NDA 022496/S-044

SUPPLEMENT APPROVAL

Pacira Pharmaceuticals, Inc.
5 Sylvan Way, Suite 300
Persippany, NJ 07054

Attention: Aditi Vekaria, PharmD
Regulatory Project Manager

Dear Dr. Vekaria:

Please refer to your supplemental new drug application (sNDA) dated January 13, 2023, received January 13, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXPAREL (bupivacaine liposome injectable suspension).

This Prior Approval supplemental new drug application provides for the following additions to the Indications and Usage section, and edits to the Limitation of Use for EXPAREL:

> EXPAREL is indicated to produce postsurgical:
>
> - Regional analgesia via a sciatic nerve block in the popliteal fossa in adults
> - Regional analgesia via an adductor canal block in adults
>
> Limitations of Use
> The safety and effectiveness of EXPAREL have not been established to produce postsurgical regional analgesia via other nerve blocks besides an interscalene brachial plexus nerve block, a sciatic nerve block in the popliteal fossa, or an adductor canal block.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling, submitted on November 8, 2023.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on November 8, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 022496/S-044**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

---

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric study requirement for pediatric patients from birth to less than 2 years of age because necessary studies are impossible or highly impracticable.

We are also deferring submission of your pediatric studies for ages 2 to less than 17 years for this application because this product is ready for approval in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4538-1 Conduct a multicenter, randomized, double-blind, parallel-group, immediate-release bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as a sciatic nerve block in the popliteal fossa to produce postsurgical regional analgesia in pediatric patients ages 12 to less than 17 years old undergoing surgical procedures.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

4538-2 Conduct a multicenter, randomized, double-blind, parallel-group, immediate-release bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as a sciatic nerve block in the popliteal fossa to produce postsurgical regional analgesia in pediatric patients ages 6 to less than 12 years old undergoing surgical procedures.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

4538-3 Conduct a multicenter, randomized, double-blind, parallel-group, immediate-release bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as a sciatic nerve block in the popliteal fossa to produce postsurgical regional analgesia in pediatric patients ages 2 to less than 6 years old undergoing surgical procedures.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

4538-4 Conduct a multicenter, randomized, double-blind, parallel-group, immediate-release bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as an adductor canal block to produce postsurgical regional analgesia in pediatric patients ages 12 to less than 17 years old undergoing surgical procedures.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

4538-5 Conduct a multicenter, randomized, double-blind, parallel-group, immediate-release bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as an adductor canal block to produce postsurgical regional analgesia in pediatric patients ages 6 to less than 12 years old undergoing surgical procedures.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

4538-6 Conduct a multicenter, randomized, double-blind, parallel-group, immediate-release bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as an adductor canal block to produce postsurgical regional analgesia in pediatric patients ages 2 to less than 6 years old undergoing surgical procedures.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 069198, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

---

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email Wanda Nguyen, PharmD, Senior Regulatory Project Manager at Wanda.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
11/09/2023 03:41:55 PM