CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204803Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204803

COMPLETE RESPONSE

DURECT Corporation
10260 Bubb Road
Cupertino, CA 95014

Attention: Jill H. K. Burns
Senior Director, Regulatory Affairs

Dear Ms. Burns:

Please refer to your New Drug Application (NDA) dated April 12, 2013, received April 12, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for POSIMIR (bupivacaine extended-release solution for instillation) 660 mg/ 5mL (132mg/mL), 13.2%.

We acknowledge receipt of your amendments dated April 25 and 26, May 23, June 6, July 2, August, 20, September 3, 10, and 25, October 23, November 6 and 26, and December 6, 20, 30, and 31, 2013, and January 16 and February 3, 2014.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. The application does not contain sufficient information to demonstrate that POSIMIR is safe when used in the manner described in the proposed label. Specifically, we have identified the following deficiencies:

    a. There were adverse events related to the shoulder joint and surrounding tissues in subjects who underwent follow-up assessments at 18 months, after their arthroscopic subacromial decompression surgery. There were insufficient data due to the limited number of subjects and the lack of an appropriate comparator to permit a determination of whether SABER-bupivacaine causes adverse reactions affecting the joint or the surrounding structures to a clinically relevant greater extent than either bupivacaine HCl or a non-SABER containing placebo.

    b. The risk of bruising, hematoma, pruritus, and dehiscence occurred following administration of SABER-containing products (SABER-bupivacaine and SABER-placebo) substantially more often than following administration of bupivacaine HCL. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-

SABER containing placebo following the surgical procedures studied and whether the risk was greater with only certain surgical procedures.

c. There was a marked increased risk of neurologically related adverse events, i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which occurred with substantially greater frequency following administration of SABER-containing products compared to bupivacaine HCl. There were insufficient data to determine whether the risk is greater with SABER-bupivacaine than for either bupivacaine HCl or a non-SABER containing placebo following each of the surgical procedures studied and clinical impact of these reactions, e.g., whether they delayed discharge from the post-anesthesia care unit or affected time to ambulation.

Information needed to resolve the deficiency:

Conduct additional studies to adequately characterize the risk profile of SABER-bupivacaine to address the deficiencies listed above. Specifically, the following types of studies need to be conducted:

a. A safety study evaluating the occurrence of adverse reactions associated with the shoulder joint and the surrounding tissues, including the skin, following arthroscopic subacromial decompression. Safety assessments need to be performed at appropriate intervals following the administration of study drug to capture the onset and duration of the reactions and need to be carried out for an appropriate period of time to capture late-onset events. Input should be solicited from expert consultants to help design the study, particularly with respect to appropriate assessments, their frequency and the duration of follow-up.

   The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design and needs to include enough subjects to detect reactions with an incidence rate of ≥ 1%. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

   We strongly recommend that you discuss the design of this study with the Division prior to implementation.

b. A safety study evaluating the occurrence of adverse reactions associated with the skin and underlying tissues. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out until complete healing of the surgical wound has occurred. The protocol needs to incorporate standardized definitions for the reactions observed thus far in the clinical development program, e.g., hematoma, ecchymosis, dehiscence, to assure uniform classification of the reactions among investigators.

The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

We strongly recommend that you discuss the design of this study with the Division prior to implementation.

c. A safety study evaluating the occurrence of adverse reactions associated with neurotoxicity. Safety assessments need to be performed at appropriate time intervals following administration of study drug to capture the onset and duration of the reactions and to be carried out for the duration of systemic exposure to benzyl alcohol. The clinical impact of the adverse reactions needs to be captured, e.g., delayed discharge due to somnolence; delayed time to ambulation due to dizziness.

The treatments need to include SABER-bupivacaine and either bupivacaine HCL or a non-SABER containing placebo (or both). The study needs to be randomized and double-blinded in design. The study must evaluate subjects undergoing each of the surgical procedures studied to date, with the numbers of subjects undergoing each of the procedures evenly distributed. Efficacy data must be collected during the study to allow the safety data to be placed in clinical context when the benefit:risk analysis is performed.

We strongly recommend that you discuss the design of this study with the Division prior to implementation.

LABELING

1. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

RIGOBERTO A ROCA
02/12/2014