CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211988Orig1s005

Trade Name: ZYNRELEF®

Generic or Proper Name: bupivacaine and meloxicam

Sponsor: Heron Therapeutics, Inc.

Approval Date: 12/08/2021

Indication:

ZYNRELEF® contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), and is indicated 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**x**
Other Action Letters	
Labeling	**x**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	**x**
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	**x**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**x**
Other Reviews	**x**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**x**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

APPROVAL LETTER

NDA 211988/S-005

SUPPLEMENT 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 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.[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

[1] 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.

Draft Protocol Submission:	12/2022
Final Protocol Submission:	05/2023
Study Completion:	02/2024
Final Report Submission:	08/2024

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]

[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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYNRELEF® safely and effectively. See full prescribing information for ZYNRELEF.

ZYNRELEF (bupivacaine and meloxicam) extended-release solution, for soft tissue or periarticular instillation use
Initial U.S. Approval: 2021

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2021
Dosage and Administration (2.1, 2.4)	12/2021
Warnings and Precautions (5.10)	12/2021

----------INDICATIONS AND USAGE----------

ZYNRELEF contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), and is indicated 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.

Limitations of Use
Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures (1).

----------DOSAGE AND ADMINISTRATION----------

- ZYNRELEF is intended for single-dose administration only (2.1).
- The toxic effects of local anesthetics are additive. Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF (2.1).
- ZYNRELEF should only be prepared and administered with the components provided in the ZYNRELEF kit. (2.1).
- ZYNRELEF is applied without a needle into the surgical site following final irrigation and suction and prior to suturing (2.1).
  - The recommended dose of ZYNRELEF is up to a maximum dose of 400 mg/12 mg (14 mL) (2.4).
- See Full Prescribing Information for important preparation and administration instructions, dose selection, and compatibility considerations (2.2, 2.3, 2.4, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------

ZYNRELEF (bupivacaine and meloxicam) extended-release solution is available in four dosage strengths as single-dose glass vials:

- 400 mg bupivacaine and 12 mg meloxicam
- 300 mg bupivacaine and 9 mg meloxicam
- 200 mg bupivacaine and 6 mg meloxicam
- 60 mg bupivacaine and 1.8 mg meloxicam

----------CONTRAINDICATIONS----------

ZYNRELEF is contraindicated for:

- Patients with a known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to any local anesthetic agent of the amide-type, NSAIDs, or to any of the other components of ZYNRELEF (4)
- Patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients (4)
- Patients undergoing obstetrical paracervical block anesthesia (4)
- Patients undergoing coronary artery bypass graft (CABG) surgery (4)

----------WARNINGS AND PRECAUTIONS----------

Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after application of ZYNRELEF (5.3).

When using ZYNRELEF with other local anesthetics, overall local anesthetic exposure must be considered through 72 hours (5.3).

Hepatotoxicity: If abnormal liver tests persist or worsen, perform a clinical evaluation of the patient (5.5).

Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.6, 7).

Heart Failure and Edema: Avoid use of ZYNRELEF in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.7).

Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ZYNRELEF in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.8).

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.9).

Chondrolysis: Limit exposure to articular cartilage due to the potential risk of chondrolysis (5.10).

Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use (5.11).

Serious Skin Reactions: NSAIDs, including meloxicam, can cause serious skin adverse reactions. If symptoms present, evaluate clinically (5.13).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): If symptoms are present, evaluate clinically (5.14).

Fetal Toxicity: Limit use of NSAIDs, including ZYNRELEF, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the ductus arteriosus (5.15, 8.1).

Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.16).

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥10%) are constipation, vomiting, and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Heron Therapeutics, Inc. at 1-844-437-6611 and www.ZYNRELEF.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking ZYNRELEF with drugs that interfere with hemostasis (7.2).

ACE Inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers: Concomitant use with ZYNRELEF may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7.2).

ACE Inhibitors and ARBs: Concomitant use with ZYNRELEF in elderly, volume-depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function (7.2).

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effect (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Infertility: NSAIDs are associated with reversible infertility. Consider avoidance of ZYNRELEF in women who have difficulties conceiving (8.3).

Severe Hepatic Impairment: Only use if benefits are expected to outweigh risks; monitor for signs of worsening liver function (8.6).

Severe Renal Impairment: Not recommended (8.7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].**
- **ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4)* and *Warnings and Precautions (5.1)*].**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions* (*5.2*)].**

1 INDICATIONS AND USAGE

ZYNRELEF is indicated 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.

Limitations of Use

Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- ZYNRELEF is intended for single-dose administration only.
- As there is a potential risk of severe, life-threatening adverse reactions associated with the administration of bupivacaine, ZYNRELEF should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurologic or cardiac toxicity [*see Overdosage (10)*].
- The toxic effects of local anesthetics are additive. Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF.
- Avoid intravascular administration of ZYNRELEF. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

- Limit exposure to articular cartilage due to the potential risk of chondrolysis *[see Warnings and Precautions (5.10)]*.
- The safety of concomitant administration of ZYNRELEF and other NSAID medications has not been evaluated. If additional NSAID medication is indicated in the post-operative period, monitor patients for signs and symptoms of NSAID toxicity [*see Clinical Pharmacology (12.3)*].
- ZYNRELEF is a viscous solution supplied as a kit consisting of a single-dose glass vial, and the following sterile components: Luer Lock syringe(s), a vented vial spike, Luer Lock cone-shaped applicator(s), and syringe tip cap(s). ZYNRELEF should only be prepared and administered with the components provided in the ZYNRELEF kit. See the ZYNRELEF Instructions for Use included in the kit for complete administration instructions with illustrations.
- The contents of the ZYNRELEF vial are sterile. The vial exterior is not sterile. Follow your facility's standard operating procedures regarding aseptic drug preparation.
- Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator, and syringe(s) during drug withdrawal and administration.
- ZYNRELEF is applied without a needle into the surgical site following final irrigation and suctioning, and prior to suturing of each layer, when multiple tissue layers are involved.

- When ZYNRELEF comes in contact with moisture in the tissues, it becomes more viscous, allowing it to stay in place.
- ZYNRELEF does not degrade sutures. When using monofilament sutures, 3 or more knots are recommended, as contact with ZYNRELEF may cause a single knot to loosen or untie.
- ZYNRELEF should not be administered via the following routes.
  - Epidural
  - Intrathecal
  - Intravascular or intra-articular
  - Regional nerve blocks
  - Pre-incisional or pre-procedural locoregional anesthetic techniques.

2.2 Preparation Instructions

1. ZYNRELEF is a clear, pale yellow to yellow, viscous liquid. Visually inspect the ZYNRELEF vial for particulate matter and discoloration. Obtain a new vial if particulate matter or discoloration is observed.
2. Prepare vial for filling of syringe(s) by attaching vented vial spike. Prepare syringe by filling with air then attach to vented vial spike.

3. Invert to allow product to fill the vial neck and push air into vial. Withdraw dose of ZYNRELEF into syringe. (The dose volume takes into account the potential residual volume in the components.)

Nominal Dose of Bupivacaine / Meloxicam (mg/mg)	Number of Syringes and LLAs* Per Dose	Volume to be Withdrawn (mL)
60 / 1.8	1	2.3 (using 3 mL syringe provided)
200 / 6	1	7 (using 12 mL syringe provided)
300 / 9	1	10.5 (using 12 mL syringe provided)
400 / 12	2	14 (using two 12 mL syringes provided, 7 mL ZYNRELEF per syringe)

*LLA: Luer lock cone-shaped applicator

4. Repeat steps 1-3 for more than one syringe.
5. Prepare product immediately prior to use and apply syringe tip cap until product delivery.

2.3 Administration Instructions

Before administration, remove the syringe tip cap and attach the Luer lock cone-shaped applicator to the syringe.

1. Using the Luer lock cone-shaped applicator attached to the syringe, apply ZYNRELEF to the tissues within the surgical site as follows:
   a. For foot and ankle surgical procedures, apply ZYNRELEF to the proximal and distal ends (i.e., beyond the boney repair) of the wound.
   b. For small-to-medium open abdominal surgical procedures, close the peritoneum (if applicable), then apply ZYNRELEF above and below the fascial repair.
   c. For lower extremity total joint arthroplasty surgical procedures, apply ZYNRELEF directly to the joint capsule, the anteromedial tissues and periosteum, and the anterolateral tissues and periosteum after placement of the components.
2. Only apply ZYNRELEF to the tissue layers below the skin incision and not directly onto the subdermal layer or the skin.
3. Use only the amount necessary to coat the tissues, such that ZYNRELEF does not leak from the surgical wound after closure.

2.4 Dosing Instructions

As a general guidance in selecting the proper dosing of ZYNRELEF, the following examples of dosing are provided:

- For foot and ankle surgical procedures, such as bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam *[see Clinical Studies (14.1)]*.
- For small-to-medium open abdominal surgical procedures, such as open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam *[see Clinical Studies (14.2)]*.
- For lower extremity total joint arthroplasty surgical procedures, such as total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam *[see Clinical Studies (14.3)]*.

2.5 Compatibility Considerations

- Do not dilute ZYNRELEF.

- ZYNRELEF is a nonaqueous solution. It cannot be mixed with water, saline, or other local anesthetics as the product will become more viscous and difficult to administer.
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before a local anesthetic, including ZYNRELEF, is administered into the site.
- When administered in recommended doses and concentrations, ZYNRELEF does not ordinarily produce irritation or tissue damage.

ZYNRELEF is compatible with:

- All components of the ZYNRELEF kit, including syringes, Luer lock cone-shaped applicator, vented vial spike, and syringe tip caps.
- Surgical mesh materials, including polypropylene (Prolene®), Gore-tex, and polyester.
- Silicone membranes.
- Bone cement.
- Metal alloys used in surgical implants.

3 DOSAGE FORMS AND STRENGTHS

ZYNRELEF (bupivacaine and meloxicam) extended-release solution is a sterile, clear, pale-yellow to yellow, viscous liquid in a single-dose vial containing 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam and is available in the following four presentations:

- 14 mL containing 400 mg bupivacaine and 12 mg meloxicam
- 10.5 mL containing 300 mg bupivacaine and 9 mg meloxicam
- 7 mL containing 200 mg bupivacaine and 6 mg meloxicam
- 2.3 mL containing 60 mg bupivacaine and 1.8 mg meloxicam

4 CONTRAINDICATIONS

ZYNRELEF is contraindicated in:

- Patients with a known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to any local anesthetic agent of the amide-type, NSAIDs, or to any of the other components of ZYNRELEF [*see Warnings and Precautions (5.9, 5.13)*].
- Patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.9)*].
- Patients undergoing obstetrical paracervical block anesthesia. The use of bupivacaine in this technique has resulted in fetal bradycardia and death. [*see Use in Specific Populations (8.1)*].
- Patients undergoing coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular (CV) Thrombotic Events with NSAID Use

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses. The risk of these events following single-dose local application of ZYNRELEF is uncertain.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, do not exceed the recommended dose. Physicians and patients should remain alert for the development of such events following treatment with ZYNRELEF, even in the absence of previous CV symptoms. Inform patients about the signs and symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as meloxicam, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. ZYNRELEF is contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of ZYNRELEF in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ZYNRELEF is used in patients with a recent MI, monitor patients for signs of cardiac ischemia. The risk of these events following single-dose local application of ZYNRELEF is uncertain.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation with NSAID Use

NSAIDs, including meloxicam in ZYNRELEF, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or

without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most post marketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated Patients

- Use the recommended dose for each indicated surgical procedure.
- Avoid administration of analgesic doses of more than one NSAID at a time. If additional NSAID medication is indicated in the post-operative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding following treatment with ZYNRELEF.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Dose-Related Toxicity

The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. The toxic effects of local anesthetics are additive. Avoid additional local anesthetic administration within 96 hours following ZYNRELEF instillation. If additional local anesthetic administration with ZYNRELEF cannot be avoided based on clinical need, monitor patients for neurologic and cardiovascular effects related to local anesthetic systemic toxicity. Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after administration of ZYNRELEF.

Possible early warning signs of central nervous system (CNS) toxicity are restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, CNS depression, or drowsiness. Delay in proper management of dose-related toxicity, underventilation from any cause, and/or altered sensitivity may lead to the development of acidosis, cardiac arrest, and, possibly, death.

5.4 Risk of Use in Patients with Impaired Cardiovascular Function

Patients with impaired cardiovascular function (e.g., hypotension, heart block) may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by ZYNRELEF. Monitor patients closely for blood pressure, heart rate, and ECG changes.

5.5 Hepatotoxicity

Local Anesthetics, Including Bupivacaine

Because amide-type local anesthetics such as bupivacaine are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

NSAIDs

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including meloxicam. The risk of these events following single-dose local application of ZYNRELEF is uncertain.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), perform a clinical evaluation of the patient [*see Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

5.6 Hypertension

NSAIDs, including meloxicam in ZYNRELEF, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) after administration of ZYNRELEF.

5.7 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of meloxicam may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug*

Interactions (7)]. The risk of these events following single-dose local application of ZYNRELEF is uncertain.

Avoid the use of ZYNRELEF in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ZYNRELEF is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.8 Renal Toxicity and Hyperkalemia

Renal Toxicity

ZYNRELEF is a single-use product that contains an NSAID. Long-term administration of NSAIDs has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The renal effects of meloxicam may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some meloxicam metabolites are excreted by the kidney, monitor patients for signs of worsening renal function.

Correct volume status in dehydrated or hypovolemic patients prior to initiating ZYNRELEF. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of ZYNRELEF [*see Drug Interactions (7)*]. Avoid the use of ZYNRELEF in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If ZYNRELEF is used in patients with advanced renal disease, monitor patients for signs of worsening renal function [*see Clinical Pharmacology (12.3)*].

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.9 Anaphylactic Reactions

NSAIDs

Meloxicam, contained in ZYNRELEF, has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma [*see Contraindications (4)*].

Seek emergency help if an anaphylactic reaction occurs.

5.10 Chondrolysis

Limit exposure to articular cartilage due to the potential risk of chondrolysis.

Intra-articular infusions of local anesthetics, following arthroscopic and other surgical procedures is an unapproved use, and there have been post marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of glenohumeral chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are associated with chondrolysis. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

5.11 Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue any oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

5.12 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma, which may include: chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, NSAIDs are contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When ZYNRELEF is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for exacerbation of asthma symptoms.

5.13 Serious Skin Reactions

NSAIDs, including meloxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions.

ZYNRELEF is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.14 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ZYNRELEF. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, evaluate the patient immediately and treat as clinically indicated.

5.15 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including ZYNRELEF, in pregnant women at about 30 weeks gestation and later. NSAIDs, including ZYNRELEF, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including ZYNRELEF, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ZYNRELEF use to the lowest effective dose. Because meloxicam can be detected in plasma beyond 48 hours after administration of ZYNRELEF, consider ultrasound monitoring for oligohydramnios. If oligohydramnios occurs, follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

5.16 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with ZYNRELEF has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including meloxicam, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.17 Masking of Inflammation and Fever

The pharmacological activity of ZYNRELEF in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular System Reactions [*see Warnings and Precautions (5.1, 5.4)*]
- Gastrointestinal Bleeding, Ulceration, and Perforation [*see Warnings and Precautions (5.2)*]
- Dose-Related Toxicity [*see Warnings and Precautions (5.3)*]
- Hepatotoxicity [*see Warnings and Precautions (5.5)*]
- Hypertension [*see Warnings and Precautions (5.6)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.7)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.8)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.9)*]
- Chondrolysis [*see Warnings and Precautions (5.10)*]
- Methemoglobinemia [*see Warnings and Precautions (5.11)*]
- Exacerbation of Asthma Related to Aspirin Sensitivity [*see Warnings and Precautions (5.12)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.13)*]
- Drug Reaction with Eosinophilia and Systemic Toxicity (DRESS) [*see Warnings and Precautions (5.14)*]
- Fetal Toxicity [*see Warnings and Precautions (5.15)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.16)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of ZYNRELEF has been evaluated in a total of 1067 patients undergoing various surgical procedures across 7 randomized, double-blind, bupivacaine- and placebo-controlled and saline placebo-controlled studies designed to investigate ZYNRELEF to reduce postoperative pain for 72 hours and the need for opioid analgesics. Patients treated with ZYNRELEF ranged in age from 18 to 85 years (median age 47 years), with 61.8% female, 78.9% White, 16.0% African American, and 5.1% all other races.

Among 504 patients who received ZYNRELEF in single doses of 60 mg/1.8 mg to 400 mg/12 mg via instillation into the surgical site, the most common adverse reactions (incidence greater than or equal to 10% and higher than saline placebo) following ZYNRELEF administration were constipation, vomiting, and headache.

Common Adverse Reactions

Three randomized, bupivacaine-controlled and saline placebo-controlled studies were conducted in patients undergoing bunionectomy (STUDY 1, Table 1), open inguinal herniorrhaphy (STUDY 2, Table 3), and total knee arthroplasty (STUDY 3, Table 4). The bunionectomy procedures in STUDY 1 were performed under regional anesthesia, a lidocaine Mayo block, and intravenous sedation. The herniorrhaphy procedures in STUDY 2 were performed under general anesthesia. The total knee

arthroplasty procedures in STUDY 3 were performed under either general or spinal anesthesia. Patients in STUDY 1 and STUDY 2 were allowed opioid rescue with intravenous (IV) morphine and oral oxycodone, and/or non-opioid rescue with oral acetaminophen. Patients in STUDY 3 were pretreated with oral pregabalin and acetaminophen, and allowed opioid rescue with IV morphine and oral oxycodone postoperatively.

Table 1. Adverse Reactions with ZYNRELEF in Study 1 (Bunionectomy) Occurring with ≥5% Incidence and Higher than with Saline Placebo

Preferred Term	Saline Placebo (N=101), %	Bupivacaine HCl 50 mg (N=154), %	ZYNRELEF 60 mg/1.8 mg (N=157), %
Dizziness	18	23	22
Incision site edema	13	14	17
Headache	10	13	14
Incision site erythema	8	12	13
Bradycardia	6	8	8
Impaired healing	1	4	6
Muscle twitching	5	5	6

In STUDY 1, bone healing was assessed by X-ray on Days 28 and 42. There was no clinically meaningful difference in bone healing between treatment groups. A total of four subjects had delayed bone healing: 1 in the ZYNRELEF group, 1 in the saline placebo group, and 2 in the bupivacaine HCl group.

The incidence of local inflammatory adverse events was higher in the ZYNRELEF group than in either control group (Table 2).

Table 2. Incidence of Local Inflammatory Adverse Events with ZYNRELEF in Study 1 (Bunionectomy) Occurring with ≥2% Incidence and Higher than with Saline Placebo

	Saline Placebo (N=101), %	Bupivacaine HCl 50 mg (N=154), %	ZYNRELEF 60 mg/1.8 mg (N=157), %
Incision site edema	13	14	17
Incision site erythema	8	12	13
Impaired healing	1	4	6
Incision site cellulitis	1	1	4
Wound dehiscence	2	1	4
Incision site infection	0	1	3

Table 3. Adverse Reactions with ZYNRELEF in Study 2 (Herniorrhaphy) Occurring with ≥5% Incidence and Higher than with Saline Placebo

Preferred Term	Saline Placebo (N=82), %	Bupivacaine HCl 75 mg (N=173), %	ZYNRELEF 300 mg/9 mg (N=163), %
Headache	12	14	13
Bradycardia	7	9	9
Dysgeusia	4	12	9
Skin odor abnormal[a]	1	1	8

[a] All TEAEs of skin odor abnormal were recorded at a single site.

Table 4. Adverse Reactions with ZYNRELEF in Study 3 (Total Knee Arthroplasty) Occurring with ≥5% Incidence and Higher than with Saline Placebo

Preferred Term	Saline Placebo (N=53), %	Bupivacaine HCl 125 mg (N=55), %	ZYNRELEF 400 mg/12 mg (N=58), %
Nausea	47	55	50
Constipation	23	33	24
Vomiting	19	27	26
Hypertension	15	13	19
Pyrexia	4	15	14
Leukocytosis	0	2	7
Pruritis	2	5	7
Headache	0	7	7
Anemia	2	0	5
Hyperhidrosis	4	0	5
Hypotension	4	2	5

7 DRUG INTERACTIONS

7.1 Bupivacaine Drug Interactions

In clinical studies, other local anesthetics (including ropivacaine and lidocaine) have been administered before, during, or after application of ZYNRELEF without evidence of local anesthetic systemic toxicity. Administration of ZYNRELEF with other formulations of local anesthetics, including bupivacaine liposome injectable suspension, has not been studied [*see Warnings and Precautions (5.3)*].

The toxic effects of local anesthetics are additive. Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF. If co-administration cannot be avoided, monitor patients for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [*see Dosage and Administration (2.1), Warnings and Precautions (5.1)* and *Overdosage (10)*].

Patients who are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics (Table 5).

Table 5. Examples of Drugs Associated with Methemoglobinemia

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

7.2 Meloxicam Drug Interactions

See Table 6 for clinically significant drug interactions with meloxicam.

Table 6. Clinically Significant Drug Interactions with Meloxicam

Drugs that Interfere with Hemostasis	
Clinical Impact:	Meloxicam and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of meloxicam and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of ZYNRELEF with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.16)*].
Aspirin	
Clinical Impact:	In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	If aspirin is indicated in the postoperative period, monitor patients for signs and symptoms of GI bleeding [*see Clinical Pharmacology (12.3)*].
ACE Inhibitors, Angiotensin Receptor Blockers, or Beta-Blockers	
Clinical Impact:	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).

	In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, coadministration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	During concomitant use of ZYNRELEF and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of ZYNRELEF and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs have reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. However, studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam.
Intervention:	During concomitant use of ZYNRELEF with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Digoxin	
Clinical Impact:	The concomitant use of NSAIDS with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of ZYNRELEF and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis [*see Clinical Pharmacology (12.3)*].
Intervention:	Monitor patients on lithium for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of ZYNRELEF and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of NSAIDs and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of ZYNRELEF and cyclosporine, monitor patients for signs of worsening renal function.

NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity [*see Warnings and Precautions (5.2)*].
Intervention:	If additional NSAID or salicylate medication is indicated in the post-operative period, monitor patients for signs and symptoms of GI toxicity [*see Clinical Pharmacology (12.3)*].
Pemetrexed	
Clinical Impact:	Concomitant use of NSAIDs and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of ZYNRELEF and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. Patients taking meloxicam should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration. In patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with pemetrexed is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on use of ZYNRELEF in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. However, there are available data on the individual components of ZYNRELEF, bupivacaine and meloxicam.

Bupivacaine

The available data on bupivacaine use in pregnant women for epidural anesthesia (excluding paracervical block) are insufficient to draw conclusions about a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are no adequate and well-controlled studies with bupivacaine in pregnant women. In animal studies, embryo-fetal lethality was noted when bupivacaine was administered subcutaneously to pregnant rabbits during organogenesis at a comparable bupivacaine dose level of 400 mg at the maximum recommended human dose (MRHD) of ZYNRELEF. Decreased pup survival was observed in a rat pre- and post-natal developmental study (dosing from implantation through weaning) at a comparable bupivacaine dose to the MRHD (*see Data*). Based on animal data, pregnant women should be advised of the potential risks to a fetus.

Meloxicam

Use of NSAIDs, including ZYNRELEF, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of ZYNRELEF use between about 20 and 30 weeks of gestation, and avoid ZYNRELEF use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including ZYNRELEF, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.8 and 8 times, respectively, the meloxicam dose level of 12 mg at the MRHD of ZYNRELEF. Increased incidence of septal heart defects was observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 97 times the MRHD. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.1 times the MRHD. No malformations were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 3.2 and 32 times, respectively, the MRHD *(see Data)*.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as meloxicam, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Meloxicam

Premature Closure of the Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including ZYNRELEF, can cause premature closure of the fetal ductus arteriosus *(see Data)*.

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. Because meloxicam can be detected in plasma beyond 48 hours after administration of ZYNRELEF, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, follow up according to clinical practice (*see Data*).

Labor or Delivery

Bupivacaine

Bupivacaine is contraindicated in obstetrical paracervical block anesthesia. The use of bupivacaine for obstetrical paracervical block anesthesia has resulted in fetal bradycardia and death [*see Contraindications (4)*].

Bupivacaine can rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity [*see Clinical Pharmacology (12.3)*]. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Meloxicam

There are no studies on the effects of meloxicam during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Meloxicam

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Reproduction studies have not been conducted with ZYNRELEF.

Bupivacaine

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, and 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are comparable to the daily MRHD of 400 mg on a mg/m^2 (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level representing approximately 0.3 times the MRHD on a BSA basis.

In a rat pre- and post-natal developmental study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, and 40 mg/kg, decreased pup survival was observed at the high dose. The high dose is comparable to the daily MRHD of 400 mg on a BSA basis.

Meloxicam

Meloxicam did not cause malformations when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (3.2 times the meloxicam dose level of 12 mg at the MRHD of ZYNRELEF based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (97 times the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (32 times the MRHD based on BSA comparison). In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.8 and 8 times the MRHD, respectively, based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.1 times the MRHD based on BSA comparison).

8.2 Lactation

Risk Summary

Limited published literature reports that bupivacaine and its primary metabolite, pipecoloxylidine (PPX), are present in human milk at low levels. There are no human data available on whether meloxicam is present in human milk. There is no available information on effects of bupivacaine or meloxicam in the breastfed infant or effects of the drugs on milk production.

Clinical Considerations

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYNRELEF and any potential adverse effects on the breastfed infant from ZYNRELEF or from the underlying maternal condition.

Data

Animal Data

Following administration of ZYNRELEF to lactating pigs, bupivacaine and meloxicam were detected in milk, but only bupivacaine was detected in the plasma of piglets allowed to suckle milk from the treated animals. Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including meloxicam, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs and avoidance of ZYNRELEF in women who have difficulties conceiving or who are undergoing investigation of infertility.

Males

In a published study, oral administration of meloxicam to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular degeneration at 0.8 times the MRHD based on BSA comparison [*see Nonclinical Toxicology (13.1)*]. It is not known if these effects on fertility are reversible. The clinical relevance of these findings is unknown.

8.4 Pediatric Use

Safety and effectiveness of ZYNRELEF in pediatric patients has not been established.

8.5 Geriatric Use

Of the total number of patients undergoing various surgical procedures who were exposed to ZYNRELEF in clinical studies (N=1067), 136 patients (12.7%) were ≥ 65 years old, while 30 (2.8%) were ≥75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions, although the applicability of this to a single administration of low-dose meloxicam in ZYNRELEF is uncertain [*see Warnings and Precautions (5.1, 5.2, 5.8)*].

In clinical studies, differences in various pharmacokinetic parameters have been observed with bupivacaine HCl between elderly and younger patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in ZYNRELEF dose selection, and it may be useful to monitor renal function [*see Clinical Pharmacology (12.3)*]. Consider reducing the dose of ZYNRELEF for elderly patients.

8.6 Hepatic Impairment

Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity.

Because meloxicam is primarily metabolized in the liver and hepatotoxicity may occur, monitor patients with hepatic impairment for signs and symptoms of worsening disease. Meloxicam has not been adequately studied in patients with severe hepatic impairment.

No dose adjustment of ZYNRELEF is necessary in patients with mild to moderate hepatic impairment. ZYNRELEF should only be used in patients with severe hepatic impairment if the benefits are expected to outweigh the risks; monitor patients for signs of worsening liver function. Consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease [*see Warnings and Precautions (5.5),* and *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

Because bupivacaine and meloxicam and their metabolites are excreted by the kidney, the risk of toxic reactions to these drugs may be greater in patients with impaired renal function. This should be considered when performing dose selection of ZYNRELEF. Consider reducing the dose of ZYNRELEF for patients with mild to moderate renal impairment.

Patients with severe renal disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Patients with severe renal impairment have not been studied. The use of ZYNRELEF in patients with severe renal impairment is not recommended. Meloxicam is not dialyzable. When using ZYNRELEF in patients on hemodialysis do not exceed maximum recommended dose or use with other meloxicam-containing products [*see Clinical Pharmacology (12.3)*].

8.8 Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin or phenytoin), consider dose reduction, as these patients may have abnormally high plasma levels of meloxicam due to reduced metabolic clearance. Monitor these patients for adverse effects.

10 OVERDOSAGE

No data are available with regard to overdose of ZYNRELEF. Findings related to the individual active substances are listed below.

10.1 Bupivacaine

Clinical Presentation

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution [*see Warnings and Precautions (5.3)* and *Adverse Reactions (6)*].

Signs and symptoms of overdose include CNS symptoms (dizziness, sensory and visual disturbances, and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia, and asystole).

Plasma levels of bupivacaine associated with toxicity can vary. Although concentrations of 2,000 to 4,000 ng/mL have been reported to elicit early subjective CNS symptoms of bupivacaine toxicity, symptoms of toxicity have been reported at levels as low as 800 ng/mL.

Management of Local Anesthetic Overdose

At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask.

Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine to enhance myocardial contractile force).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs, and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

10.2 Meloxicam

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.2, 5.6, 5.8)*]. There is limited experience with meloxicam overdosage. Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

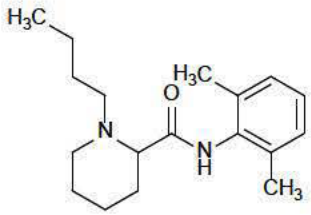
For additional information about overdosage treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION

ZYNRELEF (bupivacaine and meloxicam) extended-release solution, for soft tissue or periarticular instillation use, contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID).

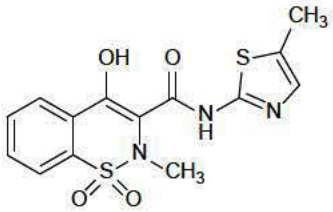
Bupivacaine

Bupivacaine is a white to off-white crystalline powder, crystals, or granules. The chemical name for bupivacaine is (±)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide, and its empirical formula is $C_{18}H_{28}N_2O$. The molecular weight of bupivacaine is 288.4. Bupivacaine is sparingly soluble in water and freely soluble in alcohol. Bupivacaine has a log P_{ow} of 1.82 and a pKa of 8.1. Bupivacaine has the following structural formula:



Meloxicam

Meloxicam is a pale yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient $(\log P)_{app} = 0.1$ in *n*-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2. Meloxicam is chemically designated as 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is $C_{14}H_{13}N_3O_4S_2$ and it has the following structural formula:



ZYNRELEF is a sterile, clear, pale yellow to yellow, viscous liquid provided in single-dose vials (10 mL or 20 mL) for instillation into the surgical site. Each mL of the solution contains active ingredients bupivacaine 29.25 mg and meloxicam 0.88 mg; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg), triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZYNRELEF is a fixed-dose combination of bupivacaine and meloxicam.

Bupivacaine

Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Meloxicam

The mechanism of action of meloxicam, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Meloxicam is a potent inhibitor of prostaglandin synthesis in vitro. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

Contribution of Meloxicam and Bupivacaine to Activity of ZYNRELEF

The contribution of each active ingredient in ZYNRELEF was demonstrated in Phase 2 double-blind, randomized, active- and placebo-controlled clinical studies in subjects undergoing herniorrhaphy or bunionectomy, utilizing ZYNRELEF and formulations of meloxicam alone or bupivacaine alone in the

ZYNRELEF vehicle. In both studies, meloxicam alone demonstrated negligible local analgesia and bupivacaine alone demonstrated greater analgesia compared with placebo through 24 hours post surgery, despite exposure to bupivacaine for approximately 72 hours. Compared with bupivacaine alone in both studies, ZYNRELEF (at the same bupivacaine doses) demonstrated greater and longer analgesia through 24, 48, and 72 hours.

Effect on Cardiac Repolarization

The effect of ZYNRELEF on cardiac repolarization as assessed by the QTc interval was evaluated following a single administration in patients undergoing surgical procedures. ZYNRELEF, at single doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval.

Bupivacaine

Systemic absorption of local anesthetics, including bupivacaine, produces effects on the cardiovascular and central nervous systems (CNS), which can be serious at toxic blood concentrations [*see Warnings and Precautions (5.3)]*. At blood concentrations achieved with normal therapeutic doses, manifestations of CNS stimulation and depression or changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. Clinical reports and animal research suggest that cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine.

12.3 Pharmacokinetics

The instillation of ZYNRELEF into the surgical site results in systemic plasma levels of bupivacaine and meloxicam for up to the duration as described in Table 7. Systemic plasma levels of bupivacaine or meloxicam following application of ZYNRELEF do not correlate with local efficacy.

Absorption

The rate of systemic absorption of bupivacaine or meloxicam from ZYNRELEF is dependent upon the total dose of drug administered and the vascularity of the administration site.

Pharmacokinetic parameters of bupivacaine and meloxicam after single dose administration by instillation of ZYNRELEF were evaluated following multiple surgical procedures.

Descriptive statistics of pharmacokinetic parameters of representative ZYNRELEF doses are provided in Table 7.

Table 7. Summary of Pharmacokinetic Parameters for Bupivacaine and Meloxicam After Single Dose Administration of ZYNRELEF by Instillation

Active Ingredient	Parameter	Bunionectomy: 60 mg/1.8 mg ZYNRELEF	Herniorrhaphy: 300 mg/9 mg ZYNRELEF	Total Knee Arthroplasty: 400 mg/12 mg ZYNRELEF
		(N=17)	(N=16)	(N=53)
Bupivacaine	C_{max} (ng/mL)	54 (33)	271 (147)	695 (411)
	T_{max} (h)	3.0 (1.6, 24)	18 (3, 30)	21 (4, 59)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	1681 (1154)	15174 (8545)	35890 (28400)
	$AUC_{(inf)}$ (h×ng/mL)	1718 (1211)	15524 (8921)	38173 (29400) [b]
	$t_{½}$ (h)	15 (8)	16 (9)	17 (7) [b]
	C_{72h} (ng/mL)	5.0 (5.3)	96 (75)	227 (283)
	C_{96h} (ng/mL)	1.7 (2.9) [e]	37 (43)	NS
	C_{144h} (ng/mL)	NS	NS	5.3 (21) [c]
Meloxicam	C_{max} (ng/mL)	26 (14) [e]	225 (96)	275 (134)
	T_{max} (h)	18 (8, 60) [e]	54 (24, 96)	36 (12, 72)
	$AUC_{(0-t)}$ (h×ng/mL)	1621 (927) [e]	18721 (7923)	19525 (12259)
	$AUC_{(inf)}$ (h×ng/mL)	2079 (1631) [e]	NR	25673 (17666) [d]
	$t_{½}$ (h)	33 (36) [e]	NR	42 (37) [d]
	C_{72h} (ng/mL)	13 (9) [e]	197 (95)	202 (120)
	C_{96h} (ng/mL)	7.7 (5.8) [f]	146 (86)	NS
	C_{144h} (ng/mL)	NS	NS	28 (37) [g]

Note: Arithmetic mean (standard deviation) except T_{max} where it is median (min, max). Doses of ZYNRELEF are shown as bupivacaine dose (mg)/meloxicam dose (mg).

[a] $AUC_{(0-t)}$: 0 to 120 h post-dose for bunionectomy and herniorrhaphy; 0 to 144 h post-dose for total knee arthroplasty.

[b] N=50; [c] N=32; [d] N=35; [e] N=16; [f] N=15; [g] N=28

NS = not sampled; NR= not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

Distribution

After bupivacaine and meloxicam have been released from ZYNRELEF and are absorbed systemically, their distribution is expected to be the same as for other bupivacaine HCl solution formulations or meloxicam oral formulation.

Bupivacaine

Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma proteins.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionized drugs, such as bupivacaine, readily enter the fetal blood from the maternal circulation.

Meloxicam

Meloxicam is ~99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range of oral meloxicam. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to ~99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam. Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of this penetration is unknown.

Elimination

Metabolism

Bupivacaine

Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxylidine is the major metabolite of bupivacaine. The elimination of drug from tissue distribution depends largely upon the ability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized. [*see Use in Specific Populations (8.6)*].

Meloxicam

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P450 mediated metabolism formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). In vitro studies indicate that CYP2C9 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively. The four metabolites are not known to have any in vivo pharmacological activity.

Excretion

After bupivacaine and meloxicam have been released from ZYNRELEF and are absorbed systemically, their excretion is expected to be the same as for other bupivacaine HCl solution formulations or meloxicam oral formulations.

Bupivacaine

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage. The mean apparent terminal half-life ($t_{1/2}$) for bupivacaine from ZYNRELEF is approximately 14 to15 hours.

Meloxicam

Meloxicam excretion is predominately in the form of metabolites, and occurs to equal extents in the urine and feces. Following oral meloxicam, only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg oral meloxicam doses: 0.5%, 6%, and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.

The mean apparent terminal half-life ($t_{1/2}$) for meloxicam from ZYNRELEF is approximately 22 to 25 hours.

Specific Populations

Effect of Age, Sex, Race, and Ethnicity on Pharmacokinetics

Based on the population pharmacokinetic analysis, age, sex, race, and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of bupivacaine and meloxicam in ZYNRELEF [*see Use in Special Populations (8.5)*].

Hepatic Impairment

After bupivacaine and meloxicam have been released from ZYNRELEF and are absorbed systemically, the effects of hepatic impairment are expected to be the same as for other bupivacaine and meloxicam formulations [*see Warnings and Precautions (5.5)*].

Bupivacaine

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic disease. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics [*see Use in Specific Populations (8.6)*].

Meloxicam

Following a single 15 mg dose of oral meloxicam there was no marked difference in plasma concentrations in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of oral meloxicam was not affected by hepatic impairment. No dosage adjustment of ZYNRELEF is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied [*see Use in Specific Populations* (*8.6*)].

Renal Impairment

After bupivacaine and meloxicam have been released from ZYNRELEF and are absorbed systemically, the effects of renal impairment are expected to be the same as for other bupivacaine and meloxicam formulations.

Bupivacaine

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow [*see Warnings and Precautions (5.8)* and *Use in Specific Populations (8.7)*].

Meloxicam

Meloxicam pharmacokinetics with oral meloxicam have been investigated in patients with mild and moderate renal impairment. Following oral meloxicam, total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all groups. The higher meloxicam clearance in patients with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment of ZYNRELEF is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of ZYNRELEF in patients with severe renal impairment is not recommended [*see Warnings and Precautions (5.8)* and *Use in Specific Populations (8.7)*].

Hemodialysis: Following a single oral dose of meloxicam, the free C_{max} plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the total drug concentration in plasma. Meloxicam is not dialyzable [*see Use in Specific Populations (8.7)*].

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 6 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

Cholestyramine: Pretreatment for four days with cholestyramine significantly increased the clearance of oral meloxicam by 50%. This resulted in a decrease in $t_{1/2}$, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for oral meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

Cimetidine: Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 30 mg oral meloxicam.

Digoxin: Oral meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after β-acetyldigoxin administration for 7 days at clinical doses. In vitro testing found no protein binding drug interaction between digoxin and meloxicam.

Lithium: In a study conducted in healthy patients, mean pre-dose lithium concentration and AUC were increased by 21% in patients receiving lithium doses ranging from 804 to 1072 mg twice daily with oral meloxicam 15 mg QD every day as compared to patients receiving lithium alone [*see Drug Interactions (7)*].

Methotrexate: A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. In vitro, methotrexate did not displace meloxicam from its human serum binding sites.

Warfarin: The effect of oral meloxicam on the anticoagulant effect of warfarin was studied in a group of healthy patients receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these patients, oral meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one patient showed an increase in INR from 1.5 to 2.1. Caution should be used when administering oral meloxicam with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced.

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic variants such as CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from three published reports showed that meloxicam AUC was substantially higher in individuals with reduced CYP2C9 activity, particularly in poor metabolizers (e.g., *3/*3), compared to normal metabolizers (*1/*1). The frequency of CYP2C9 poor metabolizer genotypes varies based on racial/ethnic background but is generally present in <5% of the population.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

The maximum recommended human dose (MRHD) of ZYNRELEF is 400 mg and 12 mg of bupivacaine and meloxicam, respectively.

Carcinogenesis

Bupivacaine

Long-term studies in animals to evaluate the carcinogenic potential of ZYNRELEF or bupivacaine have not been conducted.

Meloxicam

There was no increase in tumor incidence in long-term carcinogenicity studies in rats (104 weeks) or mice (99 weeks) administered meloxicam at oral doses up to 0.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 0.6 and 3.2 times, respectively, the meloxicam dose level of 12 mg at the MRHD of ZYNRELEF based on BSA comparison).

Mutagenesis

Bupivacaine

The mutagenic potential of bupivacaine has not been determined.

Meloxicam

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Impairment of Fertility

Bupivacaine

The effect of ZYNRELEF and bupivacaine on fertility has not been determined.

Meloxicam

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 7.3 and 4 times, respectively, the MRHD based on BSA comparison).

In a published study, oral administration of 1 mg/kg (0.8 times the MRHD) meloxicam to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular degeneration. The clinical relevance of these findings is unknown.

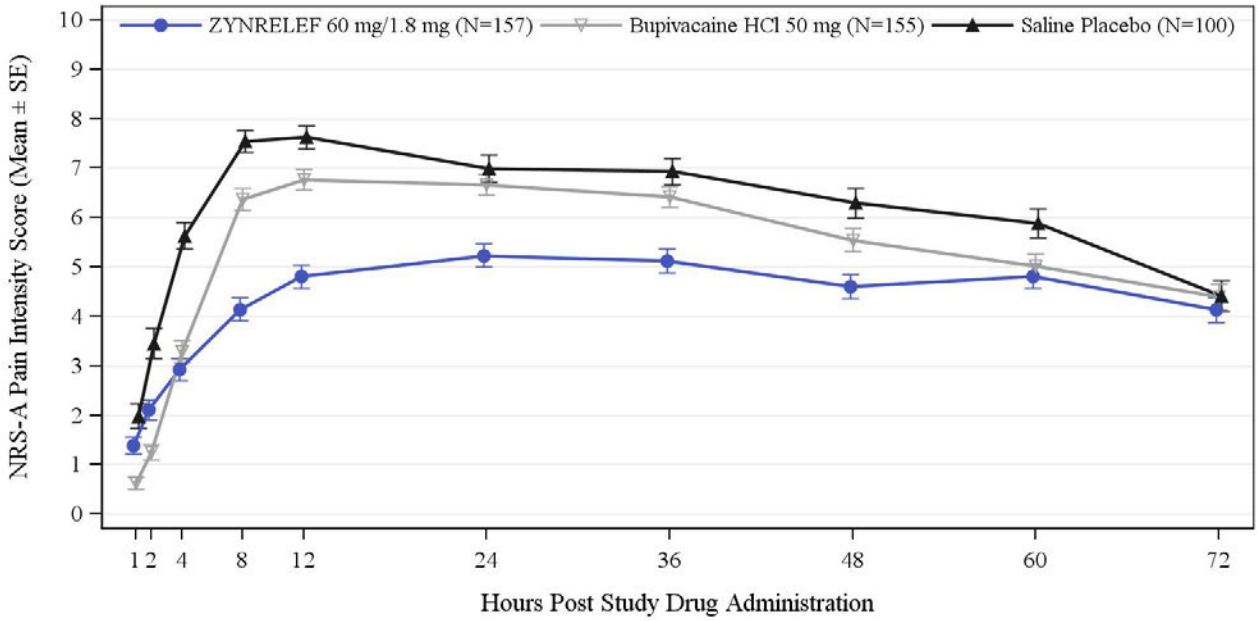
14 CLINICAL STUDIES

14.1 Study 1

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical trial (NCT03295721), 412 patients undergoing unilateral simple bunionectomy with a lidocaine Mayo block were randomized to 1 of the following 3 treatment groups in a 3:3:2 ratio (respectively): ZYNRELEF 60 mg/1.8 mg, bupivacaine HCl 50 mg, or saline placebo. The mean patient age was 47 years (range 18 to 77) and patients were predominantly female (86%). ZYNRELEF was applied directly into the surgical site, using the cone-shaped applicator, at the end of the procedure, after final irrigation and suction but prior to closure. Bupivacaine HCl and saline placebo were administered by injection and instillation, respectively. Pain intensity was rated by patients using an 11-point numeric rating scale (NRS) out to 72 hours post-dose. Postoperatively, there was no scheduled pain medication regimen; however, patients were allowed rescue medication as needed, and included oxycodone 10 mg orally every 4 hours, morphine 10 mg IV every 2 hours, and/or acetaminophen 1000 mg orally every 6 hours. The primary endpoint was the mean area under the curve (AUC) of the NRS pain intensity scores (cumulative pain scores) with activity over the 72-hour period for the ZYNRELEF treatment group compared to the saline placebo treatment group. Secondary endpoints included mean AUC of NRS pain intensity scores over the 72-hour period for the ZYNRELEF treatment group compared to the bupivacaine HCl treatment group, proportion of patients who did not receive opioid analgesia, and total opioid consumption.

Patients treated with ZYNRELEF demonstrated a significant reduction in pain intensity compared to those treated with either bupivacaine HCl or saline placebo for up to 72 hours (Figure 1). A significant proportion of patients treated with ZYNRELEF did not receive opioid analgesia (29%) over 72 hours compared to those treated with either bupivacaine HCl (11%) or saline placebo (2%).

Figure 1. Mean Pain Intensity with Activity Over 72 Hours for STUDY 1 (Bunionectomy)



Based on similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, between bunionectomy and other foot and ankle surgical procedures, the pharmacokinetic profile and effectiveness of ZYNRELEF are not expected to be clinically significantly different when ZYNRELEF is administered at the same dose.

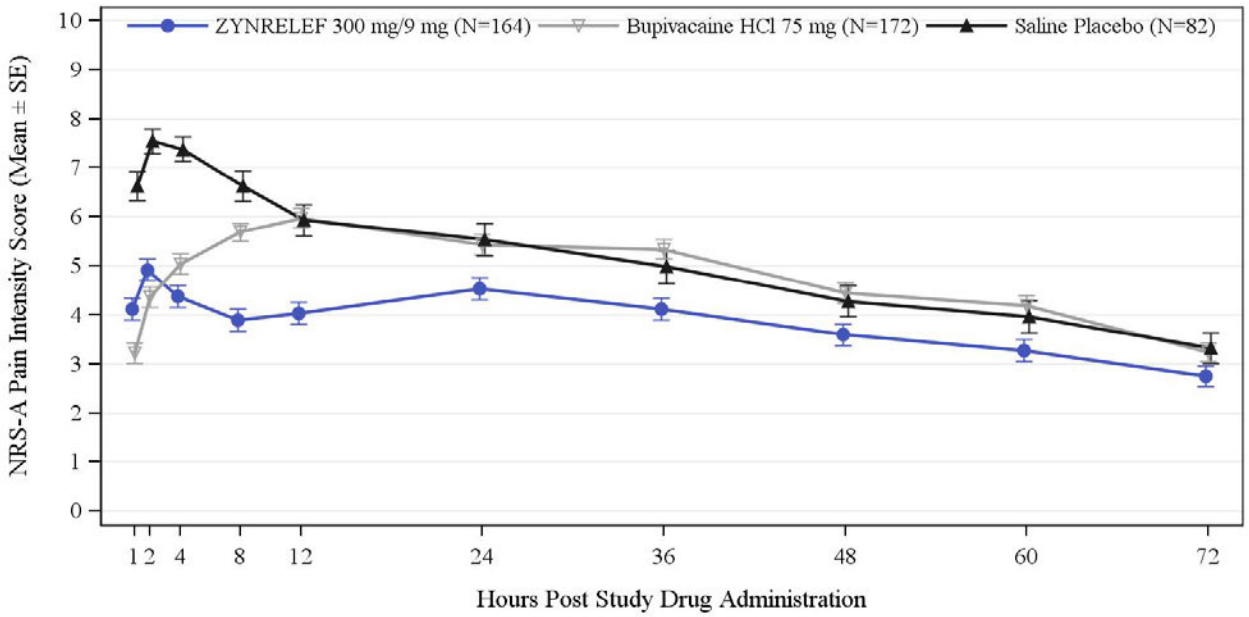
14.2 Study 2

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical trial (NCT03237481), 418 patients undergoing unilateral open inguinal herniorrhaphy with mesh under general anesthesia were randomized to 1 of the following 3 treatment groups in a 2:2:1 ratio (respectively): ZYNRELEF 300 mg/9 mg, bupivacaine HCl 75 mg, or saline placebo. The mean patient age was 49 years (range 18 to 83) and patients were predominantly male (94%). ZYNRELEF was applied directly into the surgical site, using the cone-shaped applicator, at the end of the procedure, following irrigation and suction of each fascial layer but prior to closure. Bupivacaine HCl and saline placebo were administered by injection and instillation, respectively. Pain intensity was rated by patients using an 11-point NRS out to 72 hours post-dose. Postoperatively, there was no scheduled pain medication regimen; however, patients were allowed rescue medication as needed, which included oxycodone 10 mg orally every 4 hours, morphine 10 mg IV every 2 hours, and/or acetaminophen 1000 mg orally every 6 hours. The primary endpoint was the mean AUC of the NRS pain intensity scores (cumulative pain scores) with activity over the 72-hour period for the ZYNRELEF treatment group compared to the saline placebo treatment group. Secondary endpoints included mean AUC of NRS pain intensity scores over the 72-hour period for the ZYNRELEF treatment group compared to the bupivacaine HCl treatment group, proportion of patients who did not receive opioid analgesia, and total opioid consumption.

Patients treated with ZYNRELEF demonstrated a statistically significant reduction in pain intensity compared to those treated with either bupivacaine HCl or saline placebo for up to 72 hours (Figure 2). A significant proportion of patients treated with ZYNRELEF did not receive opioid analgesia (51%) over

72 hours compared to those treated with either bupivacaine HCl (40%) or saline placebo (22%). A significant reduction in total opioid consumption over 72 hours was also observed for patients treated with ZYNRELEF (median consumption 0 mg) compared to those treated with either bupivacaine HCl (7.3 mg) or saline placebo (11.3 mg).

Figure 2. Mean Pain Intensity with Activity Over 72 Hours for STUDY 2 (Herniorrhaphy)



Based on similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, between open inguinal herniorrhaphy and other small-to-medium open abdominal surgical procedures, the pharmacokinetic profile and effectiveness of ZYNRELEF are not expected to be clinically significantly different when ZYNRELEF is administered at the same dose.

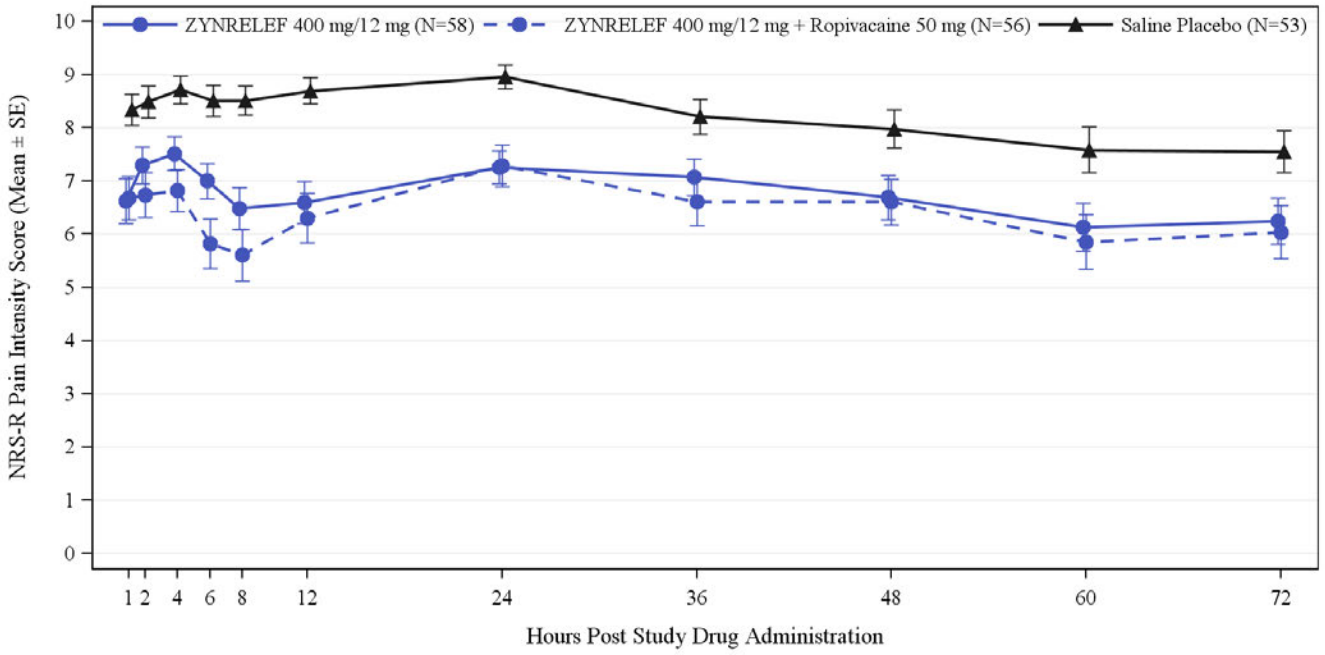
14.3 Study 3

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical study (NCT03015532), 222 patients undergoing primary unilateral total knee arthroplasty under general anesthesia were randomized to one of the following treatment groups in a 1:1:1:1 ratio; ZYNRELEF 400 mg/12 mg, ZYNRELEF 400 mg/12 mg plus ropivacaine 50 mg (injected into the posterior capsule), bupivacaine HCl 125 mg, or saline placebo. The mean age was 62 years (range 33 to 85) and 51% of patients were female.

ZYNRELEF was administered, using the cone-shaped applicator, onto the posterior capsule, the anteromedial tissues and periosteum, and the anterolateral tissues and periosteum after cementation of the components. Preoperatively, patients were administered pregabalin 150 mg as a single oral dose and acetaminophen up to 1 g IV. Pain intensity was rated by the patients using an 11-point NRS out to 72 hours post-dose. Postoperatively, there was no scheduled pain medication regimen, and patients were allowed only opioid rescue medication as needed (10 mg oxycodone orally every 4 hours, and/or 10-15 mg morphine IV every 2 hours). The primary endpoint was the AUC of the NRS pain intensity scores (cumulative pain scores) at rest collected over the first 48 hours.

Patients treated with ZYNRELEF demonstrated a significant reduction in pain intensity compared to patients treated with saline placebo for the first 48-hour and 72-hour postoperative periods (Figure 3). There were two patients who did not receive opioid analgesia over 72 hours; one in the ZYNRELEF 400 mg/12 mg + ropivacaine treatment group and one in the bupivacaine HCl treatment group.

Figure 3. Mean Pain Intensity at Rest Over 72 Hours for STUDY 3 (Total Knee Arthroplasty)



Based on similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, between total knee arthroplasty and other lower extremity total joint arthroplasty surgical procedures, the pharmacokinetic profile and effectiveness of ZYNRELEF are not expected to be clinically significantly different when ZYNRELEF is administered at the same dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYNRELEF® (bupivacaine and meloxicam) extended-release solution is a clear, pale-yellow to yellow viscous liquid available in 4 presentations. Each single-dose glass vial is filled with a solution of 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam. Each presentation described below is supplied in the ZYNRELEF kit containing a vial (packaged in an individual carton) along with sterile, individually packaged components for administration.

Product Presentation			Vented Vial Spike Provided	Luer Lock Syringe(s) Provided	Luer Lock Applicator(s) Provided	Syringe Tip Cap(s) Provided
NDC	Bupivacaine/ Meloxicam (mg/mg)	Net Quantity Volume* (mL)				
47426-301-02	400/12	14	1	2 x 12 mL	2	2
47426-302-02	300/9	10.5	1	1 x 12 mL	1	1
47426-303-01	200/6	7	1	1 x 12 mL	1	1
47426-304-01	60/1.8	2.3	1	1 x 3 mL	1	1

* Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator, and syringe(s) during drug withdrawal and administration

The following replacement components are individually supplied separate from the kit:

- Carton containing 5 vented vial spikes
- Carton containing 10 Luer lock applicators
- Carton containing 10 sterile 3 mL Luer lock syringes
- Carton containing 8 sterile 12 mL Luer lock syringes

Storage

Store ZYNRELEF kits at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture and light.

If ZYNRELEF vials are removed from the kit, store them at controlled room temperature. Protect from light during storage.

17 PATIENT COUNSELING INFORMATION

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Warnings and Precautions (5.9)*].

Serious Skin Reactions, including DRESS

Advise patients to contact their healthcare provider as soon as possible if they develop any type of rash or fever [*see Warnings and Precautions (5.13, 5.14)*].

Methemoglobinemia

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue [*see Warnings and Precautions (5.11)*].

Fetal Toxicity

Inform pregnant women of the risk of the premature closing of the fetal ductus arteriosus if ZYNRELEF or other NSAIDs are used starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with ZYNRELEF is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios because meloxicam can be detected in plasma beyond 48 hours after administration [*see Warnings and Precautions (5.15)* and *Use in Specific Populations (8.1)*].

Temporary Loss of Sensation Near the Surgical Site

Inform patients in advance that ZYNRELEF can cause temporary loss of sensation near the surgical site.

Use of NSAIDs

Inform patients of the increased risk of gastrointestinal toxicity if an NSAID or salicylate (e.g., diflunisal, salsalate) is used in the postoperative period following administration of ZYNRELEF [*see Drug Interactions (7)*].

Manufactured for: Heron Therapeutics, Inc., 4242 Campus Point Court, Suite 200, San Diego, CA, 92121, USA.

ZYNRELEF® is a registered trademark of Heron Therapeutics, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

CROSS DISCIPLINE TEAM LEADER REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review for Regulatory Action

Date	December 8, 2021
From	Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD
NDA# and Supplement#	211988, Supplement 005
Applicant	Heron Therapeutics, Inc.
Date of Submission	September 29, 2021
PDUFA Goal Date	July 29, 2022
Proprietary Name	Zynrelef®
Established or Proper Name	Bupivacaine and meloxicam extended-release solution
Dosage Form / Strengths	Solution for soft tissue or periarticular instillation Single dose administration for the following doses: – 400 mg bupivacaine and 12 mg meloxicam – 300 mg bupivacaine and 9 mg meloxicam – 200 mg bupivacaine and 6 mg meloxicam – 60 mg bupivacaine and 1.8 mg meloxicam
Applicant Proposed Indication	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
Regulatory Action	Approval

Material Reviewed/Consulted **OND Action Package, including reviews by:**	
Clinical Pharmacology Team	Suresh Naraharisetti, PhD; Yun Xu, PhD
Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis Team (DMEPA)	Cameron Johnson, PharmD; Otto L. Townsend, PharmD
Office of Prescription Drug Promotion (OPDP)	Sam Skariah, Phillip Williams, Catherine Gray
Reviews Completed During Previous Review Cycles:	
Pharmacology Toxicology Team	Jaime D'Agostino, PhD; Jay Chang, PhD; Dan Mellon, PhD
Office of Product Quality Team (OPQ)	Joe Leginus, PhD; Donna Christner, PhD; Venakteswara Pavuluri, PhD; Julia Pinto, PhD; Yoon Oh, PhD; Pei-I Chu, PhD; Christine Craig, PhD; Jonathan Swoboda, PhD; Hansong Chen, PharmD; Kelly Kitchens, PhD; Anika Lalmansingh, PhD; Xiaofei Liu, PhD; Cindy Diem Ngo, PhD; Cynthia Sommers, PhD; Caryn McNab, PhD; Michael Tollon, PhD
Center for Devices and Radiological Health Team (CDRH)	Florencia T. Wilson; Sarah Mollo; Capt. Alan M. Stevens; Rumi Young
Office of Scientific Investigations Team (OSI)	John Lee, PhD; Phillip Kronstein, MD; Kassa Ayalew, MD, MPH
Division of Pediatrics and Maternal Health Review (DPMH, formerly)	Christos Mastroyannis, MD; Tamara Johnson, MD, MS; Lynne P. Yao, MD

1. Benefit-Risk Assessment

Post-operative pain is a serious condition. Current treatment options include the use of local anesthetics administered via wound infiltration, or for peripheral nerve blockade or neuraxial anesthesia/analgesia; opioid and non-opioid analgesics; and multimodal therapy, which may include the administration of two or more drugs acting via different mechanisms. The standard of care for the majority of surgical procedures is the use of local anesthetic medications administered via various routes and for variable durations. Because immediate-release local anesthetics have a relatively short duration of action, and the clinical benefits (i.e., analgesia) are limited, there is a need for longer-acting local anesthetics to not only improve post-operative analgesia, but to also facilitate rehabilitation and reduce opioid analgesic use.

Zynrelef®, an extended-release solution composed of bupivacaine and meloxicam, was approved on May 12, 2021, for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty in adults. During labeling negotiations, Heron Therapeutics, Inc. (Heron) (b) (4) (b) (4) the Division's proposed indication in approval. After several teleconferences and written correspondence regarding the data to support expanding the labeled indication, Heron submitted NDA supplement 005 on September 29, 2021, with the remaining clinical documents submitted on October 14, 2021. This efficacy supplement includes a summary of previously reviewed clinical safety data and additional information to support expansion of the labeled indications for Zynrelef to include foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty, surgical procedures considered closely related to the three approved respective procedures. Because many of the safety data were previously reviewed, and the amount of new data submitted was not substantial, the Division was able to complete the review of this supplemental NDA in an expedited manner.

Heron has not conducted additional PK, safety, or efficacy studies that were designed to support the proposed expansion of the indication for Zynrelef. However, they did conduct five open-label studies subsequent to the initial NDA submission to evaluate the safety and efficacy of multimodal analgesic (MMA) regimens in combination with a single intra-operative dose of Zynrelef. Many of the data from these studies were submitted in safety updates included in the (b) (4) for the initial approval, and the pertinent safety findings of each study are presented in this review to further support the safety profile of Zynrelef. These open-label studies will not be described in the approved labeling for Zynrelef.

The Division agreed to accept summary documents to support extrapolation of clinical data from evaluated procedures to what are described as closely related. Heron and the Division agreed that based on similarities in surgical site characteristics, the procedures summarized in Appendix A are considered closely related to those evaluated during clinical development,

such that the data from clinical studies conducted in any of the closely related procedures are unlikely to be clinically significantly different from the evaluated respective procedures.

Based on the totality of the PK, safety, and efficacy data summarized in the initial NDA and the two NDA resubmissions for approval of the initial NDA, and this efficacy supplement, Heron is proposing to expand the indication for Zynrelef as follows:

> *...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*

Heron has included information in Section 2 describing dosing, administration technique, and the approved procedures as representative examples of each closely related category.

This benefit:risk assessment will discuss the efficacy, PK, and safety data reviewed to support the proposed expanded indication, with emphasis on the benefits and risks of administration of Zynrelef during closely related procedures.

Supportive Efficacy Data

The Applicant proposes that, based on the consistent and reproducible efficacy profile for Zynrelef demonstrated throughout clinical development, there is no reason to believe that its use during closely related procedures would not demonstrate a similar postsurgical analgesic benefit. Additionally, the efficacy of Zynrelef was demonstrated to be superior to standard of care immediate-release bupivacaine HCl, an efficacy endpoint not easily met.

Based on the similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, the Division agrees that the efficacy profile for Zynrelef is likely to be similar between respective evaluated procedures and those considered closely related. While the analgesic benefit of Zynrelef 60 mg/1.8 mg administered during larger closely related foot and ankle procedures, such as repair of a trimalleolar fracture, may be expected to be less than that observed following smaller closely related procedures, orthopedic surgeons have expertise in intra-operative bupivacaine dosing for a given analgesic benefit and can make a clinical determination on whether Zynrelef is the best postsurgical analgesic treatment for their surgical patients.

Review of the results from the completed and ongoing studies conducted subsequent to the initial NDA submission, including the five open-label studies, do not change the Division's previous conclusion regarding the efficacy of Zynrelef and its clinical benefits.

Supportive PK Data

As discussed in the CDTL/DD Summary Review completed on May 12, 2021, the Division (b) (4) . Specifically, regarding the 400 mg/12 mg dose, the maximum concentration (C_{max}) of bupivacaine, the drug of most concern in this combination product with regard to safety, varied across the three procedures evaluated (i.e., (b) (4)

(b) (4), (b) (4), and total knee arthroplasty), with the highest mean value reported in the (b) (4) study. The Division continues to conclude that extrapolation of PK data from procedures evaluated to (b) (4) is not acceptable because the PK profile is variable across the procedures evaluated. However, the Division does agree that small variations in the bupivacaine PK profile, specifically C_{max} values, between the procedures evaluated and those proposed as closely related are unlikely to result in clinically significant differences in systemic exposure, and consequently, the risk of local anesthetic systemic toxicity (LAST), the adverse event of most concern related to systemic exposure to bupivacaine. The Division also recognizes that a clinical PK evaluation in all possible surgical procedures is impractical, infeasible, and, depending on the drug product and existing clinical data, likely unnecessary.

Therefore, the Division concludes that the benefits of Zynrelef administration during closely related surgical procedures, including the availability of an additional bupivacaine product, and the novel, needle-less route of administration, outweigh the seemingly low risk of LAST.

Supportive Safety Data

The data reviewed to support the safety profile of Zynrelef for use in the indicated procedures, and extrapolation to proposed closely related procedures included results from studies evaluating multimodal analgesic regimens with Zynrelef conducted subsequent to the initial NDA submission, information regarding the risk of chondrolysis due to exposure of articular cartilage to Zynrelef, data submitted in support of the initial NDA, and clinical pharmacology analyses to support the systemic safety of Zynrelef administration during closely related procedures (discussed above, and in more detail in Section 5 of this review).

There were five open-label studies conducted subsequent to the initial NDA submission, in subjects undergoing open inguinal herniorrhaphy, bunionectomy, TKA, and caesarean delivery. These studies evaluated the impact of different MMA regimens on postsurgical analgesia when used in combination with a single intra-operative dose of Zynrelef, as well as other study-specific objectives. While definitive safety conclusions based on data from open-label studies are challenging, the results do suggest there is a low risk of LAST-, wound-, or nonsteroidal anti-inflammatory drug (NSAID)-related adverse events with administration of Zynrelef in doses up to 400 mg/12 mg.

There were reported cases of vital sign changes or symptoms that could have been indicative of LAST; however, lack of a blinded comparator treatment, the timing of the event, the corresponding bupivacaine level, or time to resolution did not support a causal relationship between Zynrelef and LAST. Wound-related adverse events appeared to be primarily limited to the bunionectomy procedure, a surgical wound known to have potential healing concerns due to the limited blood supply to the distal foot and toes. Individualized dosing, evaluated in Study 218, discussed further in Section 8 of this review, did appear to mitigate some of the wound issues reported, when compared to the results from the larger Phase 3 study in the same model. Potential NSAID-related gastrointestinal (GI) adverse events were rare and more likely related to the MMA regimens which included ibuprofen, versus the meloxicam component of Zynrelef. There did not appear to be any cases of NSAID-related cardiovascular or renal adverse events. Therefore, the data from these studies support the acceptable safety profile and

favorable benefit:risk assessment of Zynrelef. Because expansion of the labeled indications is limited to procedures considered closely related to respective evaluated procedures, these safety data are unlikely to be clinically significantly different and support the safety profile of Zynrelef when administered during closely related surgical procedures.

Regarding the risk of chondrolysis after Zynrelef administration to articular cartilage, there are three main reasons the Applicant does not believe this risk is clinically significant during closely related foot and ankle procedures. First, there were no reports of chondrolysis during the three studies conducted in subjects undergoing bunionectomy (Studies 208, 301, and 218), where Zynrelef was administered directly into the joint space of the first metatarsophalangeal joint, and exposure to articular cartilage was likely extensive. Heron contends that exposure of articular cartilage to the same dose of Zynrelef (i.e., 60 mg/1.8 mg) is likely to be lower in the proposed closely related foot and ankle procedures, where exposure will generally be due to drug seepage versus direct administration. Second, the proposed closely related procedures are similar to bunionectomy in anatomic location, tissue type, length and depth of the surgical area, and vascularity of the surgical site, such that more extensive exposure of articular cartilage to Zynrelef is unlikely. And third, Heron states that the risk of chondrolysis during ankle fracture repair, the procedure likely at highest risk, is low based on data suggesting that bupivacaine-induced chondrolysis appears to be dose-dependent, such that the small amount of Zynrelef that may reach the ankle joint is unlikely to cause chondrolysis.

The Division agrees with Heron that the risk of chondrolysis in closely related foot and ankle procedures appears low. The Division also notes that while the articular surfaces of the long bones are resected during TKA, some articular cartilage may remain on the posterior patellar surface, and there have been no reports of patellar chondrolysis in any of the TKA studies. That being said, because the risk may not be negligible and additional nonclinical data are needed, the Division recommends inclusion of the proposed cautionary statement in the label informing the prescriber to limit exposure to articular cartilage if possible. Additionally, the Division recommends that juvenile animal studies address the risk of possible adverse impacts on the growth plate prior to initiation of studies in pediatric subjects to support an expanded indication for foot and ankle procedures.

Regarding LAST, the safety data submitted in support of the initial NDA contained small and inconsistent differences in LAST-related adverse events across treatment groups that were not clinically meaningful, particularly in the setting of concomitant administration of general anesthesia, which can confound the detection of LAST. Subjects undergoing TKA in Study 209, who received the highest proposed dose of Zynrelef, had the highest individual C_{max} values. Specifically, there were 10 subjects with C_{max} values greater than 1000 ng/mL (the concentration above which the Division generally believes the risk of LAST increases). The Division concluded there did not appear to be an increased incidence in LAST-related adverse events in these subjects compared to subjects with C_{max} values less than 1000 ng/mL. There were no subjects in any study who received Zynrelef alone and had C_{max} values greater than 2000 ng/mL, the concentration reported in the published literature above which the risk of LAST-related neurological adverse events increases, at any measured time point. There was one subject in Study 209 who had a C_{max} value of 2810 ng/mL in the Zynrelef 400 mg/12 mg plus ropivacaine treatment group. This subject experienced tachycardia, a three-beat-run of a

ventricular rhythm, and mild dizziness. The observed cardiac signs may have been related to the relatively high bupivacaine levels; however, the events were considered mild and resolved by the end of the study with no long-term complications.

Regarding the risk of local inflammatory and wound-related adverse events, there did appear to be an increased incidence of wound-related adverse events primarily observed in patients undergoing bunionectomy in the Phase 3 study, 301, and the Phase 2a study, 208. However, the Division concluded, that Zynrelef could be approved for this indication based on plausible explanations and/or justifications, including excess drug leakage from the wound, mild adverse events of short duration, no reported cases of osteomyelitis, over-grading wounds due to clinical study protocols, and the incidence of wound-related adverse events appeared to be consistent with reports in the published literature. There did not appear to be an increased incidence of clinically significant wound-related adverse events in patients undergoing open inguinal herniorrhaphy, the only indicated soft tissue surgical procedure prior to submission of this sNDA.

The Division concluded during review of the initial NDA submission and two resubmissions that the clinical benefits of Zynrelef administration during bunionectomy, open inguinal herniorrhaphy, and TKA outweigh the clinical risks discussed. The Division noted that a main advantage of Zynrelef over other currently available bupivacaine products is the proposed route of administration, instillation, using a needle-less Luer lock syringe and a unique cone-shaped applicator. Because a needle is not used for administration, the risk of inadvertent intravascular administration and catastrophic LAST is minimal, thereby increasing the margin of safety for this bupivacaine-containing product.

Based on the acceptable safety profile demonstrated in the totality of clinical studies conducted in five diverse surgical models (i.e., bunionectomy, open inguinal herniorrhaphy, TKA, bilateral augmentation mammoplasty, and abdominoplasty) and the ongoing study in subjects undergoing caesarean delivery, the Division has no concerns regarding the extrapolation of safety data to the proposed closely related procedures. It appears unlikely that a new safety signal would be identified when Zynrelef is administered during procedures with surgical site characteristics similar to those explicitly evaluated in clinical studies. Therefore, the Division agrees with the Applicant that the totality of the safety data, including information in the initial NDA submission, the two NDA resubmissions, and this sNDA, are adequate to support expansion of the label indications to include closely related foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty procedures.

Summary / Conclusion

Based on the demonstration of a consistent postsurgical analgesic benefit, and the PK and safety profiles of Zynrelef in several surgical models, the Division agrees there are adequate data to support the use of Zynrelef during the proposed closely related procedures and expansion of the labeled indications. Based on the similarities in the anatomic location, tissue type, length and depth of the surgical area, and vascularity, the Division believes that the PK, safety, and efficacy data from studies conducted in subjects undergoing bunionectomy, open inguinal herniorrhaphy, and TKA can be extrapolated to the proposed closely related procedures, and that the risks of Zynrelef administration are unlikely to be clinically

significantly different from what has been previously observed. The Division still contends, however, that extrapolation of PK, safety, and efficacy data to all possible surgical procedures is not appropriate, and additional clinical data are needed to support expansion of the labeled indications further. As discussed in Section 12 of this review, the proposed cautionary statement regarding chondrolysis and the Limitations of Use statement regarding Zynrelef use during vascular surgeries will help mitigate the risks of chondrolysis and LAST, respectively, and are included in the prescribing information.

2. Background

This document will serve as the Cross-Discipline Team Leader (CDTL) and Division Director (DD) Summary Review of this supplemental application, received on September 29, 2021. Heron submitted this supplemental NDA (referred to as sNDA #1 in meeting correspondence) to expand the labeled indications for Zynrelef, initially approved via the 505(b)(2) regulatory pathway on May 12, 2021, for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty, to include what Heron has described as closely related procedures. This review will discuss the Applicant's proposal, the acceptability of the data relied upon to support expansion of the indication, and issues encountered during the review cycle. Note that Zynrelef was designated HTX-011 during development and clinical studies were designated Study HTX-011-unique number, abbreviated by study number.

NDA 211988 was received on October 30, 2018. Due to unresolved issues regarding device sterility, drug product quality, and nonclinical safety concerns, the application received a Complete Response Letter (CRL) on April 30, 2019. A Complete Response submission was received on September 26, 2019, and also received a CRL on June 26, 2020, due to unresolved nonclinical concerns. A second Complete Response submission was received on November 12, 2020, and the application was approved on May 12, 2021. During the labeling negotiations for the third review cycle, Heron (b) (4) and that the clinical development program was designed based on previous advice, including information in the now withdrawn guidance for industry, *Analgesic Indications: Developing Drug and Biological Products*, commonly referred to as the analgesic guidance. (b) (4) .

While the Division agreed that not every procedure could or should be evaluated, the Division (b) (4) There were concerns regarding the number of treated subjects and the route of administration of Zynrelef in the abdominoplasty study (Study HTX-011-203, or simply 203), divided dosing (i.e., Zynrelef 200 mg/6 mg per breast pocket) in the bilateral augmentation mammoplasty study (Study HTX-011-211, or simply 211), and the absence of supportive data in a shoulder model. Furthermore, the Division (b) (4)

(b) (4) . The Division did agree, however, that the loss of drug due to suctioning and irrigation prior to wound closure likely contributed to the outlying, lower observed systemic exposure in Study 203. Heron accepted the Division's proposed limited postsurgical indications (i.e., bunionectomy, open inguinal hernia repair, and total knee arthroplasty), (b) (4)

On June 18, 2021, the Division received a Type B Post-Action Meeting Request from Heron, seeking clarity on the data Heron should submit to obtain an expanded indication for soft tissue and orthopedic postsurgical analgesia for Zynrelef. The meeting request included a brief summary of the (b) (4) approach Heron was proposing to expand the indication for Zynrelef, initially to include (b) (4) foot and ankle procedures, small-to-medium open abdominal procedures, and lower extremity total joint arthroplasty procedures (based on data submitted in the current sNDA, sNDA #1), and (b) (4) Based on the information requested during the meeting, the Division granted a Type C guidance meeting, which was held on September 14, 2021. The following table is a high-level summary by general category of the key issues discussed during this meeting.

Table 1. Summary of September 14, 2021, Post-Action Type C Meeting

Label Edits and Indication	• Heron provided additional information to support the use of Zynrelef in orthopedic procedures, and stated they would include a cautionary statement in the label regarding the risk of chondrolysis. Specifically, they proposed to include the following statement: (b) (4) exposure to articular cartilage due to the potential risk for chondrolysis". They also agreed to conduct nonclinical studies to further inform this risk. • (b) (4) • The Division stated that (b) (4) . • The Division confirmed that data from studies 302 (open inguinal hernia repair), 211 (bilateral augmentation mammoplasty), 401 (abdominoplasty), and 220 (caesarean delivery) (b) (4) , and data from studies 301 (bunionectomy), 209 (total knee arthroplasty), 401 (total shoulder arthroplasty), 221 (lumbar laminectomy and fusion) (b) (4) The Division stated that inclusion of more invasive procedures in Study 221 in subjects undergoing laminectomy will provide additional safety and PK information for orthopedic procedures.

Procedures	The Division agreed that the procedures described in the meeting package may be considered closely related to those evaluated during clinical development.
Content of (b) (4) and Presentation of Data	• The content in what is referred to as sNDA #1 (the current supplemental application, 005) (b) (4) • (b) (4) • (b) (4)
(b) (4)	(b) (4)
Pediatric Study Information	Heron initially proposed to include the agreed iPSP submitted in support of the initial NDA for sNDA #1 (b) (4)

Refer to the meeting minutes dated October 8, 2021, for additional information.

A follow-up teleconference was held on September 28, 2021, at the Division's request, to discuss submission of sNDA #1 and the Division's proposed review timeline. The following table is a high-level summary by general category of the key issues discussed.

Table 2. Summary of September 28, 2021, Teleconference

Review Timeline	• The Division proposed a review timeline of eight weeks, (b) (4) • Based on the pending lapse in government funding and the potential for a government shutdown, in which new NDAs are not accepted for review, Heron proposed to submit sNDA #1 by September 30, 2021, (b) (4) (b) (4). The Division agreed with this proposal but indicated that the review clock would not begin until receipt of all required documents, (b) (4)
Exposure to Articular Cartilage	The Division was concerned regarding (b) (4) (b) (4) to inform prescribers to "limit" (b) (4), exposure to articular cartilage. The Division stated this was acceptable.
Pediatric Study Information	The Division further clarified that an iPSP would be required for sNDA #1.
Safety Data	The Division stated that either an ISS or Summary of Clinical Safety would be required for sNDA #1.

Refer to the meeting minutes dated October 1, 2021, for additional information.

This sNDA was received on September 29, 2021, and remaining clinical summaries and the initial Pediatric Study Plan were received on October 14, 2021. Because there was not a substantial amount of new data submitted, the Division felt review of the application on an expedited timeline was possible.

3. Product Quality

The following information is adapted from the product quality reviews completed during the third NDA review cycle.

Zynrelef is a fixed-dose combination product consisting of bupivacaine, 29.25 mg/mL, and meloxicam, 0.88 mg/mL, approved for administration into bunionectomy, open inguinal herniorrhaphy, and TKA wounds for postsurgical analgesia through 72 hours. The currently marketed presentations are as follows:

- Bupivacaine 400 mg + meloxicam 12 mg in 20 mL vial
- Bupivacaine 300 mg + meloxicam 9 mg in 20 mL vial
- Bupivacaine 200 mg + meloxicam 6 mg in 10 mL vial
- Bupivacaine 60 mg + meloxicam 1.8 mg in 10 mL vial

The proposed shelf-life is 36 months for the 400 mg/12 mg, 300 mg/9 mg, and 200 mg/6 mg presentations, and 24 months for the 60 mg/1.8 mg presentation.

There were no additional product quality data submitted in support of this sNDA; therefore, there are no outstanding issues that would prevent approval.

4. Nonclinical Pharmacology/Toxicology

There were no additional nonclinical data submitted in support of this sNDA. The Applicant has agreed to conduct additional nonclinical studies to evaluate the risk of chondrolysis due to Zynrelef administration to, or in close proximity to, articular cartilage. Until those studies are completed and the data indicate there is negligible risk, the proposed cautionary statement, *Limit exposure to articular cartilage due to the potential risk of chondrolysis*, will be included in the prescribing information for Zynrelef.

5. Clinical Pharmacology

Because the development of LAST is the primary concern from the clinical pharmacology perspective regarding administration of Zynrelef, the discussion in this section will focus on the systemic exposure to bupivacaine. The Applicant provided a summary of existing clinical pharmacology data and additional PK analyses to support their position that the PK profile, specifically the risk of bupivacaine toxicity, for Zynrelef does not change in a clinically meaningful way across proposed closely related surgical procedures when compared to the respective approved procedures. The following discussion is supported by information from Dr. Suresh Naraharisetti's clinical pharmacology reviews completed during previous and the current review cycles.

The Applicant states that Zynrelef demonstrates dose-linearity across four of the evaluated surgical procedures (bunionectomy, inguinal hernia repair, TKA, and bilateral augmentation mammoplasty). Data from Study 203, conducted in subjects undergoing abdominoplasty, were not included in the Applicant's analysis based on the lower-than-expected bupivacaine levels possibly due to drug loss during final irrigation and suctioning prior to wound closure. Refer to Table 3 for a summary of PK data from the four evaluated procedures, and Figure 1 for a summary of the Applicant's calculated correlation between bupivacaine C_{max} and the dose administered across the four procedures.

Table 3. Summary of PK Parameters for Bupivacaine and Meloxicam After Single-Dose Administration of Zynrelef by Instillation in Four Evaluated Procedures

Active Ingredient	Parameter	Bunionectomy: 60 mg/1.8 mg ZYNRELEF (N=17)	Herniorrhaphy: 300 mg/9 mg ZYNRELEF (N=16)	Total Knee Arthroplasty: 400 mg/12 mg ZYNRELEF (N=53)	Augmentation Mammoplasty: 400 mg/12 mg ZYNRELEF (N=49)
Bupivacaine	C_{max} (ng/mL)	54 (33)	271 (147)	695 (411)	710 (246)
	T_{max} (h)	3.0 (1.6, 24)	18 (3, 30)	21 (4, 59)	3.58 (1.3, 35)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	1,681 (1,154)	15,174 (8,545)	35,890 (28,400)	26,400 (8,930)
	$AUC_{(inf)}$ (h×ng/mL)	1,718 (1,211)	15,524 (8,921)	38,173 (29,400)[b]	27,000 (8,960)
Meloxicam	C_{max} (ng/mL)	26 (14)[d]	225 (96)	275 (134)	527 (149)
	T_{max} (h)	18 (8, 60)[d]	54 (24, 96)	36 (12, 72)	20 (5.6, 49)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	1,621 (927)[d]	18,721 (7,923)	19,525 (12,259)	29,700 (9,320)
	$AUC_{(inf)}$ (h×ng/mL)	2,079 (1,631)[d]	NR	25,673 (17,666)[c]	30,400 (9,750)

Abbreviations: AUC_{0-t}, area under the concentration-time curve from Time 0 to Time t; AUC_{inf}, area under the concentration-time curve from Time 0 extrapolated to infinity; C_{max}, maximum concentration; NR= not reported (the terminal elimination phase was not adequately characterized in sufficient number of patients); PK, pharmacokinetic; T_{max}, time of occurrence of maximum concentration.

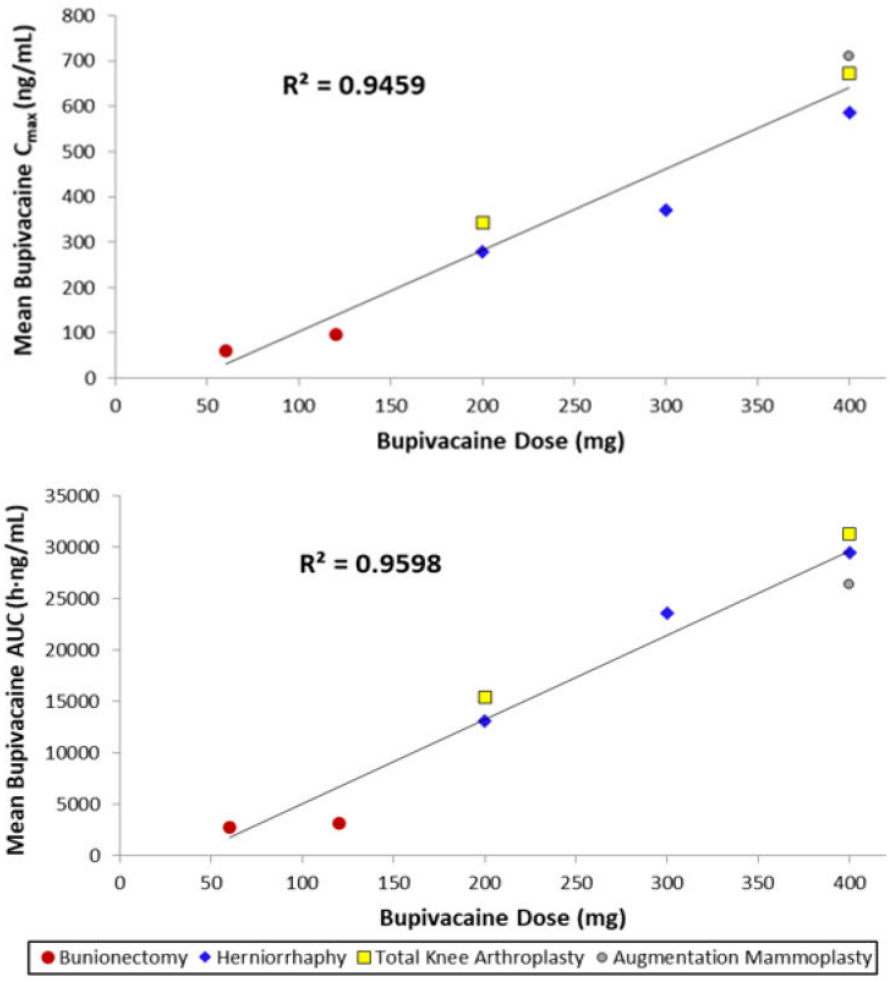
[a] $AUC_{(0-t)}$: 0 to 120 h postdose for bunionectomy, herniorrhaphy, and augmentation mammoplasty; 0 to 144 h postdose for total knee arthroplasty.

[b] N=50; [c] N=35; [d] N=16.

Note: Arithmetic mean (standard deviation) except T_{max} where it is median (min, max).

Source: Summary of Clinical Safety, p. 90 (PDF), Applicant's sNDA submission (Oct. 14. 2021), NDA 211988.

Figure 1. Linear Bupivacaine C_{max} and AUC Versus Dose Following Instillation of Zynrelef in Various Surgical Procedures (PK Populations)



Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; PK, pharmacokinetic.
Source: Type C Post-Approval Meeting Background Package, p. 47 (PDF), Applicant's submission, NDA 211988.

Based on data in this table and figure, the Applicant concludes that the systemic exposure to bupivacaine is similar and increases linearly with increasing Zynrelef doses across the four procedures, and that Zynrelef should be granted a broad post-surgical analgesic indication, and at a minimum a closely related procedures indication. While some of the measured PK parameters did increase linearly relative to the dose administered, the clinical pharmacology review team did not agree that a strong correlation between dose administered and mean maximum concentration of bupivacaine (C_{max}) or area under the curve (AUC) had been demonstrated. Specifically, review of the PK data from the initial NDA submission suggested there were differences in bupivacaine and meloxicam C_{max} and AUC values across different procedures following administration of the same Zynrelef dose (i.e., 400 mg/12 mg). In addition, the team did have concerns that some of the data used by the Applicant were estimates based on a few intermittent PK samples, and not based on full PK sampling data.

The team did note, however, that based on data from subjects undergoing bunionectomy or open inguinal herniorrhaphy, it did appear that Zynrelef demonstrated dose-linearity for different administered doses in the same evaluated surgical procedure. Specifically, doubling the administered Zynrelef dose within these surgical procedures (i.e., 60 mg/1.8 mg and 120 mg/3.6 mg for bunionectomy; 200 mg/6 mg and 400 mg/12 mg for open inguinal herniorrhaphy) resulted in doubling of the systemic exposure of both bupivacaine and meloxicam.

The team concluded that pooling of PK data across different surgical procedures, including soft tissue and orthopedic procedures, and dose cohorts is not acceptable for dose-linearity assessments based on differences in surgical site characteristics, including anatomic location and vascularity. The team did agree, however, that for dose-linearity assessments, pooling data from closely related procedures with similar surgical site characteristics may be acceptable, and that the above analyses appear to support the Applicant's claim that the PK profile of Zynrelef across closely related procedures is unlikely to differ in a clinically significant way from that demonstrated in the evaluated respective procedures when administered at the same dose. The team has advised the Applicant that future dose-linearity evaluations should include data from studies using full PK sampling. Additionally, PK data from planned Study 401, in subjects undergoing abdominoplasty or total shoulder arthroplasty, will further inform the PK profile of Zynrelef in more invasive, and potentially more vascular, procedures than those previously evaluated.

In conclusion, based on the review of all available PK information, including the demonstration of dose-linearity within the same procedure, the clinical pharmacology review team agrees with the Applicant that the PK profile for Zynrelef is unlikely to be clinically significantly different across similar or closely related procedures defined by similar surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, and that extrapolation of PK data from evaluated procedures to those considered closely related is acceptable. Furthermore, the team has no concerns with expanding the labeled indication for Zynrelef to procedures considered closely related to those explicitly evaluated during clinical development.

The Division concurs with the clinical pharmacology review team's assessment that extrapolation of PK data from procedures evaluated during clinical development to those considered closely related is acceptable, and that these data support the Applicant's request to expand the postsurgical indications for Zynrelef. The Division notes, however, that based on the unknown risk of bupivacaine toxicity, extrapolation of data to procedures which differ in surgical site characteristics and not considered closely related, or those considered highly vascular is not acceptable. Language in the label informs the prescriber of acceptable procedures for which Zynrelef can be safely administered.

Refer to the review completed by Dr. Naraharisetti for additional clinical pharmacology information, including a discussion of the Applicant's conclusions regarding (b) (4) (b) (4)

6. Clinical Microbiology

Zynrelef is not a therapeutic antimicrobial, therefore clinical microbiology data were neither required nor submitted for this sNDA.

7. Clinical/Statistical- Efficacy

There were no new efficacy data submitted in support of this sNDA. The studies relied upon during the initial NDA review cycle for approval of Zynrelef for the three indicated procedures are also relied upon for approval of this sNDA. The Applicant concludes that, based on the consistent and reproducible efficacy profile for Zynrelef demonstrated throughout clinical development, there is no reason to believe that Zynrelef administration during closely related procedures would not demonstrate a similar postsurgical analgesic benefit. Specifically, it seems unlikely that the efficacy profile for Zynrelef in subjects undergoing bunionectomy, open inguinal herniorrhaphy, or TKA would be clinically significantly different in subjects undergoing phalangectomy, open umbilical hernia repair, or total hip arthroplasty (THA), representative closely related procedures, respectively. Additionally, the postsurgical benefit of Zynrelef was demonstrated to be superior to standard of care immediate-release bupivacaine HCl, an efficacy endpoint not easily or commonly met in studies of newer formulations of local anesthetics.

Based on the similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, the Division agrees that the efficacy profile for Zynrelef is likely to be similar in closely related procedures. The analgesic benefit of Zynrelef 60 mg/1.8 mg administered during larger closely related foot and ankle procedures, where several incisions are required, such as repair of a trimalleolar fracture, may be less than that observed following smaller closely related procedures. However, orthopedic surgeons have expertise in intra-operative bupivacaine dosing for a given analgesic benefit, and can make a clinical determination on whether Zynrelef is the best postsurgical analgesic treatment for their patients.

The results from the completed and ongoing studies conducted subsequent to the initial NDA submission lend support for the efficacy of Zynrelef; however, the majority of these studies were open-label evaluations of various non-opioid MMA regimens in combination with a single intra-operative dose of Zynrelef in subjects undergoing different procedures. While efficacy conclusions based on data from these studies can be challenging, it does appear that Zynrelef in combination with MMA may offer superior postsurgical analgesia compared to Zynrelef administration alone. This is not surprising, given that MMA regimens are considered a standard of postsurgical care, not only in an attempt to minimize opioid consumption, but to also provide a multi-target approach to acute postsurgical pain management.

In conclusion, based on the similarities in surgical site characteristics between the evaluated procedures and those considered closely related, the Division agrees that extrapolation of efficacy data is acceptable. Furthermore, based on the demonstration of a consistent postsurgical analgesic benefit of Zynrelef in several surgical models and superiority over bupivacaine HCl, the Division agrees there are adequate data to support the use of Zynrelef

during closely related procedures and expansion of the labeled indications. Refer to the primary clinical review dated April 30, 2019, and the CDTL/DD Summary Reviews dated April 30, 2019; June 26, 2020; and May 12, 2021, for additional information regarding the efficacy data relied upon for initial approval.

8. Safety

The Summary of Clinical Safety submitted in support of this sNDA included the following information.

- A summary of the safety data from 368 subjects who participated in five open-label studies, listed below, conducted after submission of the initial NDA.
    - Study 215 – open inguinal herniorrhaphy model, 63 subjects, completed
    - Study 218 – bunionectomy model, 78 subjects, completed
    - Study 304 – open inguinal herniorrhaphy model
        - Part 1: 93 subjects, concluded, interim synopsis report submitted
        - Part 2: On-going
    - Study 306 – TKA model, 116 subjects, concluded, final study report submission pending
    - Study 220 – caesarean delivery model, 18 subjects, ongoing. As agreed to by the Division, the Summary of Clinical Safety does not include safety data for additional subjects in this study.

  With the exception of Study 220, the primary objective of these studies was to assess the safety and efficacy of administration of different MMA regimens in combination with a single intra-operative dose of Zynrelef.
- Supportive information regarding the risk of chondrolysis due to exposure of articular cartilage to Zynrelef.
- A brief summary of the safety data reviewed in support of the initial NDA, including data from the pooled safety population of 504 subjects who received Zynrelef via instillation.
- A summary of clinical pharmacology data and additional analyses to support the systemic safety of Zynrelef administration during closely related procedures (discussed in Section 5 of this review).

Safety Data Reviewed from Studies Completed Subsequent to the Initial NDA Submission

The five studies conducted subsequent to submission of the initial NDA were open-label and evaluated use of non-opioid MMA regimens in combination with a single intra-operative dose of Zynrelef. The MMA regimens generally included additional NSAID and acetaminophen administration. While many of these data were submitted in safety updates included in the two NDA resubmissions and previously reviewed, the pertinent safety findings of each study are discussed to further support the safety profile of Zynrelef, and subsequently support the ability to extrapolate these safety data to procedures with similar surgical site characteristics.

<u>Study 215 (open inguinal herniorrhaphy)</u>

This completed study evaluated an MMA regimen that included intra-operative Zynrelef (300 mg/9 mg) and round-the-clock NSAIDs and acetaminophen post-operatively (Cohort 1).

Cohort 2 received the same MMA regimen in addition to a single intravenous (i.v.) dose of ketorolac intra-operatively. There were reported vital sign changes or symptoms that could have been indicative of LAST; however, the lack of a blinded comparator treatment, the timing of the vital sign changes or symptoms, the corresponding bupivacaine level, or time to resolution did not support a causal relationship between Zynrelef and LAST. The majority of reported adverse events were mild in severity. There was one subject in Cohort 2 who reportedly had severe bradycardia and hypotension approximately 45 minutes after administration of Zynrelef and ketorolac. Both resolved within six minutes of administration of ephedrine and atropine. While these are concerning for LAST, this subject had an abnormal screening ECG, significant for bradycardia (rate not provided), and pre-operative vital sign assessments indicated a heart rate of 59 beats per minute. Additionally, a bupivacaine level drawn two hours and 24 minutes after the onset of the adverse events was 197 ng/mL. It is also worth noting that all subjects in this study received general anesthesia, which makes definitive conclusions regarding the occurrence of LAST challenging, particularly in an open-label study.

The incidence of wound-related adverse events was similar to those reported in the Phase 3 study in the same model (Study 302), and it does not appear that administration of Zynrelef increased the risk of development of local inflammatory or wound-related adverse events. Specifically, the overall incidence of local inflammatory adverse events reported in Study 215 was approximately 2%, compared to approximately 4% in Study, 302. There was one subject who reportedly had moderate cellulitis; however, further review of the medical record identified the location as the left side of the face, a location far removed from the inguinal canal surgical site. While definitive safety conclusions based on data from this open-label study where all treatment groups received Zynrelef are challenging, it is reassuring that the reported local inflammatory and wound-related adverse events occurred with similar frequency as that observed in the larger Phase 3 study.

Both cohorts in this study received additional NSAIDs post-operatively, with Cohort 2 receiving an intra-operative dose of i.v. ketorolac. There were no reported cases of NSAID-related cardiovascular, renal, or gastrointestinal (GI) adverse events.

Study 218 (bunionectomy)

In addition to an evaluation of an MMA regimen, this completed study evaluated individualized Zynrelef dosing, and the impact on wound healing and occurrence of wound-related adverse events. The Applicant attributed the increased incidence in some short-term (i.e., less than 42 days) wound-related adverse events in the Zynrelef treatment group in subjects undergoing bunionectomy in Study 301, the Phase 3 study, to leakage of excess Zynrelef from the relatively small bunionectomy wound. The Applicant hypothesized that for some subjects the maximum recommended volume, 2.1 mL, may have been too large for the surgical wound, such that excess Zynrelef leaked out resulting in delayed approximation of the wound edges, delayed healing, and subsequent wound-related adverse events. Study 218 was conducted to evaluate the safety (and efficacy) of individualized dosing in this surgical population.

Investigators in this study were advised to apply only as much drug as was necessary to "coat the pain-generating tissues ensuring there was not an excess that could be expressed from the site during closure". The volume of Zynrelef administered ranged from 0.7 mL to the maximum recommended volume, 2.1 mL. Because this was an open-label study, all groups received Zynrelef, and the total number of evaluated patients was low (78), definitive safety conclusions are challenging; however, there did appear to be a lower incidence in local inflammatory adverse events (approximately 4% overall, three patients total) in this study compared to those reported in Study 301 (approximately 29%). Regarding abnormal wound healing assessments, there appeared to be a lower incidence in this study (approximately 74%) compared to Study 301 (approximately 81%), with bruising, edema, and erythema most commonly reported. The Applicant stated that a lower administered volume of Zynrelef appeared to result in a decreased incidence of abnormal wound healing assessments. Based on this information, it is reasonable to conclude that leakage of excess drug from the wound may play a role in the development of wound-related adverse events in this surgical model. The Division also acknowledges that bunionectomy wounds tend to heal more slowly than other orthopedic wounds due to the limited blood supply to the distal foot and toes.

Study 304, Part 1 (open inguinal herniorrhaphy)
Part 1 of this study evaluated whether alternating or concurrent non-opioid MMA, in combination with intra-operative Zynrelef administration (300 mg/9 mg), resulted in a larger proportion of subjects not requiring a post-operative opioid prescription. To mimic real-world clinical situations, subjects in this study were discharged per investigative site standard practice versus remaining at the facility for 72 hours. Part 2 of the study, which is on-going, is evaluating the proportion of subjects who do not require a post-operative opioid prescription after administration of a single intra-operative dose Zynrelef in combination with a post-operative MMA regimen.

Part 1 of the study has concluded, an interim synopsis report was submitted, and is the focus of this discussion. Subjects in both cohorts in Part 1 received one pre-operative dose of ibuprofen and acetaminophen and intra-operative Zynrelef. In Cohort 1, subjects also received post-operative ibuprofen and acetaminophen during waking hours only (versus round-the-clock). Subjects in Cohort 2 received ibuprofen and acetaminophen together (at the same time) post-operatively during waking hours only. Ninety- six subjects have been randomized and 92 have completed the study through Day 29.

There did not appear to be any subject who experienced LAST; however, there were subjects who reportedly experienced dizziness, and one subject each who experienced hypotension and tinnitus. Because only the interim study synopsis for Part 1 was available for review at the time of completion of this summary review, individual subject data was not analyzed. Regarding wound-related adverse events, there was one subject who developed a moderate post-operative wound infection on Day 4, which resolved on Day 10. Similarly, subject-level data was not available for review. There were reportedly no NSAID-related cardiovascular, renal, or GI adverse events reported to date for subjects in Part 1. In the Safety Update, received November 12, 2020, with the second NDA resubmission, there was one subject in Part 2 of this study who reportedly had the serious adverse event (SAE) of peptic ulcer hemorrhage requiring esophagogastroduodenoscopy with cauterization and hospitalization.

The investigator felt this was likely related to the NSAID MMA, but unrelated to Zynrelef administration.

Study 306 (TKA)

This study evaluated analgesia following one of two doses of Zynrelef (400 mg/12 mg or 300 mg/9 mg) in combination with different non-opioid MMA regimens, including additional bupivacaine HCl administration. There were four cohorts, three evaluated acetaminophen and celecoxib then ibuprofen, and one evaluated acetaminophen and ibuprofen. Subjects in all cohorts also received acetaminophen, celecoxib, and pregabalin pre-operatively, and tranexamic acid and acetylsalicylic acid (ASA) post-operatively. The primary objective of the study was to evaluate post-operative analgesia with Zynrelef as part of an MMA following TKA. All 116 subjects treated completed the study. Safety data for the first three cohorts were presented in the previous safety updates submitted with the two NDA resubmissions. At the time of completion of this summary review, the study was completed, but only the preliminary synopsis report was available. A thorough safety review for all treated subjects will be performed once the final study report has been submitted.

In Cohort 4, treated subjects received the maximum recommend dose of Zynrelef, 400 mg/12 mg, in combination with MMA. There were LAST-related adverse events reported in this cohort; however, for several events there did not appear to be a temporal relationship (e.g., tachycardia on Day 7), and for others the serum bupivacaine level did not support a LAST-related event (e.g., dizziness). Only one subject with a LAST-related adverse event had a serum bupivacaine level of >1000 ng/mL; however, the timing of the event and the relatively high serum bupivacaine level did not correlate. Specifically, left hand twitching was noted three hours post-dose and recovered by 20 hours post-dose. Reported serum bupivacaine levels were 404 ng/mL, 570 ng/mL, and 1210 ng/mL (C_{max}) at two, four, and 48 hours post-dose, respectively. In response to an Information Request dated November 8, 2021, the Applicant clarified that there were a total of 14 subjects with bupivacaine levels greater than 1000 ng/mL; 12 subjects in Cohorts 1 and 4 who received Zynrelef 400 mg/12 mg and two subjects in Cohort 3 Group B who received Zynrelef 300 mg/9 mg + bupivacaine HCl. Of these 14 subjects, only one had a potential LAST-related adverse event, described above.

With respect to wound healing in Cohort 4, 90% of treated subjects had normal healing reported at their last assessment. One subject had a mild post-operative wound infection which began on Day 22 and resolved on Day 52, and was unlikely related to study drug treatment.

Regarding NSAID-related adverse events, there were no GI events reported for Cohort 4. As previously noted in the CDTL/DD Summary Review completed during the third review cycle (dated May 12, 2021), there was one subject in Cohort 2, who received Zynrelef 400 mg/12 mg and developed gastritis requiring hospitalization, and one subject in Cohort 3 who developed hematemesis. The investigator felt the gastritis was related to the post-operative MMA regimen and ASA versus the meloxicam component of Zynrelef, and the hematemesis was related to pre-operative comorbid conditions (i.e., history of bleeding ulcer, chronic alcohol use, gastroesophageal reflux disease). There were reports of hypertension in two subjects in this cohort, but no specific NSAID-related cardiac adverse events. There were no NSAID-related renal adverse events reported in this cohort.

Study 220 (caesarean delivery)
This is an ongoing study evaluating the PK, in both breast milk and blood, and safety of two different doses of Zynrelef, 400 mg/12 mg and 300 mg/9 mg, in women undergoing caesarean delivery under ropivacaine spinal anesthesia. At the time of this review, there were no subjects who reportedly experienced potential LAST- or wound-related adverse events. Two subjects had SAEs; gestational hypertension in one subject, and pneumonia and congestive cardiac failure in the other. Given the premorbid medical conditions, the investigator concluded they were unrelated to the administration of Zynrelef.

Summary / Conclusion
The data from these five open-label studies suggest that there is a low risk of LAST-, wound-, or NSAID-related adverse events with administration of Zynrelef in doses up to 400 mg/12 mg in the evaluated procedures. Wound-related adverse events appear to be primarily limited to the bunionectomy procedure, a surgical wound known to have potential healing concerns due to the limited blood supply to the distal foot and toes. The GI-related adverse events were rare and more likely related to the MMA regimen involving ibuprofen versus the meloxicam component of Zynrelef. Because these studies were open-label and all subjects received a dose of Zynrelef, definitive safety conclusions are challenging; however, the data do support the previous conclusions regarding the acceptable safety profile. Additionally, while these studies were conducted to evaluate various MMA regimens in combination with a single intra-operative dose of Zynrelef, and not to explicitly support expansion of the labeled indications, the additional safety data support the favorable benefit:risk assessment of Zynrelef, and, based on similarities in surgical site characteristics, can be extrapolated to closely related procedures. Due to the limitations on drawing conclusions from open-label studies, and because these five open-label studies provided additional supportive information to demonstrate safety, descriptions of these studies have not been added to the labeling for the expanded indication.

Risk of Chondrolysis Due to Articular Cartilage Exposure to Zynrelef
During discussions with Heron regarding expansion of the indication to closely related foot and ankle procedures, the Division expressed concern regarding the risk of chondrolysis when Zynrelef is administered to articular cartilage. The Division was particularly concerned about this risk during the proposed closely related ankle fracture repair. There was less concern regarding phalangectomy, foot fracture repair, and ankle arthrodesis either because the procedure was considered very similar to bunionectomy (phalangectomy, foot fracture repair) such that exposure to articular cartilage and the risk of chondrolysis would be similar between procedures, or because the procedure likely involves removal of articular cartilage and fusion of the joint (ankle fusion), such that there is negligible risk. Heron contends that the risk of chondrolysis after administration of Zynrelef during all closely related foot and ankle procedures is low for four main reasons.

First, there were no reports of chondrolysis during the three studies conducted in subjects undergoing bunionectomy (Studies 208, 301, and 218), where Zynrelef was administered directly into the joint space of the first metatarsophalangeal joint, and exposure to articular cartilage would have been extensive. Heron contends that exposure of articular cartilage to the same dose of Zynrelef (i.e., 60 mg/1.8 mg) is likely to be lower in the proposed closely related

foot and ankle procedures, where exposure will generally be due to drug seepage versus direct administration. Second, the proposed closely related procedures are similar to bunionectomy in anatomic location, tissue type, length and depth of the surgical area, and vascularity of the surgical site, such that more extensive exposure of articular cartilage to Zynrelef is unlikely. Third, Heron states that the risk of chondrolysis during ankle fracture repair is low based on data suggesting that bupivacaine-induced chondrolysis appears to be dose-dependent, such that the small amount of Zynrelef that may reach the ankle joint is unlikely to cause chondrolysis. And fourth, the highest recommend dose of Zynrelef (i.e., 400 mg/12 mg) was demonstrated to be safe in TKA, which is arguably one of the most extensive orthopedic procedures performed.

The Division agrees with Heron that the risk of chondrolysis in closely related foot and ankle procedures appears low; however, because the risk may not be negligible and additional nonclinical data are needed, the Division recommends inclusion of the proposed cautionary statement in the label informing the prescriber to limit exposure to articular cartilage if possible. Additionally, the Division recommends that juvenile animal studies address the risk of possible adverse impacts on the growth plate prior to initiation of studies conducted to support an expanded indication for foot and ankle procedures in pediatric subjects.

Safety Data Reviewed in Support of the Initial NDA and Resubmissions
The review of safety data included in the initial NDA submission and the two subsequent safety updates (included in the NDA resubmissions) focused on the occurrence of LAST-related adverse events, and wound-related adverse events specifically in subjects who underwent bunionectomy.

LAST-Related Adverse Events
As noted in the primary clinical review completed during the first review cycle, there did not appear to be a clinically significant increased incidence in potential LAST-related adverse events in patients treated with Zynrelef 300 mg/9 mg undergoing open inguinal herniorrhaphy, or in patients treated with Zynrelef 400 mg/12 mg undergoing TKA, bilateral augmentation mammoplasty, or abdominoplasty, compared to patients treated with saline placebo or bupivacaine HCl. There were small and inconsistent differences across treatment groups that were not clinically meaningful, particularly in the setting of concomitant administration of general anesthesia, which can confound the detection of LAST. Subjects undergoing TKA in Study 209 had the highest individual C_{max} values. Specifically, there were 10 subjects with C_{max} values greater than 1000 ng/mL (the concentration above which the Division generally believes the risk of LAST increases) and six had time of maximum concentration (T_{max}) later than 24 hours' post-operatively. The Division concluded there did not appear to be an increased incidence in LAST-related adverse events in these subjects compared to subjects with C_{max} values less than 1000 ng/mL.

As noted in Table 3 in Section 5 of this review, the highest mean C_{max}, 710 ng/mL, was reported in Study 211 in subjects undergoing bilateral augmentation mammoplasty and five subjects had C_{max} values greater than 1000 ng/mL with the latest reported T_{max} approximately six hours. There did not appear to be an increased incidence of LAST-related adverse events reported for these subjects. There did appear to be an overall increased incidence of the LAST-related adverse events of hypotension, dysgeusia, and bradycardia in Zynrelef-treated subjects

compared to those treated with saline placebo or bupivacaine HCl in this study; however, the highest incidence of LAST-related adverse events was reported in the exploratory Zynrelef 240 mg/7.2 mg treatment group, and not the Zynrelef 400 mg/12 mg treatment group. In Study 203, conducted in patients undergoing complete abdominoplasty, there were no reported C_{max} values greater than 1000 ng/mL.

As discussed in the CDTL/DD Summary Review dated May 12, 2021, there were no subjects in any study who received Zynrelef alone and had C_{max} values greater than 2000 ng/mL, the concentration reported in the published literature above which the risk of LAST-related adverse events increases, at any measured time point. However, there was one subject in Study 209 who received Zynrelef 400 mg/12 mg plus ropivacaine and had a C_{max} value of 2810 ng/mL. This subject experienced mild tachycardia around the time of T_{max} (approximately 8 hours) that lasted until Day 29. The investigator considered this event unlikely related to study drug administration based on the duration of tachycardia. This subject also experienced three ventricular beats 26 hours post-dose, with a reported serum bupivacaine level of 2500 ng/mL at 24 hours post-dose, the sample time closest to the reported event. There were no other cardiac conduction abnormalities reported from Holter monitoring. Mild dizziness was also reported as an adverse event, but occurred on Days 24 through 26; therefore, considered to be unlikely related to study drug administration. Ropivacaine levels were also assessed and reported to be less than those commonly associated with toxicity (2200 ng/mL); i.e., 843 ng/mL at two hours and 171 ng/mL at 24 hours post-dose. While the cardiac signs may have been related to the relatively high bupivacaine levels, the events were considered mild and resolved by the end of the study with no long-term complications.

There were subjects who experienced what could have been considered LAST-related adverse events throughout clinical development; however, it is challenging to identify such events, particularly neurologic-related adverse events, in subjects also receiving general anesthesia, particularly in open-label studies without a blinded comparator treatment. Interestingly, based on the preliminary data from 18 subjects undergoing caesarean delivery under spinal anesthesia in Study 220, there were no reports of potential LAST-related adverse events. This suggests that the concomitant administration of general anesthesia may have a greater than previously suspected impact on the detection and subsequent incidence of adverse events reported to be potentially related to bupivacaine toxicity.

Based on the totality of the safety and PK data, the overall risk of development of LAST due to administration of the three doses of Zynrelef is low and does not adversely impact the benefit:risk assessment for this product.

Wound-Related Adverse Events

Regarding the risk of local inflammatory and wound-related adverse events, there did appear to be an increased incidence of wound-related adverse events primarily observed in patients undergoing bunionectomy in the Phase 3 study, 301, and the Phase 2a study, 208. However, the Division concluded, during the previous review cycles, that Zynrelef could be approved for this indication, for five reasons.

First, the Division agreed with the Applicant that leakage of excess Zynrelef from the relatively small bunionectomy wound potentially contributed to the development of local inflammatory changes in the short-term (less than 42 days) by interrupting the approximation of wound edges, resulting in an increased risk of adverse events. The Division felt this risk could be adequately mitigated by language in the drug product label, advising clinicians to administer only as much HTX-011 as is necessary to coat the exposed tissues. Results from Study 218, conducted in subjects undergoing bunionectomy who received individualized dosing, are discussed in the section regarding data from studies conducted subsequent to the initial NDA submission. Second, the Division concluded that the majority of wound-related adverse events were mild, of relatively short duration, and resolved by the end of the study. Third, there were no reported cases of osteomyelitis in any patient who underwent a bunionectomy, suggesting that while there may be an increased incidence in short-term soft tissue adverse events, they do not appear to result in adverse effects on the underlying boney structures. Of the low number of reported boney changes, such as malunion, there did not appear to be clinically meaningful differences between treatment groups and several cases were associated with trauma (e.g., stubbed operative toe). Fourth, because the conditions under which clinical studies are conducted may not represent standard clinical practice, it is possible that the surgical wounds may have been over-graded and reported as impaired healing. And lastly, the reported incidences of wound-related adverse events appeared to be consistent with reports in the published literature in patients undergoing bunionectomy.

Regarding the safety profile of Zynrelef in soft tissue surgical models, there did not appear to be an increased incidence of clinically significant wound-related adverse events in patients undergoing open inguinal herniorrhaphy, the only indicated soft tissue surgical procedure. In Study 203, conducted in patients undergoing complete abdominoplasty, there was an increased incidence of wound dehiscence in patients treated with HTX-011 300 mg/9 mg administered via a combination of injection and instillation, which may have been due to disruption of the posterior rectus plication and umbilicus repositioning. The Division concluded that the risk of this adverse event could be mitigated by language in the drug product label, including limited indicated surgical procedures and route of administration, instillation, not injection or infiltration.

Safety Conclusions

During review of the initial NDA submission and two resubmissions, the Division concluded that the clinical benefits of Zynrelef administration during bunionectomy, open inguinal herniorrhaphy with mesh, and TKA outweigh the clinical risks discussed. The Division noted that a main advantage of Zynrelef over other currently available bupivacaine products is the proposed route of administration, instillation, using a needle-less Luer lock syringe and a unique cone-shaped applicator. Because a needle is not used for administration, the risk of inadvertent intravascular administration and catastrophic LAST is minimal, thereby increasing the margin of safety for this bupivacaine-containing product. Increased intravascular and systemic absorption are still possible in the setting of large doses or administration in areas of increased vascularity; however, these risks are mitigated by the Limitations of Use statement included the prescribing information.

Expansion of labeled indications for Zynrelef to lower extremity total joint arthroplasty procedures would include total hip arthroplasty (THA), a procedure not evaluated during clinical development. The Division was initially concerned about the acceptability of extrapolation of data from studies conducted in TKA to subjects undergoing THA. Based on internal conversations with two orthopedic surgeons in the Center for Devices and Radiological Health (CDRH), however, it appears there is no reason to believe that the PK and safety (and efficacy) data from TKA would be clinically significantly different and not able to be extrapolated to THA. Specifically, Drs. Neil Barkin and Marc DeHart confirmed that TKA is considered a more vascular and painful procedure than THA, suggesting that the systemic exposure to bupivacaine is likely higher during TKA than THA, and potentially postsurgical pain may be less.

Based on the acceptable safety profile demonstrated in the totality of clinical studies conducted in five diverse surgical models (i.e., bunionectomy, open inguinal herniorrhaphy, TKA, bilateral augmentation mammoplasty, and abdominoplasty) and the ongoing study in subjects undergoing caesarean delivery, the Division has no concerns regarding the extrapolation of safety data to the proposed closely related procedures. It appears unlikely that a new safety signal would be identified when Zynrelef is administered during procedures with surgical site characteristics similar to those explicitly evaluated in clinical studies. Therefore, the Division agrees with the Applicant that the totality of the safety data, including information in the initial NDA submission, the two NDA resubmissions, and this sNDA, are adequate to support expansion of the labeled indications to include closely related foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty procedures.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for review of the initial application or this supplemental application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

With the approval of Zynrelef on May 12, 2021, the following clinical and nonclinical post-marketing requirements (PMRs) were issued.

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.
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.
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.
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.

A draft protocol for Study HTX-011-216 was submitted on September 11, 2018, which proposed to evaluate the safety, efficacy, and pharmacokinetic profiles of HTX-011 in pediatric patients 3 to less than 17 years of age. The draft protocol was reviewed, comments provided to the Applicant, and the final study protocol was submitted on December 28, 2018. On May 8, 2020, the Applicant submitted revised clinical (and nonclinical) study timelines based on an inability to enroll patients for the 72-hour in-patient stay, COVID-19 pandemic-related delays, and slow enrollment for older children requiring inguinal hernia repair. There were several communications with the Applicant regarding an acceptable duration of in-patient monitoring. The Division proposed, and the Applicant agreed, that the first 12 subjects in Cohort 1, Part A of the study be monitored in-patient for at least 60 hours postoperatively to obtain safety data and to establish an adequate PK profile. If the data for all 12 subjects indicates that T_{max} occurs before 48 hours, subjects treated in Cohort 1, Part B may be discharged after 48 hours.

As discussed during the teleconference on September 28, 2021, under the Pediatric Research Equity Act (PREA) the Applicant was required to submit an initial pediatric study plan (iPSP) for the closely related procedures proposed in adult patients to support sNDA #1. An iPSP was received on October 14, 2021, which included the following information.

(b) (4)

The Division had the following two concerns with the proposed iPSP. First, (b) (4) The Division agrees that extrapolation of efficacy data for locally-acting products, such as local anesthetics, from adults to subjects two years of age and older is acceptable in most instances.

The Division does not agree, however, that (b) (4)

The Division also notes Heron's reference in the iPSP to the recent public workshop hosted by FDA entitled, *Public Workshop: Analgesic Clinical Trial Designs, Extrapolation, and Endpoints in Patients From Birth to Less Than Two Years of Age.* Because no final decisions have been made regarding changes in the regulatory requirements for clinical studies in subjects (b) (4), the Division does not believe information discussed during this workshop supports Heron's position that (b) (4)

During the internal meeting with the Pediatric Review Committee (PeRC) held on November 2, 2021, there was agreement that PK, safety, and efficacy must be evaluated in pediatric subjects from birth to less than three years of age undergoing foot and ankle procedures, assuming that the juvenile animal data support the safe administration of Zynrelef in this population as it relates to the growth plate in developing bones and chondrocyte function. PeRC and the Division agreed that the (b) (4) the (b) (4).
Comments were sent to the Applicant regarding their proposed iPSP. They accepted all recommendations and agreed to conduct a study in pediatric subjects from birth to less than three years of age undergoing foot and ankle procedures.

PeRC recommended four clinical post-marketing requirements be issued with approval of this sNDA. Refer to Section 13 of this review for additional information on the specific PMRs.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues that needed to be addressed during review of this efficacy supplement.

12. Labeling

Zynrelef was approved on May 12, 2021, for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty in adults. As previously discussed, the Applicant did not agree with the Division's (b) (4).

ZYNRELEF contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), and is indicated 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.

Based on the limited number of foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty procedures and the fact that surgeons can determine whether the procedure being performed falls into one of those three general categories, the Division (b) (4) however, ultimately decided that including the information in Section 2.4 Dosing Instructions, with the three evaluated procedures as example procedures, is more appropriate.

To ensure all relevant safety information for Zynrelef is included in promotional materials, the review team in the Office of Prescription Drug Promotion advised that the proposed cautionary statement regarding Zynrelef administration to articular cartilage be elevated to a warning in Section 5. Therefore, the Division included it in the existing chondrolysis warning, subsection 5.10.

5.10 Chondrolysis
Limit exposure to articular cartilage due to the potential risk of chondrolysis.

Additional edits were made throughout the label to correct misspellings, and grammatical and punctuation errors, and to clarify drug interactions in Section 7.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit:Risk Assessment
The Applicant has provided adequate justification to support extrapolation of pharmacokinetic, safety, and efficacy data to procedures considered closely related to those explicitly evaluated during clinical development. The benefit:risk assessment for the use of Zynrelef in closely related procedures is favorable, and the application is approvable.

Post-Marketing Requirements (PMRs)
PREA applies to this NDA; therefore, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing in pediatric subjects. The following clinical pediatric PMRs will be issued to support expansion of the labeled indications in the pediatric population.

- 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: December 2021
  Study Completion: December 2025 (same date as PMR 4059-1)
  Final Report Submission: May 2026 (same date as PMR 4059-1)

  This PMR may be satisfied with studies conducted in pediatric subjects undergoing unilateral open inguinal herniorrhaphy.

- 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: February 2025
  Final Protocol Submission: August 2025
  Study Completion: April 2028 (same date as PMR 4059-2)
  Final Report Submission: October 2028 (same date as PMR 4059-2)

  This PMR can be satisfied with studies conducted in pediatric subjects undergoing unilateral open inguinal herniorrhaphy.

- 4059-8: 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 foot and ankle procedures.
  Draft Protocol Submission: July 2022
  Final Protocol Submission: January 2023
  Study Completion: June 2027
  Final Report Submission: December 2027

- 4059-9: Conduct a multicenter study to evaluate the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric patients from birth to less than 3 years of age undergoing foot and ankle procedures.
  Draft Protocol Submission: August 2027
  Final Protocol Submission: February 2028
  Study Completion: February 2031
  Final Report Submission: August 2031

(b) (4)

14. Comments to the Applicant

None.

15. References

None.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

RENEE L PETIT-SCOTT
12/08/2021 11:18:23 AM

ALLA T BAZINI
12/08/2021 11:19:40 AM

RIGOBERTO A ROCA
12/08/2021 11:40:50 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA SUPPLEMENT REVIEW

Application number:	211988/S-005 (Efficacy)
Supporting document/s:	219
Applicant's letter date:	9/29/2021
CDER stamp date:	9/29/2021
Product:	Zynrelef (bupivacaine and meloxicam)
Indication:	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
Applicant:	Heron Therapeutics, Inc.
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Pharm/Tox Division:	Division of Pharm/Tox for Neuroscience (DPT-N)
Reviewer:	Jaime D'Agostino, PhD
Supervisor/Team Leader:	Jay H. Chang, PhD
Clinical Division Director:	Rigoberto Roca, MD
Project Manager:	Rita Joshi, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211988 are owned by Heron Therapeutics or are data for which Heron Therapeutics has obtained a written right of reference.
Any information or data necessary for approval of NDA 211988 that Heron Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 211988.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The Applicant, Heron Therapeutics, submitted an NDA for Zynrelef on 9/21/2018, which was approved following two resubmissions on 5/12/2021 for the indication of "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". The approval included two nonclinical Pediatric Research Equity Act (PREA) Post Marketing Requirements (PMRs) to conduct the following: 1) a juvenile animal study to address the impact of DMSO on the developing brain to support clinical studies in pediatric patients under three years of age and 2) a juvenile animal study to characterize the impact of meloxicam on the developing kidney, liver, lung, and testes to support clinical studies in pediatric patients under two years of age.

In this submission, the Sponsor has submitted an efficacy supplement to expand the indication to "for soft tissue of 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". No new nonclinical information was provided with this submission and no changes were made to the nonclinical portions of the label. As such, the nonclinical team defers to the clinical team regarding the acceptability of expanding the clinical indication.

As part of the submission, the Sponsor submitted an initial Pediatric Study Plan (iPSP), which included a (b) (4) In addition, the Sponsor has proposed (b) (4) since there is clinical information indicating that bupivacaine and other local anesthetics have a potential to cause chondrolysis. The Sponsor's proposals were discussed at a Pediatric Review Committee meeting held on 11/2/2021. During the meeting, a particular concern for potential adverse effects on the growth plates in pediatric patients was identified by a pediatric orthopedic surgeon, emphasizing the need for nonclinical juvenile testing prior to the clinical studies. Thus, if the efficacy supplement is approved, we recommend that a nonclinical study be performed as a post-marketing requirement to evaluate the potential for Zynrelef to cause chondrolysis in juvenile animals prior to conducting clinical pediatric studies in children 0 to <17 years of age.

1.3 Recommendations

1.3.1 Approvability

There is no new nonclinical information or changes to the nonclinical information in the label. We defer to the clinical team regarding the approvability of the efficacy supplement.

1.3.2 Additional Nonclinical Recommendations

If the NDA supplement is approved, the following study is recommended as a post-marketing requirement:

- 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 0 to <17 years of age.

1.3.3 Labeling

None.

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/

JAIME R D'AGOSTINO
11/22/2021 01:16:04 PM

JAY H CHANG
11/22/2021 03:01:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA:	211988; Supplement 005
Submission Date	09/29/2021; 10/14/2021
Link to EDR	\\CDSESUB1\evsprod\NDA211988\0101 \\CDSESUB1\evsprod\NDA211988\0104
Submission Type; Code:	Efficacy supplement for expanded indication to closely related procedures
Brand Name:	ZYNRELEF
Generic Name:	Bupivacaine (2.5% bupivacaine base) and Meloxicam (0.075%)
Formulation; Strength(s):	ZYNRELEF® (Bupivacaine and Meloxicam) Extended-Release Solution
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Neuropsychiatric Pharmacology (DNP)
OND Division:	Division of Anesthesiology, Addiction Medicine, Pain Medicine
Sponsor:	Heron Therapeutics, Inc.
Current approved indication	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. Limitations of Use • Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.
Proposed indication:	ZYNRELEF is indicated 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. Limitations of Use • Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.
Dosage Regimen:	Single dose by instillation

1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information submitted on 09/29/2021 and 10/14/2021 in the current supplemental NDA 211988 S005 to expand the indication for Zynrelef to other closely related procedures to three currently approved procedures approved in the NDA. For this supplemental NDA, no new clinical pharmacology information is submitted, and no changes were proposed to section 12.3 and other clinical pharmacology related sections of the label by the applicant. For the expanded indications in closely related procedures, the review team has added additional language relating to PK and effectiveness to clinical studies sections, 14.1, 14.2 and 14.3. When this review is finalized, the drafted labeling language is still under discussion. The finalized language may be referred in the label. From a clinical pharmacology perspective, the submitted information in this supplemental NDA is acceptable.

1.2 Regulatory Background

The NDA 211988 for Zynrelef (bupivacaine and meloxicam) extended-release solution, was approved on May 12, 2021 for soft tissue or periarticular instillation in adults to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty. The dosages of Zynrelef approved of each of the procedures were as follows:

- Bunionectomy: up to 2.3 mL to deliver 60 mg./1.8 mg
- Open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg/9 mg
- Total knee arthroplasty: up to 14 mL to deliver 400 mg/12 mg

Post-Action Type C Guidance Meeting:

The Applicant's plan to expand the indications of Zynrelef, and in this regard, (b) (4) supplemental NDAs (e.g., sNDA #1 (b) (4) was discussed in a post action Type C guidance meeting held on 09/14/2021. (b) (4), the current supplemental NDA, 005, (b) (4) (herein after also referred to as sNDA #1 in the review). The Applicant (b) (4) can be found in Post-Action Meeting Minutes in DAARTS dated 10/08/2021.

In the post-action meeting, it was agreed that for sNDA #1, no new clinical pharmacology information will be submitted by the Applicant. Hence, the Applicant has not submitted new clinical pharmacology information for the current sNDA #1. (b) (4) The details of these studies and their status of completion are shown in the Table 1.

Table 1: Future studies (b) (4)

Procedure	Study # Phase	Dose	Status	PK
Bunionectomy	HTX-011-218 P2	up to 60 mg/1.8 mg	Complete	Yes (full PK)
Lumbar laminectomy	HTX-011-221 P2	200 mg/6 mg	Planned	Yes (full PK)
Herniorrhaphy with multimodal analgesia (MMA)	HTX-011-215 P2	300 mg/9 mg	Complete	No
	HTX-011-304 P3	300 mg/9 mg	Ongoing	No
Total knee arthroplasty with MMA	HTX-011-306 P3	300 mg/9 mg and 400 mg/12 mg	Complete	Yes (full PK)
C-Section	HTX-011-220 P2	300 mg/9 mg and 400 mg/12 mg	Ongoing	Yes (full PK)
Multiple surgeries with MMA (Total shoulder arthroplasty, Abdominoplasty)	HTX-011-401 P4	400 mg/12 mg	Planned	Yes (full PK)
(b) (4)		NA	Ongoing	NA

NA: Not applicable

In the Post-Action Meeting, the discussions with the Applicant were held with respect to PK dose-linearity assessment across surgical procedures, and (b) (4) which were elucidated briefly below.

PK dose-linearity assessment:

- In the Post-Action Meeting materials, the Applicant has evaluated the PK dose-linearity of bupivacaine from Zynrelef across all evaluated surgical procedures (bunionectomy, herniorrhaphy, total knee arthroplasty and augmentation mammoplasty) and tried to show that bupivacaine systemic exposure increases linearly with increasing Zynrelef dose across all surgical procedures. It is noted that these surgical procedures were different in terms of anatomic location, length and depth of the incision, and vascularity of the surgical site. In addition, there were some issues with the data used for the linearity assessment analyses by the Applicant, which were pointed-out in detail in the preliminary meeting comments to the Applicant.
  With regards to this dose-linearity assessment, in the meeting, clinical pharmacology team informed the Applicant that, it is not reasonable to pool PK data across all evaluated procedures because they are completely different in terms of vascularity, incision size, etc., but stated that it may be acceptable to pool data from closely related procedures. In the studies evaluated in the original NDA, we noticed, that within the same surgical procedure, the PK dose-linearity for both bupivacaine and meloxicam of ZYNRELEF was observed with two doses (a low dose and a high dose) evaluated separately in bunionectomy (60 mg /1.8 mg and 120 mg/3.6 mg) and herniorrhaphy (200 mg/ 6 mg and 400 mg/12 mg) surgical procedures. Specifically, the doubling of dose within these surgical procedures have shown doubling of systemic exposure of both bupivacaine and meloxicam. The details of these analyses can be found in the NDA clinical pharmacology review, dated 04/10/2019.
  In the meeting, the clinical pharmacology team, based on the observed data in the NDA, also substantiated the discussion that the PK profile for Zynrelef is different depending on the procedure, and therefore, not recommended to pool data from different procedures. The clinical pharmacology team further commented that,

mathematically, having the R^2 value close to 1 (i.e., 0.8 or 0.9) across all procedures does not necessarily translate to dose proportionality across all procedures because the PK profiles are different. For example, for the three procedures in which the same bupivacaine/meloxicam (400 mg/12 mg) dose was evaluated, the AUC and Cmax values were different, which does not support dose proportionality. As can be noted above in Table 1, the Applicant is conducting additional studies, with obtained data from the studies (b) (4) The clinical pharmacology team stated that (b) (4)

(b) (4):

- In the Post-Action Meeting materials, the Applicant also provided preliminary data on (b) (4). The Applicant provided the information from the literature and data from some patients on increased levels of (b) (4) in the setting of surgical trauma. The Applicant hypothesized that increase in (b) (4) concentration post-surgery leads to a higher fraction of (b) (4). In theory, the concept may be agreeable. However, based on the preliminary review of the information provided in the meeting package, the clinical pharmacology team did not agree with the Applicant's conclusion that increases in (b) (4) provided exclusive protection from the development of LAST-related symptoms. In this regard, the clinical pharmacology team provided detailed reasons in the preliminary comments of the meeting package. During the meeting, the Applicant agreed and mentioned that, (b) (4), therefore, (b) (4)

1.3 The Current Submission:

For this supplemental NDA 005 (sNDA#1), no new clinical pharmacology information is submitted, and no new changes were proposed to section 12.3 and other clinical pharmacology related sections of the label.

The dosage for other closely related procedures for each of the approved procedures is similar to the currently approved procedures. The Applicant proposes the following dosing instructions for the procedures:

- For foot and ankle surgical procedures, such as bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam

- For small-to-medium open abdominal surgical procedures, such as open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam
- For lower extremity total joint arthroplasty surgical procedures, such as total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam

The bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty procedures have already been approved, and the sponsor plans to expand the indication to other closely related procedures, respectively. The examples of the closely related procedures to each of the approved procedures provided by the Applicant, namely, foot and ankle, small-to-medium open abdominal and lower extremity total joint arthroplasty procedures, are shown below in Table 2, 3 and 4, respectively. It is noted that these example procedures are not presented in the Zynrelef label. For additional details for these procedures, refer to the clinical team's review.

Table 2: Examples of foot and ankle surgical procedures closely related to bunionectomy

Surgical Procedure	Tissue Type	Wound Size	Vascularity	ZYNRELEF Administration	Approximate Adult Dose	Surgical Specialty
Bunionectomy	*Bony*	*Small*	*Low*	*Periarticular instillation*	*Up to 60 mg/1.8 mg (2.3 mL)*	*Podiatrist or Orthopedic surgeon*

(b) (4)

[redacted]

Table 3: Examples of small-to-medium open abdominal surgical procedures closely related to inguinal herniorrhaphy

Surgical Procedure	Tissue Type	Wound Size	Vascularity	ZYNRELEF Administration	Approximate Adult Dose	Surgical Specialty
Open inguinal hernia repair	*Soft tissue*	*Medium*	*Moderate*	*Soft tissue instillation*	*Up to 300 mg/9 mg (10.5 mL)*	*General surgeon*

(b) (4)

[redacted]

Table 4: Lower extremity total joint arthroplasty surgical procedures closely related to total knee arthroplasty

Surgical Procedure	Tissue Type	Wound Size	Vascularity	ZYNRELEF Administration	Approximate Adult Dose	Surgical Specialty
Total knee arthroplasty	*Bony*	*Large*	*Moderate to High*	*Periarticular instillation*	*Up to 400 mg/12 mg (14 mL)*	*Orthopedic surgeon*

(b) (4)

[redacted]

1.4 PK information for the Original NDA:

In the original NDA, the full PK profiles of Zynrelef is obtained from the following procedures/studies:

- Bunionectomy (dosage 60 mg./1.8 mg, Study HTX-011-208),
- Open inguinal herniorrhaphy (dosage 300 mg/9 mg, Study HTX-011-202 P2),
- Total knee arthroplasty (dosage 400 mg/12 mg, HTX-011-209),
- Augmentation mammoplasty (dosage 400 mg/12 mg, HTX-011-211) and
- Complete abdominoplasty (dosage 400 mg/12 mg, HTX-011-203).

Out of these procedures, during the Post-Action Meeting, the [redacted] (b) (4) the abdominoplasty procedure in a planned Study HTX-011-401. The obtained PK parameters of bupivacaine and meloxicam in these procedures (except [redacted] (b) (4)) is shown in the Table 5 and 6, respectively.

Table 5: PK parameters of bupivacaine following single dose Zynrelef (bupivacaine/meloxicam) administered by instillation (Phase 2 studies with full PK sampling).

Surgical Procedure	**Bunionectomy (Study 208)**	**Herniorrhaphy (Study 202)**	**Total Knee Arthroplasty (Study 209)**	**Augmentation Mammoplasty (Study 211)**
Dose (volume)	**60 mg/1.8 mg (2.1 mL)**	**300 mg/9 mg (10.3 mL)**	**400 mg/12 mg (13.7 mL)**	
N	17	16	53[a]	49
C_{max} (ng/mL)	54 ± 33	271 ± 147	695 ± 411	710 ± 246
AUC_{0-24} (h·ng/mL)	883 ± 538	4712 ± 2144	11223 ± 6142	11758 ± 3990
AUC_{0-48} (h·ng/mL)	1371 ± 910	9740 ± 5021	23580 ± 14035	19042 ± 6692
AUC_{0-72}(h·ng/mL)	1595 ± 1085	12980 ± 6687	30807 ± 20122 (n=50)	23563 ± 8192
AUC_{0-t} [b] (h·ng/mL)	1681 ± 1154	15174 ± 8545	35890 ± 28400	27363 ± 9227
AUC_{inf} (h·ng/mL)	1718 ± 1211	15524 ± 8921	38173 ± 29400 (n=50)	31072 ± 17998
Tmax	3 [1.55, 24]	18 [3, 30]	21 [4, 59]	4 [1, 35]
Clast (120 h) (ng/mL)	0.18 ± 0.14	10 ± 15	5 ± 20 [C]	35 ± 71
Half-life (h)	15 ± 8	16 ± 9	17 ± 7 (n=50)	25 ± 20

PK parameters values are arithmetic mean ± standard deviation, except for Tmax where it is median (minimum, maximum)

[a] In TKA study, HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). PK parameters of only HTX-011 without ropivacaine (N=53) are reported

[b] AUC_{0-t} is 0 to 120 h post-dose for all studies, expect for Study 209, where it is 240h post dose

[C] Conc at 144 h

Table 6: PK parameters of meloxicam following single dose Zynrelef (bupivacaine/ meloxicam) administered by instillation in surgical procedures (Phase 2 studies with full PK sampling).

Surgical Procedure	**Bunionectomy (Study 208)**	**Herniorrhaphy (Study 202)**	**Total Knee Arthroplasty (Study 209)**	**Augmentation Mammoplasty (Study 211)**
Dose (Volume)	**60 mg/1.8 mg (2.1 mL)**	**300 mg/9 mg (10.3 mL)**	**400 mg/12 mg (13.7 mL)**	
N	16	16	53 [a]	49
C_{max} (ng/mL)	26 ± 14	225 ± 96	275 ± 134	527 ± 149
AUC_{0-24} (h·ng/mL)	437 ± 250	2569 ± 855	3350 ± 1442	9034 ± 1924
AUC_{0-48} (h·ng/mL)	904 ± 516	6996 ± 2685	8926 ± 4102	17995 ± 4245
AUC_{0-72} (h·ng/mL)	1285 ± 745	11973 ± 4592	13483 ± 6625	24331 ± 6332
AUC_{0-t} [b] (h·ng/mL)	1621 ± 927	18721 ± 7923	19525 ± 12259	30499 ± 9460
AUC_{inf} (h·ng/mL)	2079 ± 1631	NR	25673 ± 17666 (n=35)	41808 ± 38413
Tmax	18 [8.13, 60]	54 [24, 96]	36 [12, 72]	20 [6, 49]
Clast (120 h) (ng/mL)	3 ± 3	85 ± 53	4 ± 10 [C]	76 ± 86
Half-life (h)	33 ± 36	NR	42 ± 37 (n=35)	42 ± 70

PK parameters values are arithmetic mean ± standard deviation, except for Tmax where it is median (minimum, maximum)

a In TKA study, HTX-011 was instilled with or without ropivacaine (0.5%, 50 mg). PK parameters of HTX-011 without ropivacaine (N=53) are reported

b AUC_{0-t} is 0 to 120 h post-dose for all studies, expect for Study 209, where it is 240h post dose
C Conc at 240 h
NR Not reported, since terminal elimination phase was not adequately characterized in sufficient number of patients

For detailed PK information of Zynrelef, the reader is referred to the clinical pharmacology reviews of the original NDA and the resubmission in DARRTS dated 04/10/2019 and 06/04/2020, respectively.

1.5 Labelling Comments.

No new labeling changes were proposed to the section 12.3 of the label by the Applicant.
For the expanded indications in closely related procedures, the review team has added additional language relating to PK and effectiveness to Section 14, Clinical Studies (14.1, 14.2 and 14.3). When this review is finalized, the drafted labeling language is still under discussion. The finalized language may be referred in the label.

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/

SURESH B NARAHARISETTI
11/23/2021 11:20:06 AM

YUN XU
11/23/2021 03:27:30 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

OTHER REVIEW(S)

Division of Anesthesiology, Addiction Medicine, and Pain Medicine

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 211988/ S005 (efficacy supplement)

Name of Drug: Zynrelef (bupivacaine and meloxicam) extended-release solution

Applicant: Heron Therapeutics, Inc.

Labeling Reviewed

Submission Date/Receipt Dates: September 29, 2021 (Initial efficacy supplement submission)
November 23 and November 30, 2021 (labeling discussions)
December 3, 2021 (final agreed labeling)

Background and Summary Description:

Zynrelef was originally approved on May 12, 2021, for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty in adults.

This sNDA proposes to expand the indication to closely related procedures: 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.

The following disciplines reviewed proposed changes and concluded that the proposed revisions are acceptable:

- Renee Petit-Scott, MD: Clinical; 12/8/2021 review in DARRTS
- Suresh Naraharisetti, PhD; Clinical Pharmacology: 11/23/2021 review in DARRTS
- Cameron Clark, PharmD; DMEPA: 10/21/2021 review in DARRTS
- Phillip Williams, PharmD; OPDP: 11/23/2021 review in DARRTS

Review

The proposed PI submitted on December 3, 2021 (most recent labeling) submission was compared to the approved labeling in the original NDA approved on May 12, 2021. Additions to the approved labeling are shown in underline, while deletions are shown in ~~strikethrough~~.

16 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

RITA K JOSHI
12/09/2021 01:47:55 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 11/23/2021

To: Rita Joshi, PharmD, Regulatory Project Manager
Division of Regulatory Operations, Neuroscience (DRO-N)

From: Phillip Williams, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZYNRELEF (bupivacaine and meloxicam) solution

NDA: 211988/S-005

In response to DAAP's consult request dated October 1, 2021, OPDP has reviewed the proposed prescribing information (PI), for ZYNRELEF (bupivacaine and meloxicam) solution. This submission (S-005) provides for expanding 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.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on September 30, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

37 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

PHILLIP A WILLIAMS
11/23/2021 10:49:20 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 20, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988/S-005
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 400 mg bupivacaine and 12 mg meloxicam 300 mg bupivacaine and 9 mg meloxicam 200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam
Applicant/Sponsor Name:	Heron Therapeutics Inc.
OSE RCM #:	2021-1937
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Heron submitted an efficacy prior approval supplement (PAS) received on September 29, 2021 to expand the indication for Zynrelef to the following:

- Use 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.

Subsequently, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Prescribing Information (PI) and Instructions for Use (IFU) for Zynrelef (Appendix A) for areas of vulnerability that may lead to medication errors.

2 CONCLUSION

Our evaluation of the proposed PI and IFUs did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDIX A. LABELING RECEIVED ON SEPTEMBER 29, 2021

Instructions for Use (Image not shown) can be accessed in EDR via the following link:

- \\CDSESUB1\evsprod\nda211988\0101\m1\us\draft-ifu-60-expand-indication-close-related-procedures.pdf
- \\CDSESUB1\evsprod\nda211988\0101\m1\us\draft-ifu-200-expand-indication-close-related-procedures.pdf
- \\CDSESUB1\evsprod\nda211988\0101\m1\us\draft-ifu-300-expand-indication-close-related-procedures.pdf
- \\CDSESUB1\evsprod\nda211988\0101\m1\us\draft-ifu-400-expand-indication-close-related-procedures.pdf

Prescribing Information (Image not shown) can be accessed in EDR via the following link:

- \\CDSESUB1\evsprod\nda211988\0101\m1\us\annot-draft-pi-expand-indication-close-related-proc-word.docx

---

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/

CAMERON D CLARK
10/20/2021 12:29:43 PM

VALERIE S VAUGHAN
10/21/2021 12:02:52 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 211988/S-005

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

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:

We have received your supplemental new drug application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 211988

SUPPLEMENT NUMBER: S-005

PRODUCT NAME: Zynrelef (bupivacaine and meloxicam) extended-release solution

DATE OF SUBMISSION: September 29, 2021

DATE OF RECEIPT: September 29, 2021

This supplemental application proposes 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.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 28, 2021, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

RESPONSIBILITIES UNDER TITLE VIII OF FDAAA AND 42 CFR PART 11

You are also responsible for complying with the applicable provisions of section 402(j) of the Public Health Service Act (PHS Act) [42 U.S.C. § 282(j)], including its implementing regulations in 42 CFR part 11. Section 402(j) of the PHS Act was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Unless you have delegated your responsibilities to another entity, you are the "responsible party" and are required to submit registration and results information for each "applicable clinical trial" to the ClinicalTrials.gov data bank, as provided by section 402(j) of the PHS Act and 42 CFR part 11.

As discussed during the teleconference held on September 28, 2021, you are planning to submit the following information to support the efficacy supplement received on September 29, 2021, for consideration of an expanded indication for Zynrelef.

- Summary of Clinical Safety, to include a summary of clinical pharmacology data to support extrapolation to closely related procedures, with emphasis on the systemic safety of Zynrelef.
- The required Amended initial Pediatric Study Plan, which will include a request for deferral of pediatric studies.

If you have questions, contact me at rita.joshi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rita K. Joshi, PharmD
Regulatory Project Manager
Division of Anesthesiology, Addiction Medicine,
and Pain Medicine
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/

RITA K JOSHI
10/06/2021 11:10:13 AM