NDA 211988/S-013

SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

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

Attention: Bill Forbes, PharmD
Executive Vice President and Chief Development Officer

Dear Dr. Forbes:

Please refer to your supplemental new drug application (sNDA) dated and received December 23, 2022, 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.

We acknowledge receipt of your major amendment dated July 20, 2023, which extended the goal date by three months.

This Prior Approval sNDA proposes the following changes:

- To expand the indication in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures.

- To revise the Limitation of Use statement to include large 4 or more level spinal procedures instead of large multilevel spinal 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.[1] 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 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 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 211988/S-013**." Approval of this submission by FDA is not required before the labeling is used.

RELEASE FROM POSTMARKETING REQUIREMENT

Reference is made to your Annual Report dated July 10, 2023, in which you reported on the following postmarketing requirements (PMRs) listed in our May 12, 2021, Approval

[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.

Letter (PMRs 4059-1 and 4059-2) and December 8, 2021, Supplement Approval Letter (PMRs 4059-6 to 4059-9).

4059-1 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 unilateral open inguinal herniorrhaphy.

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

4059-2 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 unilateral open inguinal herniorrhaphy.

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

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

We have reviewed your submission and have determined that you are released from the above postmarketing requirements. These PMRs stipulated the following procedures to be evaluated in the pediatric patient population: open inguinal herniorrhaphy, small-to-medium open abdominal surgeries, and foot and ankle procedures. Upon expansion of the indication to broadly include use after soft tissue and orthopedic surgical procedures, additional procedures will also need to be evaluated in the pediatric studies. Therefore, the PMRs must be revised to include the possible procedures, both soft tissue and orthopedic, needing to be evaluated in pediatric patients. Based on the changes to the approved indication of Zynrelef, the above PMRs are released because the above requirements are no longer needed, and the revised PMRs below are more reflective of the new indication, now approved under this Supplement 013.

The above postmarketing requirements will be replaced by the new postmarketing requirements as described below:

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.

4059-10 Conduct a multicenter study to assess the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients three to less than 17 years of age undergoing representative soft tissue surgical procedures.

The timetable you submitted on January 9, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2024
Study Completion:	03/2029
Final Report Submission:	09/2029

4059-11 Conduct a multicenter study to assess the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients three to less than 17 years of age undergoing representative orthopedic surgical procedures.

The timetable you submitted on January 9, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	09/2024
Study Completion:	02/2030
Final Report Submission:	08/2030

4059-12 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 representative soft tissue and orthopedic surgical procedures.

The timetable you submitted on January 9, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2026
Final Protocol Submission:	09/2026
Study Completion:	09/2030
Final Report Submission:	03/2031

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]

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

[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.
[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

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).

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, contact Sandy Truong, Regulatory Project Manager, at 301-796-5719 or sandy.truong@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
  - Instructions for Use
- 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
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