Pacira and the U.S. Food and Drug Administration (FDA) Reach Amicable Legal Resolution

SITUATION OVERVIEW

On December 14, 2015, Pacira and the United States reached an amicable resolution with respect to the lawsuit filed on September 8, 2015, *Pacira Pharmaceuticals, Inc. et al v. United States Food & Drug Administration et al*, 15-cv-07055 (SDNY Sept. 8, 2015)(LAK). Highlights of the resolution include the approval of a labeling supplement that affirms the broad indication of EXPAREL beyond the two procedures from the pivotal studies, formal rescission of the September 2014 Warning Letter, and acknowledgment that procedures involving infiltration in oral surgery or into the transversus abdominis plane (TAP block) are on-label. As the resolution terms achieve the Company's litigation goals, the Company has agreed to dismiss its lawsuit.

Click to view recap of events leading to the resolution announcement.

RESOLUTION SUMMARY

Following a series of productive and collaborative discussions, the FDA and Pacira agreed to the following key resolution terms:

- The FDA confirms that EXPAREL has, since October 28, 2011, been approved for "administration into the surgical site to produce postsurgical analgesia" in a variety of surgeries not limited to those studied in its pivotal trials.
- The FDA approved a labeling supplement which amends the EXPAREL Package Insert (PI) to clarify and reinforce that:
  - The use, efficacy and safety of EXPAREL is not limited to any specific surgery type or site;
  - The proper dosage and administration of EXPAREL is based on various patient and procedure-specific factors, with the two surgical models utilized in the pivotal trials provided as examples for the purpose of providing general guidance;
  - There was a significant treatment effect for EXPAREL compared to placebo over the first 72 hours in the pivotal hemorrhoidectomy study;
    - The description of that duration of effect now includes a graphical representation of the mean pain intensity scores over time for the EXPAREL and placebo groups for the full 72-hour efficacy period, as well as information about median time to first opioid use and percentage of opioid-free patients in each treatment group
  - EXPAREL may be admixed with bupivacaine—including co-administered in the same syringe—provided certain medication ratios are observed.
- The September 2014 Warning Letter is formally withdrawn via a "Rescission Letter" from Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research (CDER) to Dave Stack.
  - At the request of Pacira, the Rescission Letter includes FDA guidance related to two key procedures:
    - Infiltration into the transversus abdominis plane (TAP), which is a field block technique covered by the approved indication for EXPAREL
    - Infiltration to produce postsurgical analgesia at the site of oral surgery procedures including tooth extractions, which is also covered by the approved indication for EXPAREL
- The United States acknowledges that the rescission of the Warning Letter and approval of the Labeling Supplement reflect the scope of the indication in the NDA that FDA approved on October 28, 2011.
- Pacira and FDA agree that, in future interactions, they will deal with each other in an open, forthright and fair manner.

KEY DETAILS ON RESOLUTION AGREEMENT

Revisions to Prescribing Information/Package Insert (PI)

SECTION 1: Indications and Usage

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.

- No significant alterations were made to the indication language, as the originally approved indication always supported the use of EXPAREL in a variety of surgical settings.

SECTION 2: Dosing and Administration

- The procedure-specific dosing table has been replaced with guidance around dosing based on various patient and procedure-specific factors.
- The two specific surgical examples (bunionectomy and hemorrhoidectomy) are provided “as general guidance in selecting the proper dosing for the planned surgical site.”

FULL PRESCRIBING INFORMATION

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~~ following factors:

- Size of the surgical site
- Volume required to cover the area
- Individual patient factors that may impact the safety of an amide local anesthetic
- Maximum dose of 266 mg (20 mL)

As general guidance in selecting the proper dosing for the planned surgical site, two examples of dosing are provided. One example of the recommended dose comes from a study in patients undergoing bunionectomy. A total of 8 mL (106 mg) was administered as 7 mL of EXPAREL infiltrated into the tissues surrounding the osteotomy, and 1 mL infiltrated into the subcutaneous tissue.

Another example comes from a study of patients undergoing hemorrhoidectomy. A total of 20 mL (266 mg) of EXPAREL was diluted with 10 mL of saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

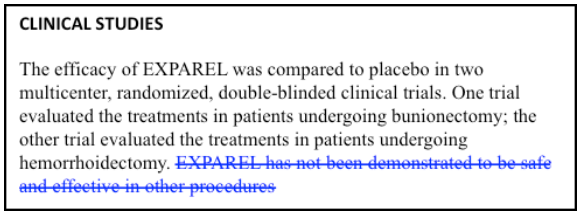
~~Surgery~~	~~Dose of EXPAREL~~	~~Volume of EXPAREL~~
~~Bunionectomy[1]~~	~~106 mg~~	~~8 mL~~
~~Hemorrhoidectomy[2]~~	~~266 mg~~	~~30 mL~~

KEY DETAILS ON RESOLUTION AGREEMENT CONTINUED

Revisions to Prescribing Information/Package Insert (PI)

SECTION 14: Clinical Studies

- The sentence "EXPAREL has not been demonstrated to be safe and effective in other procedures" has been removed to eliminate any ambiguity or confusion about the broad scope of the approved indication for EXPAREL.
- All references to the bunionectomy and hemorrhoidectomy studies have been recharacterized as "Study 1" and "Study 2" to reflect that two surgical models (hard tissue and soft-tissue) are required to extrapolate the efficacy and safety of an analgesic to other surgery types.



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~~

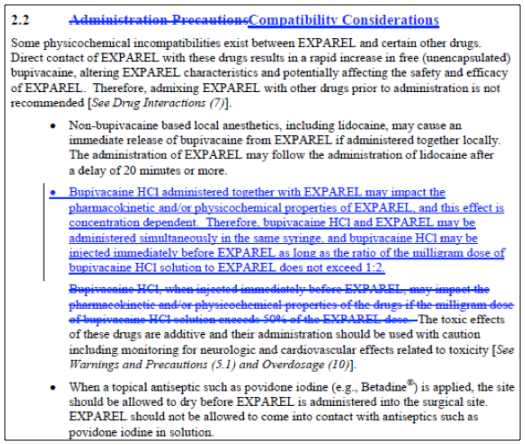
SECTION 14.2: Study 2 (formerly Hemorrhoidectomy)

- The label states that the primary outcome measure for the study looked at cumulative pain scores over 72 hours and that there **was a significant treatment effect for EXPAREL compared to placebo.**
- Language stating there was "minimal to no difference between EXPAREL and placebo on pain intensity scores between 24 and 72 hours" was removed.
- Instead, the 72-hour duration of effect for EXPAREL was illustrated by a graph of mean pain intensity scores over the 72-hour period and specific information related to opioid use:
  - % of opioid-free patients at 72 hours (28% for EXPAREL vs 10% for placebo).
  - Median time to first rescue (15 hours for EXPAREL vs 1 hour for placebo).

KEY DETAILS ON RESOLUTION AGREEMENT CONTINUED

SECTION 2.2: Compatibility Considerations *(formerly Administration Precautions)*

- Guidelines on admixing (i.e., simultaneous administration in the same syringe) of bupivacaine HCl and EXPAREL were inserted to provide guidance to the medical community on this common practice of co-administration to achieve immediate pain relief (with bupivacaine HCl) as well as prolonged analgesia (with EXPAREL).



2.2 ~~Administration Precautions~~Compatibility Considerations

Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL. Therefore, admixing EXPAREL with other drugs prior to administration is not recommended [*See Drug Interactions (7)*].

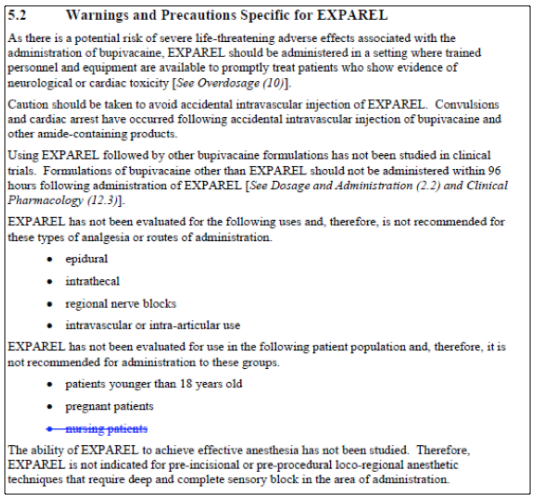
- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

~~Bupivacaine HCl, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physicochemical properties of the drugs if the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose.~~ The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity [*See Warnings and Precautions (5.1) and Overdosage (10)*].

- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

SECTION 5.2: Warnings and Precautions Specific for EXPAREL

- Restrictions on the use of EXPAREL in nursing mothers was removed, which allows physicians to utilize EXPAREL in this patient population at their discretion.



5.2 Warnings and Precautions Specific for EXPAREL

As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Using EXPAREL followed by other bupivacaine formulations has not been studied in clinical trials. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL [*See Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks
- intravascular or intra-articular use

EXPAREL has not been evaluated for use in the following patient population and, therefore, it is not recommended for administration to these groups.

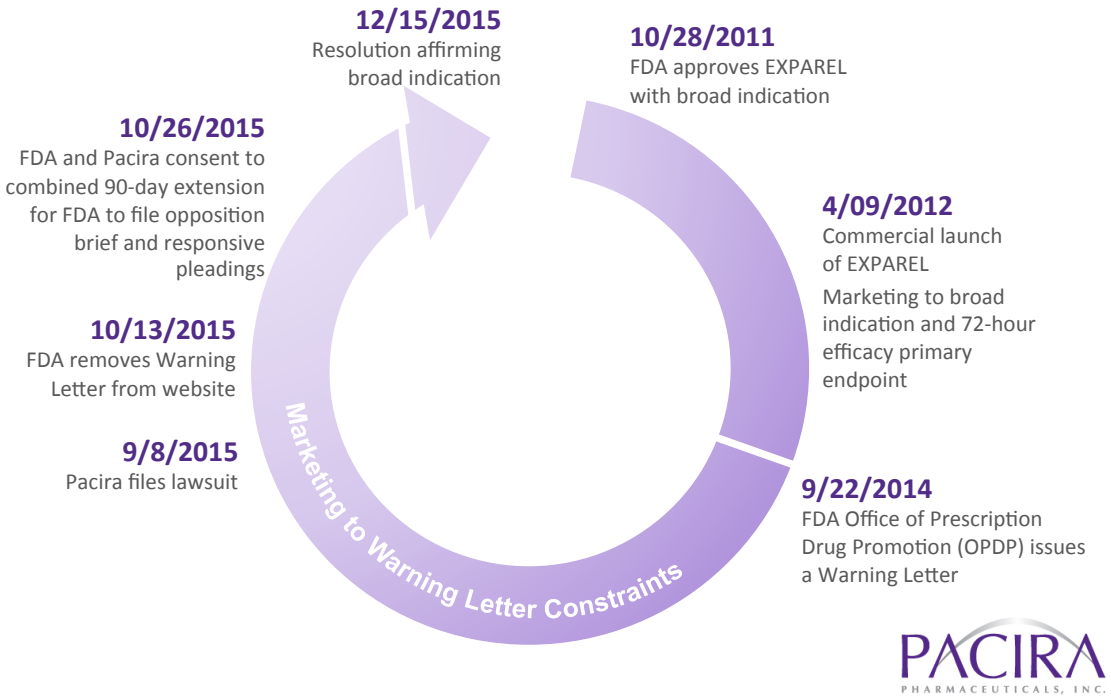
- patients younger than 18 years old
- pregnant patients
- ~~nursing patients~~

The ability of EXPAREL to achieve effective anesthesia has not been studied. Therefore, EXPAREL 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.

CONCLUSION

Pacira and the FDA share a commitment to improving postsurgical patient care and addressing the need for effective pain management alternatives that minimize the risk of opioid use, misuse, abuse, or addiction. With the FDA's support, the reaffirmation of a broad indication, and a clarified label, Pacira is eager to return to the important task of educating healthcare providers and hospitals on optimizing the value and benefit of EXPAREL to patients, and to consider EXPAREL as a part of a comprehensive solution to reduce our nation's reliance on opioids.

LEGAL PROCESS RECAP OF EVENTS



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