Heron Therapeutics, Inc.
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Attention: Kimberly J. Manhard
Executive Vice President, Drug Development

Dear Ms. Manhard:

Please refer to your supplemental new drug application (sNDA) dated and received September 29, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zynrelef (bupivacaine and meloxicam) extended-release solution for soft tissue or periarticular instillation use.

This Prior Approval sNDA provides for the following change: to expand the indication in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use), with the addition of any labeling

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
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).

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 deferring submission of your pediatric studies according to the timelines listed below, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under 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.

4059-5 Conduct a juvenile animal study in an appropriate model to characterize the potential toxicity of bupivacaine on chondrocytes and growth plates to support clinical studies in pediatric patients from birth to less than 17 years of age.

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.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov
4059-6 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients three to less than 17 years of age undergoing small-to-medium open abdominal procedures.

Final Protocol Submission: 12/2021
Study Completion: 12/2025
Final Report Submission: 05/2026

4059-7 Conduct a multicenter study to assess the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric patients from birth to less than three years of age undergoing small-to-medium open abdominal procedures.

Draft Protocol Submission: 02/2025
Final Protocol Submission: 08/2025
Study Completion: 04/2028
Final Report Submission: 10/2028

4059-8 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric subjects three to less than 17 years of age undergoing foot and ankle procedures.

Draft Protocol Submission: 07/2022
Final Protocol Submission: 01/2023
Study Completion: 06/2027
Final Report Submission: 12/2027
4059-9 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric subjects from birth to less than 3 years of age undergoing foot and ankle procedures.

Draft Protocol Submission: 08/2027
Final Protocol Submission: 02/2028
Study Completion: 02/2031
Final Report Submission: 08/2031

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 protocols to your IND 125927, 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 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

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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

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Reference ID: 4900987
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 Rita Joshi, PharmD, Regulatory Project Manager, at 301-348-1888.

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
  - Instructions for Use
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
12/08/2021 12:00:01 PM