CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211988Orig1s000

Trade Name:	Zynrelef extended release solution 60 mg/1.8 mg, 200 mg/6 mg, 300 mg/9 mg, and 400 mg/12 mg
Generic or Proper Name:	bupivacaine and meloxicam
Sponsor:	Heron Therapeutics, Inc.
Approval Date:	May 12, 2021
Indication:	Indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty

CENTER FOR DRUG EVALUATION AND RESEARCH

211988Orig1s000

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APPLICATION NUMBER:

211988Orig1s000

APPROVAL LETTER

NDA 211988

GENERAL ADVICE

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 new drug application (NDA) dated and received October 30, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zynrelef (bupivacaine and meloxicam) extended-release solution.

We also refer to our approval letter for NDA 211988 dated May 12, 2021.

Further, we acknowledge receipt of your May 12, 2021, electronic correspondence noting that our May 12, 2021, approval letter erroneously included the term *use* [underlined below] in the following sections:

- Identifying the product indication as: the use of Zynrelef in adults for soft tissue or periarticular instillation use to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

- Requesting revised Instructions for Use (IFU) documents to reflect the indication as: Zynrelef is indicated in adults for soft tissue or periarticular instillation use to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

We also acknowledge receipt of your May 13, 2021, electronic correspondence noting that our May 12, 2021, approval letter omitted images for the following carton labels:

- Vented Vial Spike Replacement Carton
- Luer Lock Applicator Replacement Carton
- 3 mL Syringe Replacement Carton
- 12 mL Syringe Replacement Carton

This general advice letter provides for a corrected indication. This letter also provides for corrected carton and container labeling enclosures containing the images for the omitted carton labels listed above. These carton labels are considered part of the approved labels and labeling for NDA 211988, and should be included in your SPL submission prior to May 27, 2021.

The corrected indication to our approval letter dated May 12, 2021:

- Zynrelef is indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

The corrected request for revised IFU documents to reflect the corrected indication to our approval letter dated May 12, 2021:

- Revise the Instructions for Use documents to reflect the indication as:

  ZYNRELEF is indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

Note that the indication as presented in the prescribing information document is correct in all respects.

If you have any questions, contact Rita Joshi, Regulatory Project Manager, at rita.joshi@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:

- Carton and Container Labeling
  - Vented Vial Spike Replacement Carton
  - Luer Lock Applicator Replacement Carton
  - 3 mL Syringe Replacement Carton
  - 12 mL Syringe Replacement Carton

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
05/14/2021 05:23:06 PM

NDA 211988

NDA APPROVAL

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 new drug application (NDA) dated and received October 30, 2018, 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, 60 mg/1.8 mg, 200 mg/6 mg, 300 mg/9 mg, and 400 mg/12 mg.

We acknowledge receipt of your amendment dated November 12, 2020, which constituted a complete response to our June 26, 2020, action letter.

This new drug application provides for the use of Zynrelef in adults for soft tissue or periarticular instillation use to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

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, with minor editorial revisions listed below:

- Revise the Instructions For Use documents to reflect the indication as:

  ZYNRELEF is indicated in adults for soft tissue or periarticular instillation use to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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) 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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your May 11, 2021, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Zynrelef (bupivacaine and meloxicam) extended-release solution shall be 36 months for the 400 mg/12 mg, 300 mg/9 mg and 200 mg/6 mg product presentations, and 24 months for the 60 mg/1.8 mg product presentation from the date of manufacture when stored at controlled room temperature, 20°–25°C (68°–77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F), and protected from light.

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.

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[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.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act 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. The required studies are listed below.

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

4059-3 Conduct a juvenile animal study in an appropriate model to characterize the impact of meloxicam on the developing kidney, liver, lung, and testes to support clinical studies in pediatric patients from birth to less than two years of age.

Draft Protocol Submission:	12/2022
Final Protocol Submission:	05/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

4059-4 Conduct a juvenile animal study in the rodent model to characterize the impact of DMSO on the developing brain to support clinical studies in pediatric patients from birth to less than three years of age.

Final Protocol Submission:	05/2021
Study Completion:	07/2022
Final Report Submission:	02/2023

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 for 4059-2 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]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

[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

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
- 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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