



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993**TRANSMITTED BY FACSIMILE**

Dave Stack
President and CEO
Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany NJ 07054

RE: NDA # 022496
EXPAREL® (bupivacaine liposome injectable suspension)
MA# 68

WARNING LETTER

Dear Mr. Stack:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed educational technique flashcards (EXP-AP-0124-201209 & EXP-AP-0134-201210) (administration guides) and a journal ad (EXP-AP-0039-201302) for EXPAREL® (bupivacaine liposome injectable suspension) (Exparel) submitted by Pacira Pharmaceuticals, Inc. (Pacira) under cover of Form FDA-2253. The journal ad was also submitted as a complaint to the OPDP Bad Ad Program. The administration guides provide evidence that Exparel is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for use, which renders Exparel misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and make its distribution violative. See 21 U.S.C. 355(a), 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128. In addition, the journal ad is false or misleading because it overstates the efficacy of Exparel. Thus, the journal ad misbrands the drug within the meaning of the FD&C Act, and makes its distribution violative. 21 USC 352(n); 331(a); 21 CFR 202.1(e)(6)(i). These violations are extremely concerning from a public health perspective because they provide evidence of the intended use of Exparel in surgical procedures other than those for which the drug has been shown to be safe and effective and they suggest that Exparel is more effective than has been demonstrated.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Exparel.¹

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

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According to its FDA-approved product labeling (PI), 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.

Exparel is contraindicated in obstetrical paracervical block anesthesia. The PI also contains warnings and precautions regarding administration in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity, overdose, central nervous system, cardiovascular, and allergic reactions, chondrolysis, and the risk of accidental intravascular injection with resultant convulsions and cardiac arrest. Exparel is not recommended for the following types of analgesia, routes of administration, and patient populations: epidural, intrathecal, regional nerve blocks, intravascular or intra-articular use, patients younger than 18 years old, pregnant patients, or nursing patients. In addition, Exparel is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques. The most common adverse reactions following Exparel administration were nausea, constipation and vomiting.

Lack of Adequate Directions for Use

The administration guides describe specific administration techniques for Exparel in laparoscopic cholecystectomy and open colectomy and includes claims such as the following (original emphasis):

Administration Guide (EXP-AP-0124-201209)

Administration Technique Guide

Capturing Clinician Experience with EXPAREL (header)

...

CASE INFORMATION

Physician's Name	Dr. Lawrence Biskin
Affiliation	UPMC Saint Margaret Memorial Hospital
Surgical Case Performed	Laparoscopic cholecystectomy . . .

Administration Guide (EXP-AP-0134-201210)

Administration Technique Guide

Capturing Clinician Experience with EXPAREL (header)

...

CASE INFORMATION

Physician's Name	Stephen M. Cohen, MD, FACS, FASCRS
Affiliation	Atlanta Colon and Rectal Surgery, P.A.; Atlanta, GA

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Surgical Case Performed Open colectomy (ileocolic resection) with repair of the fistula . . .

These claims suggest that Exparel is safe and effective for use in cholecystectomy and colectomy. However, the DOSAGE AND ADMINISTRATION section of the PI provides recommended dosing for bunionectomy and hemorrhoidectomy only. Furthermore, the CLINICAL STUDIES section of the PI clearly states (underlined emphasis added):

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.

The approved labeling for Exparel does not provide instructions for, or otherwise indicate that Exparel will be safe and effective for postsurgical pain if used in surgical procedures other than hemorrhoidectomy or bunionectomy. Information sufficient to demonstrate that Exparel is safe and effective for these new intended uses has not been submitted to FDA in an application.

We acknowledge the inclusion of several disclaimers or disclosures^{2,3,4} in the administration guides. However, the inclusions of disclaimers or disclosures, whether in the body of the promotional piece or a footnote, do not mitigate the overwhelming impression that Exparel is safe and effective for use in cholecystectomy and colectomy. In sum, these presentations provide evidence that Exparel is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate instructions for use.

Moreover, OPDP is concerned with Pacira's suggestions, made in an array of professionally-directed promotional materials submitted under cover FDA-form 2253, not discussed within this letter, that Exparel has been demonstrated to be safe and effective in various other surgical procedures (e.g., knee arthroplasty, gastric sleeve, open hysterectomy, lumbar interbody fusion, abdominoplasty, etc.). These additional materials suggest an extensive promotional campaign by Pacira to promote the use of Exparel in surgical procedures other than those for which the drug has been shown to be safe and effective.

² From the cholecystectomy administration guide: "This educational technique guide represents the individual experience of Dr. Lawrence Bisikin and is intended to demonstrate his methodology for using EXPAREL in a specific soft tissue surgery. Pacira Pharmaceuticals recognizes that there are alternative methodologies for administering local anesthetics, as well as individual patient consideration, when selecting the dose for a specific procedure." and "The approval of Exparel was based on 2 pivotal clinical trials that demonstrated the safety and efficacy of the product injected into soft tissue surrounding the surgical site..."

³ From the colectomy administration guide: "This educational technique guide represents the individual experience of Dr. Stephen M. Cohen, MD, FACS, FASCRS and is intended to demonstrate his methodology for using EXPAREL in a specific soft tissue surgery. Pacira Pharmaceuticals recognizes that there are alternative methodologies for administering local anesthetics, as well as individual patient consideration, when selecting the dose for a specific procedure.", "Disclosures: Dr. Cohen is a paid speaker and consultant for Pacira." and "The approval of EXPAREL was based on two pivotal clinical trials, excisional hemorrhoidectomy and bunionectomy, that demonstrated the safety and efficacy of the product."

⁴ From both administration guides: "[I]t is up to the individual prescriber to determine the relevance of the demonstration of efficacy and safety in these surgical models to their own surgical setting."

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Overstatement of Efficacy

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The journal ad claims presented here, "**Patient-Focused Pain Control That Lasts For Up To 72 Hours**," and "**The only single-dose local analgesic to . . . Reduce or eliminate opioids with pain control for up to 3 days**" (original bold emphasis; underlined emphasis added), suggest that that Exparel has been shown to provide pain control beyond 24 hours when this has not been demonstrated. These claims overstate Exparel's efficacy and are misleading.

For support, the journal ad includes a reference to a publication⁵ describing one of the pivotal clinical trials (i.e., hemorrhoidectomy trial) that were used to support Exparel's approval. Although both the pivotal hemorrhoidectomy and bunionectomy trials constitute substantial evidence to support a reduction in pain intensity (i.e., "pain control") for Exparel compared to placebo for up to 24 hours, neither the cited hemorrhoidectomy trial nor the bunionectomy trial qualifies as substantial evidence to support claims regarding pain control beyond 24 hours. To the contrary, as stated in the PI, "The primary outcome measure was the AUC [area under the curve] of the NRS [numeric rating scale] pain intensity scores (cumulative pain scores) collected over the first 72 hour period. . . . 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" (emphasis added). Therefore, the claims identified above suggesting that Exparel has demonstrated pain control beyond 24 hours are misleading.

Conclusion and Requested Action

For the reasons discussed above, the administration guides provide evidence that Exparel is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for use, which renders Exparel misbranded or otherwise makes its distribution violative. See 21 USC 355(a), 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128. The journal ad also misbrands Exparel within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(n); 331(a); 21 CFR 202.1(e)(6)(I).

OPDP requests that Pacira immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before October 6, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Exparel that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audiences that received the violative promotional materials. In order to clearly identify the promotional pieces and/or activity and focus on the corrective messages, OPDP recommends that corrective piece(s) include a description of the promotional pieces and/or activity, include a summary of the false

⁵ Gorfine SR, et al. *Diseases of the Colon & Rectum*. Dec 2011;54(12):1552-1559

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or misleading messages, provide information to correct each of the messages, and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the promotional material was disseminated.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to the MA #68 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Exparel comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Andrew Haffer, Pharm.D.
Division Director
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW S HAFFER
09/22/2014