DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51, Room 6133
Silver Spring MD 20993

December 14, 2015

Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany, NJ 07054

Attn: David Stack
Chief Executive Officer & Chairman

Dear Mr. Stack:

After review of the Warning Letter the agency issued to Pacira Pharmaceuticals, Inc. ("Pacira") on September 22, 2014, as well as the approved labeling for EXPAREL and related materials, the United States Food and Drug Administration ("FDA" or the "agency") rescinded the 2014 Warning Letter and removed it from the agency's website on Tuesday, October 13, 2015. This letter explains the reasons for that decision.

Background

1. EXPAREL's Labeling

On October 28, 2011, FDA approved Pacira's new drug application ("NDA") for EXPAREL, a bupivacaine liposome injectable suspension. As part of the approval process, FDA and Pacira engaged in negotiations regarding the text for EXPAREL's label. The Indications and Usage section in the full prescribing information of the final, agreed-upon label stated that:

> EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

The first paragraph of the Clinical Studies section of the full prescribing information included in the final, agreed-upon label stated:

> 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.[1]

[1] We note that the agency recently approved a labeling supplement that you submitted to FDA on November 17, 2015 (as amended by NDA Serial No. 0123, submitted November

2. Warning Letter

After EXPAREL's approval, FDA reviewed one of Pacira's journal advertisements, as well as Pacira's educational technique flashcards (or administration guides), which provided instructions on the use of EXPAREL in cholecystectomy and colectomy procedures.[2]

Thereafter, on September 22, 2014, FDA issued a Warning Letter objecting to Pacira's materials promoting EXPAREL for surgeries other than bunionectomy and hemorrhoidectomy. The Warning Letter also objected to Pacira's general claims about EXPAREL's ability to control pain for up to 72 hours.

Discussion

1. Rescission of the Warning Letter

In a recent review of the Warning Letter, the FDA-approved labeling for EXPAREL, and related materials, FDA determined that different statements in various parts of the approved labeling created ambiguity with respect to the scope of the approved indication. Ultimately, however, the use described in EXPAREL's Indications and Usage statement broadly referred to "surgical site[s]" and was not limited to bunionectomy and hemorrhoidectomy procedures. Based on the plain language of the Indications and Usage section of the full prescribing information, as well as the clinical trials submitted in support of that approval, FDA determined that the indication approved in 2011, was not limited to bunionectomy and hemorrhoidectomy procedures.

In light of this determination, on October 13, 2015, the agency rescinded the Warning Letter issued to Pacira. As you are aware, FDA removed the Warning Letter from its website that same day. In addition, as noted, on December 14, 2015, the agency approved a labeling supplement that you submitted to FDA on November 17, 2015 (as amended by NDA Serial No. 0123, submitted November 25, 2015), which made certain changes to the EXPAREL label in order to clarify that its indication was not limited to bunionectomy and hemorrhoidectomy procedures. The labeling supplement also revised the description of the duration of EXPAREL's effect contained in the clinical studies section of the full prescribing information.

25, 2015), which removed the sentence stating that "EXPAREL has not been demonstrated to be safe and effective in other procedures" from EXPAREL's current labeling.

[2] Pacira also submitted the journal ad and flash cards to the agency under Form FDA-2253.

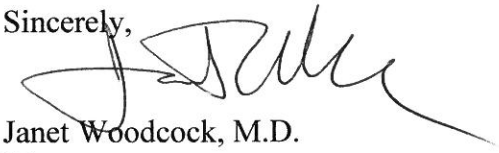
2. Your Request for FDA's Position

You requested FDA's position regarding the following: (1) whether the infiltration of EXPAREL into the transversus abdominis plane ("TAP"), sometimes referred to as a TAP block, falls within the scope of EXPAREL's current indication; and (2) the use of EXPAREL for infiltration into dental and oral surgery sites to produce postsurgical analgesia.

With respect to the first issue, FDA notes that the withdrawal of the Warning Letter, combined with FDA's recent approval of your labeling supplement, fully clarifies FDA's conclusions regarding the scope of EXPAREL's indication, as initially approved on October 28, 2011. A TAP block is a regional anesthetic technique used for post-surgical analgesia of the anterolateral abdomen. The local anesthetic is placed in the fascial plane between the internal oblique and the transverse abdominis muscles. The end result is a field block. In a field block, local anesthetic is infiltrated around the border of the surgical field, leaving the operative area undisturbed. A field block is consistent with the procedure described in your hemorrhoidectomy trial submitted in support of EXPAREL's approval. In addition, in describing one example of dosing (*i.e.,* dosing in hemorrhoidectomy procedures) the Dosage and Administration section of EXPAREL's full prescribing information, as revised on December 14, 2015, states that physicians may inject EXPAREL "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." Therefore, TAP blocks are covered by EXPAREL's labeling.

With respect to the second issue, EXPAREL's indication does not include its use as a nerve block prior to dental restorative procedures or oral surgical procedures; that is branches of the maxillary and mandibular divisions of the trigeminal nerve proximal to the operative site. However, EXPAREL's indication does encompass use for postoperative analgesia when administered as local infiltration at the site of oral surgical procedures, including tooth extractions. EXPAREL's indication also includes local anesthetic deposited near a terminal branch of the maxillary or mandibular branch of the trigeminal nerve, also referred to as periapical injections.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Douglas H. Hallward-Driemeier, Esq.
Joan McPhee, Esq.
Ropes & Gray LLP