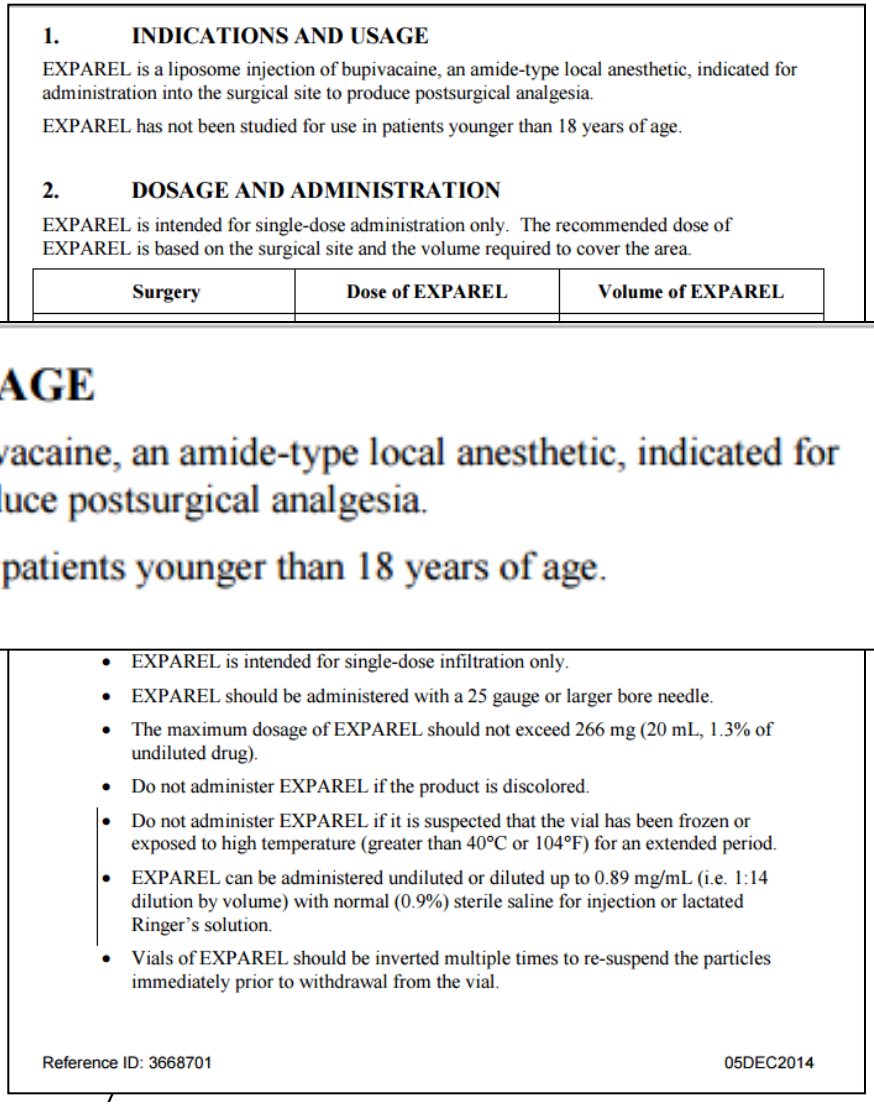
FDA Regulations for a Package Insert (PI): Indications and Usage

- The **Indications and Usage** section of an approved PI controls the breadth of the use(s) for which FDA approves a drug (21 C.F.R.57(c)(2))
  - This is the *only section* of an approved PI that limits the intended use(s) of a product (along with the Contraindication section)

EXPAREL Package Insert (PI) Contains No Limits on its Broad Indication

No limit on the type of surgical procedure

Only limit is on use in pediatric patients (younger than 18 years of age)



1. INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, 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.

2. DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL

- EXPAREL is intended for single-dose infiltration only.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- The maximum dosage of EXPAREL should not exceed 266 mg (20 mL, 1.3% of undiluted drug).
- Do not administer EXPAREL if the product is discolored.
- Do not administer EXPAREL if it is suspected that the vial has been frozen or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with normal (0.9%) sterile saline for injection or lactated Ringer's solution.
- Vials of EXPAREL should be inverted multiple times to re-suspend the particles immediately prior to withdrawal from the vial.

Reference ID: 3668701 05DEC2014

In Contrast, the Approved PI of Other Analgesic Drugs Contain Limitations on Indications and Usage

Limited to use "as an analgesic adjunct in the maintenance of balanced general anesthesia ***in patients who are intubated and ventilated***"

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated for intravenous administration *in adults and pediatric patients*:

as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SUFENTA (sufentanil citrate) is indicated for epidural administration as an analgesic combined with low dose bupivacaine, usually 12.5 mg per administration, during labor and vaginal delivery.

Broad vs. Narrow Indication in PI

EXPAREL® PI: Broad Indication

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Sufenta® PI: Narrow Indication

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SUFENTA (sufentanil citrate) is indicated for epidural administration as an analgesic combined with low dose bupivacaine, usually 12.5 mg per administration, during labor and vaginal delivery.

FDA Regulations for a Package Insert (PI): Dosage and Administration & Clinical Studies

- The **Dosage and Administration** and **Clinical Studies** sections of the approved PI are intended to further "support" or supplement the **Indications and Usage**
  - They do not—and cannot—narrow or limit in a way that is not expressly stated in the **Indications and Usage** section

EXPAREL PI: Dosage and Administration

- In the **Indications and Usage** section, FDA broadly indicated the use of EXPAREL via "administration into the surgical site"
- In the **Dosage and Administration** section, FDA supported its broad indication with a broad dosing paradigm, supplemented with specific applications
  - The specific dosing instructions supplement, NOT limit, the general dosing paradigm
  - The general dosing paradigm language prefacing the specific dosing instructions would be entirely unnecessary if the indication for EXPAREL was limited to bunionectomy and hemorrhoidectomy

EXPAREL PI: Dosage and Administration

General dosing information and injection instructions

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Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy[1]	106 mg	8 mL
Hemorrhoidectomy[2]	266 mg	20 mL

[1]Infiltrate 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

[2]Dilute 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, and divide the mixture into six 5 mL aliquots. Perform the anal block by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers.

- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with normal (0.9%) sterile saline for injection or lactated Ringer's solution.
- Vials of EXPAREL should be inverted multiple times to re-suspend the particles immediately prior to withdrawal from the vial.

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EXPAREL PI: Clinical Studies

- Language in the **Clinical Studies** section:
  - Describes the studies that FDA concluded were sufficient to support approval of the product
  - Does not purport to limit the general “postsurgical analgesia” indication in the **Indications and Usage** section

EXPAREL PI: Clinical Studies

PI describes clinical studies that supported EXPAREL's approval, and alerts doctors to additional considerations

14. CLINICAL STUDIES

The efficacy of EXPAREL was compared to placebo in two multicenter, randomized, double-blinded clinical trials. One trial evaluated the treatments in patients undergoing bunionectomy; the other trial evaluated the treatments in patients undergoing hemorrhoidectomy. EXPAREL has not been demonstrated to be safe and effective in other procedures.

14.1 Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 106 mg EXPAREL in 193 patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72). Study medication was administered directly into the wound at the conclusion of the surgery, prior to wound closure. Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) out to 72 hours. Postoperatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4 to 6

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the wound (greater than or equal to 3 cm) at the conclusion of the surgery. Pain intensity was rated by the patients on a 0 to 10 NRS at multiple time points up to 72 hours. Postoperatively, patients were allowed rescue medication (morphine sulfate 10 mg intramuscular every 4 hours as needed). The primary outcome measure was the AUC of the NRS pain intensity scores (cumulative pain scores) collected over the first 72 hour period. There was a significant treatment effect for EXPAREL compared to placebo.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity; however, there was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

EXPAREL PI: Clinical Studies

- The fact that the **Clinical Studies** section and NOT the **Indications and Usage** section contains the statement "*EXPAREL has not been demonstrated to be safe and effective in other procedures*," is further evidence that this language is not intended to modify or limit the general indication or approved use

2. The Broad Indication Is Evidenced by Scientific Considerations Recognized by FDA

Because Pain is a Challenging Area to Study, Scientists and FDA Extrapolate from Clinical Studies in Limited Clinical Settings to Broad Indications

- Pain is one of the most challenging areas of medicine to study effectively
- In light of these challenges, scientists, doctors, and FDA find it appropriate to extrapolate from different types of clinical trials to conclude that a drug is generally safe and effective to treat pain

FDA Favors Extrapolation and Broad Indications for Analgesic Medications Wherever Appropriate

- FDA has a long history of approving drugs for broad analgesic indications based on clinical trials in more limited subpopulations (e.g., NUCYNTA®, OFIRMEV®)
- 1992 FDA Guidance stated that "[e]vidence that an agent has analgesic activity in pain of several different etiologies will justify 'general purpose' analgesic labeling"
- 2014 FDA Guidance states that for "general acute pain indications," two trials in nociceptive pain "generally will be considered adequate"

Because FDA Recognized that Extrapolation is Scientifically Appropriate in the Case of EXPAREL, it Granted a Broad Indication

- FDA approved EXPAREL on the basis of two pivotal trials
  - **Soft-tissue pain**: Hemorrhoidectomy
  - **Hard-tissue (orthopedic) pain**: Bunionectomy
- These pivotal trials represent opposite ends of the spectrum of the human anatomy
  - This means EXPAREL can be expected to have a similar effect on the range of potential clinical applications in the body
- The active ingredient in EXPAREL, bupivacaine, exerts its effect by preventing transmission of nerve impulses
  - This mechanism of action means it can be expected to have a similar effect on nerves anywhere in the body

3. The Broad Indication for EXPAREL Is Evidenced by FDA's Application of the Pediatric Research Equity Act (PREA) to EXPAREL

The Text of PREA, its Legislative History, and FDA Guidance Make Clear that FDA only has Authority to Require On-Label Pediatric Studies

- The Pediatric Research Equity Act (PREA) requires NDA applicants to conduct pediatric clinical studies for certain drugs
- The law states that the studies must assess safety and effectiveness "for the claimed indications" of the drug
- The Congressional history states that the law was only intended to require pediatric studies for a drug's "claimed indications"
- FDA guidance states that PREA only requires studies for approved indications
- The law permits FDA to waive this requirement if the disease or condition that the drug is approved to treat does not exist in children

FDA's Application of PREA to EXPAREL Reflects FDA's Own Understanding that EXPAREL Is Approved for a Broad Indication

- Bunionectomy and hemorrhoidectomy procedures are not common in a pediatric population
- If FDA believed the EXPAREL indication was limited to bunionectomy and hemorrhoidectomy procedures, it would have waived the PREA requirements
- Instead, FDA's approval letter for EXPAREL requires Pacira to conduct studies of EXPAREL in pediatric patients "undergoing multiple surgical procedures"
- If FDA truly believed the approval of EXPAREL was limited to bunionectomy and hemorrhoidectomy, FDA would have objected to those proposals as unethical
  - Because FDA did not object, it is clear that FDA itself interpreted the indication for EXPAREL broadly