NDA 204803

NDA APPROVAL

DURECT Corporation
10260 Bubb Road
Cupertino, CA 95014

Attention: Jill Burns
Executive Director, Regulatory Affairs

Dear Ms. Burns:

Please refer to your new drug application (NDA) dated and received April 12, 2013, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for POSIMIR (bupivacaine solution) for infiltration use, 132 mg/mL.

We acknowledge receipt of your amendment dated June 27, 2019, which constituted a complete response to our February 12, 2014, action letter.

This new drug application provides for the use of POSIMIR in adults for administration into the subacromial space under direct arthroscopic visualization to produce post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression.

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.

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 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]

[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.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling 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 204803**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for POSIMIR (bupivacaine solution) for infiltration, 132 mg/mL, shall be 36 months from the date of manufacture when stored at 20-25°C (USP controlled room temperature).

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.

We are waiving the pediatric study requirement in all age groups for this application. In pediatric patients birth to less than 3 years of age, there is evidence strongly suggesting that the drug product would be unsafe, and we agree that the potential for benzyl alcohol toxicity outweighs any potential benefit for use in this age group.

In pediatric patients birth to less than 17 years of age, we do not believe your product represents a meaningful therapeutic benefit over existing bupivacaine products for use in this age group and is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to characterize the serious risk of inadvertent intravenous toxicity including local anesthetic systemic toxicity (LAST) which may or may not be treatable with standard medical intervention.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4014-1 Conduct a nonclinical intravenous toxicity study that includes both an acute and delayed timepoint with full histopathology to determine the ultimate impact of the drug product and fate of the vehicle if it is inadvertently administered into the intravascular space. The study should include collection of pharmacokinetic data to determine if intravascular injection results in more rapid release of the bupivacaine dose from the vehicle.

The timetable you submitted on January 29, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	08/2022
Study Completion:	06/2023
Final Report Submission:	09/2023

We recommend a small pilot study prior to the pivotal study to confirm that IV administration does not result in catastrophic moribundity.

4014-2 Conduct a study to assess the potential serious risk of POSIMIR-induced Local Anesthetic Systemic Toxicity (LAST) following inadvertent intravenous route of administration and the ability of lipid infusions to treat the clinical manifestations of LAST.

The timetable you submitted on January 29, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2022
Final Protocol Submission:	11/2022
Study Completion:	06/2023
Final Report Submission:	09/2023

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.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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, call LCDR Mavis Y. Darkwah, PharmD, GWCPM, RAC-US, Regulatory Project Manager, at (240) 402-3158.

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

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

---

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
02/01/2021 06:00:04 PM