CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211988Orig1s013

Trade Name:	ZYNRELEF
Generic or Proper Name:	bupivacaine and meloxicam extended-release solution, for instillation use
Sponsor:	Heron Therapeutics, Inc.
Approval Date:	01/23/2024
Indication:	ZYNRELEF is indicated in adults for postsurgical analgesia for up to 72 hours after: • soft tissue surgical procedures • orthopedic surgical procedures − foot and ankle procedures − other orthopedic surgical procedures (e.g., total joint arthroplasty) in which direct exposure to articular cartilage is avoided

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

APPROVAL LETTER

NDA 211988/S-013

SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

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

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

Dear Dr. Forbes:

Please refer to your supplemental new drug application (sNDA) dated and received December 23, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zynrelef (bupivacaine and meloxicam) extended-release solution.

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

This Prior Approval sNDA proposes the following changes:

- To expand the indication in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures.
- To revise the Limitation of Use statement to include large 4 or more level spinal procedures instead of large multilevel spinal procedures.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211988/S-013**." Approval of this submission by FDA is not required before the labeling is used.

RELEASE FROM POSTMARKETING REQUIREMENT

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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

4059-1 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients three to less than 17 years of age undergoing unilateral open inguinal herniorrhaphy.

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

4059-2 Conduct a multicenter study to assess the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric patients from birth to less than three years of age undergoing unilateral open inguinal herniorrhaphy.

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

4059-6 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and pharmacodynamic response of Zynrelef administered for postoperative analgesia in pediatric patients three to less than 17 years of age undergoing small-to-medium open abdominal procedures.

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

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

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

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

Draft Protocol Submission:	07/2022
Final Protocol Submission:	01/2023
Study Completion:	06/2027
Final Report Submission:	12/2027

4059-9 Conduct a multicenter study to evaluate the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric subjects from birth to less than 3 years of age undergoing foot and ankle procedures.

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred,or inapplicable.

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

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

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

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

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

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

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

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

4059-12 Conduct a multicenter study to assess the pharmacokinetics, safety, and efficacy of Zynrelef administered for postoperative analgesia in pediatric patients from birth to less than three years of age undergoing representative soft tissue and orthopedic surgical procedures.

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

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

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocols to your IND 125927, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information

[3] See the guidance for Industry Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019). https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, contact Sandy Truong, Regulatory Project Manager, at 301-796-5719 or sandy.truong@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
01/23/2024 04:16:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

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 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)	01/2024
Dosage and Administration (2.1, 2.3, 2.4)	01/2024
Warnings and Precautions (5.10)	01/2024

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

ZYNRELEF is indicated in adults for postsurgical analgesia for up to 72 hours after:

- soft tissue surgical procedures
- orthopedic surgical procedures
  - foot and ankle procedures
  - other orthopedic surgical procedures (e.g., total joint arthroplasty) in which direct exposure to articular cartilage is avoided *[see Warnings and Precautions (5.10)]*

Limitations of Use
Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large 4 or more level spinal, and head and neck procedures (1).

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

- ZYNRELEF is intended for single-dose administration only (2.1). Administer ZYNRELEF via instillation only.
- 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).

Risk of Joint Cartilage Necrosis and Degeneration with Unapproved Intra-articular Use: Animal studies evaluating the effects of ZYNRELEF following intra-articular administration in the knee joint demonstrated cartilage necrosis and degeneration (5.10, 13.2).

Chondrolysis: Limit exposure to articular cartilage due to the potential risk of chondrolysis (5.11).

Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use (5.12).

Serious Skin Reactions: NSAIDs, including meloxicam, can cause serious skin adverse reactions. If symptoms present, evaluate clinically (5.14).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): If symptoms are present, evaluate clinically (5.15).

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 (5.16, 8.1).

Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.17).

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

Most common adverse reactions (incidence ≥5%) are:
- Soft tissue procedures: vomiting (6.1).
- Orthopedic procedures: constipation 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: 01/2024

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 postsurgical analgesia for up to 72 hours after:

- soft tissue surgical procedures
- orthopedic surgical procedures
  - foot and ankle procedures
  - other orthopedic surgical procedures (e.g., total joint arthroplasty) in which direct exposure to articular cartilage is avoided *[see Warnings and Precautions (5.10)]*

Limitations of Use

Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large 4 or more level spinal, and head and neck procedures.

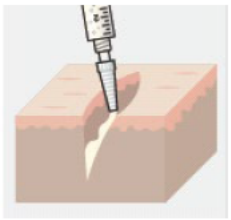
2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

ADMINISTER ZYNRELEF VIA INSTILLATION ONLY.

- ZYNRELEF should not be administered via the following routes.
  - Epidural
  - Intrathecal
  - Intravascular
  - Intra-articular *[see Warnings and Precautions (5.10), Nonclinical Toxicology (13.2)]*

  - Regional nerve blocks
  - Pre-incisional or pre-procedural locoregional anesthetic techniques.
- 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 (5.11)]*.
- 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 after placement of implant(s) (if applicable), 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 tying knots with monofilament sutures, contact with ZYNRELEF may cause knots to loosen or untie due to the viscosity of ZYNRELEF. In vitro studies showed an increase in elasticity with monofilament sutures exposed to ZYNRELEF with unknown clinical significance. Minimize administration of ZYNRELEF near the incision line and wipe off excess ZYNRELEF from the skin prior to suturing. Three (3) or more knots ending in a multi-throw knot (e.g., a Surgeon's knot) are recommended with monofilament sutures. Braided or barbed sutures are recommended, especially for closure of deeper layers.

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.
3. Prepare syringe by filling with air then attach to vented vial spike.
4. 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	Number of Syringes and LLAs* Per Dose	Volume to be Withdrawn
60 mg/ 1.8 mg	1	2.3 mL (using 3 mL syringe provided)
200 mg / 6 mg	1	7 mL (using 12 mL syringe provided)
300 mg/ 9 mg	1	10.5 mL (using 12 mL syringe provided)
400 mg/ 12 mg	2	14 mL (using two 12 mL syringes provided, 7 mL ZYNRELEF per syringe)

*LLA: Luer lock cone-shaped applicator

5. Repeat steps 1-3 for more than one syringe.
6. 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:
    - For soft tissue procedures, apply ZYNRELEF into the wound prior to closure of each layer within the surgical space.
        - For abdominal procedures, apply after closure of the peritoneum (if applicable) and avoid administration below the peritoneum.
    - In general for orthopedic procedures, apply ZYNRELEF into the wound and on the periosteum from the proximal to the distal ends of the wound (i.e., beyond the boney repair).
        - For total joint arthroplasty, apply ZYNRELEF directly into the joint capsule, onto the periosteum, and the antero-, medial-, and lateral tissues (if applicable), after placement of the component(s).
        - For spinal procedures, apply ZYNRELEF after closure of the paraspinal musculature and again after closure of the subcutaneous fascia. ZYNRELEF must not be applied to the dura or spinal cord.
2. Only apply ZYNRELEF to the tissue layers below the skin incision and not directly onto the subdermal layer or the skin. Minimize administration of ZYNRELEF near the incision line.
3. Use only the amount necessary to coat the tissues, such that ZYNRELEF does not leak from the surgical wound after closure. Wipe off excess ZYNRELEF from the skin prior to or during closure of the wound.

2.4 Dosing Instructions

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

- For soft tissue 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)]*;
  - abdominoplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam *[see Clinical Studies (14)]*;
  - Cesarean section: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam *[see Clinical Studies (14)]*;
  - augmentation mammoplasty: up to 7 mL per side to deliver total of 400 mg of bupivacaine and 12 mg of meloxicam *[see Clinical Studies (14)]*.
- For orthopedic 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)]*;
  - total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam *[see Clinical Studies (14)]*;
  - total shoulder arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam *[see Clinical Studies (14)]*;
  - 1- to 3-level spinal surgery: up to 7 mL to deliver 200 mg bupivacaine and 6 mg meloxicam *[see Clinical Studies (14)]*.

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, 5.14)]*.
- 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 postoperative 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 Risk of Joint Cartilage Necrosis with Unapproved Intra-articular Use

The safety and effectiveness of intra-articular use of ZYNRELEF in orthopedic surgical procedures other than for foot and ankle procedures have not been established, and ZYNRELEF is not approved for use via other intra-articular administration routes. Animal studies evaluating the effects of ZYNRELEF following intra-articular administration in the knee joint demonstrated cartilage necrosis and degeneration *[see Nonclinical Toxicology (13.2)]*.

5.11 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.

5.12 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.

5.13 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.

5.14 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)]*.

5.15 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.

5.16 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)]*.

5.17 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)]*.

5.18 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 have been associated with bupivacaine HCl or meloxicam and 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 (5.11)]*
- Methemoglobinemia *[see Warnings and Precautions (5.12)]*
- Exacerbation of Asthma Related to Aspirin Sensitivity *[see Warnings and Precautions (5.13)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.14)]*
- Drug Reaction with Eosinophilia and Systemic Toxicity (DRESS) *[see Warnings and Precautions (5.15)]*
- Fetal Toxicity *[see Warnings and Precautions (5.16)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.17)]*

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 1627 patients undergoing various surgical procedures across 14 clinical studies including 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, of whom 1183 received ZYNRELEF by instillation. Patients treated with ZYNRELEF ranged in age from 18 to 85 years (median age 51 years), with 53.0% female, 82.1% White, 13.7% African-American, and 4.3% all other races.

Common Adverse Reactions

The safety of ZYNRELEF has been evaluated in 1064 patients who received ZYNRELEF in single doses up to 400 mg/12 mg via instillation into the surgical site, including 533 patients undergoing a soft tissue surgical procedure (herniorrhaphy, abdominoplasty, augmentation mammoplasty, or Cesarean section) and 531 patients undergoing an orthopedic surgical procedure (bunionectomy, total knee arthroplasty, total shoulder arthroplasty, or lumbar spinal surgery). The most common adverse reactions (incidence greater than or equal to 5% and higher than placebo) following ZYNRELEF administration among patients undergoing soft tissue procedures was vomiting and among patients undergoing orthopedic procedures were constipation and headache.

The safety of ZYNRELEF as part of a scheduled, non-opioid multimodal analgesic regimen including 1 or more other NSAIDs has been evaluated in a total of 473 patients undergoing soft tissue procedures or orthopedic procedures. NSAIDs included ibuprofen, ketorolac, and celecoxib. In these studies, the most common adverse reactions (incidence of greater than or equal to 2%) potentially associated with NSAIDs were pruritus and postoperative anemia. Rare but clinically serious NSAID-related adverse events, including peptic ulcer hemorrhage, gastritis requiring hospitalization, hematemesis and melena, gastrointestinal hemorrhage, and increased hepatic enzymes, were observed in subjects with predisposing risk factors (i.e., concomitant comorbidities and/or on concomitant medications such as anticoagulant and/or antiplatelet medications) that increased the risk for NSAID-related gastrointestinal toxicity.

Adverse Reactions Reported in Phase 3 and 2b Placebo-controlled Trials

Three randomized, bupivacaine-controlled and saline placebo-controlled studies were conducted in patients undergoing bunionectomy (STUDY 1, Table 1 and Table 2), 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 4 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

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ZYNRELEF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions involve the following 2 system organ classes: *Injury, Poisoning, and Procedural Complications* (wound necrosis, wound dehiscence) and *Surgical and Medical Procedures* (post-procedural drainage).

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 (5.17)]*.

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 postoperative 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 HCl was administered subcutaneously to rats at doses of 4.4, 13.3, and 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.

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=1627), 288 patients (17.7%) were ≥ 65 years old, while 83 (5.1%) were ≥75 years old. No overall differences in safety or efficacy were observed between elderly 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)]*.

Following administration of ZYNRELEF (400 mg/12 mg) by instillation, a highest individual maximum plasma concentration (C_{max}) of bupivacaine of 1830 ng/mL was reported. No apparent bupivacaine-related systemic toxicity was observed.

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.

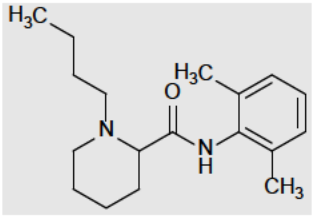
For additional information about overdosage treatment, call a poison control center (1-800-222-1222).

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).

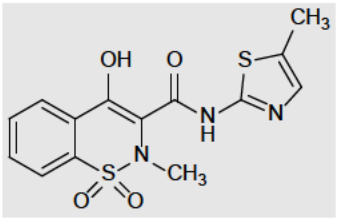
Bupivacaine

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

Additional pharmacodynamic data in clinical studies
Additional pharmacodynamic data for ZYNRELEF was evaluated in patients undergoing abdominoplasty, Cesarean section, total shoulder arthroplasty, and 1- to 3-level lumbar spinal surgery. Refer to Dosage and Administration for specific doses used for each study *[see Dosage and Administration (2.4)]*.

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 for soft tissue surgical procedures and Table 8 for orthopedic surgical procedures. 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 for soft tissue surgical procedures and Table 8 for orthopedic surgical procedures.

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

Active Ingredient	Parameter	Herniorrhaphy: 300 mg/9 mg ZYNRELEF (N=16)	Abdominoplasty: 400 mg/12 mg ZYNRELEF (N=22)	Augmentation Mammoplasty: 400 mg/12 mg ZYNRELEF (N=49)	Cesarean Section: 400 mg/12 mg ZYNRELEF (N=11)
Bupivacaine	C_{max} (ng/mL)	271 (147)	382 (149)	710 (246)	291 (70)
	T_{max} (h)	18 (3, 30)	31 (20, 54)	3.6 (1.3, 35)	24 (1.1, 48)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	15174 (8545)	24411 (10072)	27363 (9227)	17923 (5069)
	$AUC_{(inf)}$ (h×ng/mL)	15524 (8921)	24930 (10105)	31072 (17998)	17983 (5065)
	$t_{½}$ (h)	16 (9)	20 (8)	25 (20)	10 (2)
	C_{72h} (ng/mL)	96 (75)	202 (118)	149 (68) [b]	127 (56)
	C_{96h} (ng/mL)	37 (43)	86 (52) [c]	NS	27 (16)
	C_{144h} (ng/mL)	NS	16 (11) [c]	NS	0.8 (1.0) [d]
Meloxicam	C_{max} (ng/mL)	225 (96)	116 (62)	527 (149)	114 (49)
	T_{max} (h)	54 (24, 96)	24 (4.0, 72)	20 (5.6, 49)	60 (8.5, 73)
	$AUC_{(0-t)}$ (h×ng/mL)	18721 (7923)	7924 (4197)	30499 (9460)	9710 (4560)
	$AUC_{(inf)}$ (h×ng/mL)	NR	8304 (4422)	41809 (38414)	9778 (4592)
	$t_{½}$ (h)	NR	21 (9)	42 (70)	21 (9)
	C_{72h} (ng/mL)	197 (95)	70 (44)	214 (105) [b]	86 (43)
	C_{96h} (ng/mL)	146 (86)	33 (25) [c]	NS	48 (32)
	C_{144h} (ng/mL)	NS	7.1 (10) [c]	NS	11 (12) [d]

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 herniorrhaphy, augmentation mammoplasty, and Cesarean section; 0 to 144 h post-dose for abdominoplasty.

[b] N=48; [c] N=21; [d] N=10

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

Table 8. Summary of Pharmacokinetic Parameters for Bupivacaine and Meloxicam After Single Dose Administration of ZYNRELEF by Instillation for Orthopedic Surgical Procedures

Active Ingredient	Parameter	Bunionectomy: 60 mg/1.8 mg ZYNRELEF (N=17)	Total Knee Arthroplasty: 400 mg/12 mg ZYNRELEF (N=53)	Total Shoulder Arthroplasty: 400 mg/12 mg ZYNRELEF (N=20)	1-Level Spinal Surgery: 92 mg/2.8 mg ZYNRELEF (N=13)	2- or 3-Level Spinal Surgery: 191 mg/5.7 mg ZYNRELEF (N=13)
Bupivacaine	C_{max} (ng/mL)	54 (33)	695 (411)	372 (165)	95 (105)	163 (67)
	T_{max} (h)	3.0 (1.6, 24)	21 (4, 59)	20 (1.8, 48)	23 (1.9, 38)	24 (4.1, 69)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	1681 (1154)	35889 (28399)	21132 (12331)	4467 (4977)	8488 (4086)
	$AUC_{(inf)}$ (h×ng/mL)	1718 (1211)	38173 (29401) [b]	21193 (12329)	5535 (6091) [c]	8659 (4288) [d]
	$t_{½}$ (h)	15 (8)	17 (7) [b]	10 (3)	25 (25) [c]	14 (5) [d]
	C_{72h} (ng/mL)	5.0 (5.3)	227 (283)	145 (117)	34 (48) [d]	61 (49) [c]
	C_{96h} (ng/mL)	1.7 (2.9) [e]	NS	30 (32)	5.2 (7.3) [d]	24 (27) [d]
	C_{144h} (ng/mL)	NS	5.3 (21) [f]	1.1 (2.2) [g]	NS	NS
Meloxicam	C_{max} (ng/mL)	26 (14) [e]	275 (134)	248 (125) [h]	53 (41) [i]	90 (36) [c]
	T_{max} (h)	18 (8, 60) [e]	36 (12, 72)	57 (12, 72) [h]	18 (12, 72) [i]	43 (23, 69) [c]
	$AUC_{(0-t)}$ (h×ng/mL)	1621 (927) [e]	19525 (12259)	22292 (12250) [h]	3556 (2665)	6269 (3133) [c]
	$AUC_{(inf)}$ (h×ng/mL)	2079 (1631) [e]	25673 (17666) [j]	24133 (15285) [k]	3826 (3890) [d]	8265 (5874) [l]
	$t_{½}$ (h)	33 (36) [e]	42 (37) [j]	29 (11) [k]	35 (15) [d]	38 (22) [l]
	C_{72h} (ng/mL)	13 (9) [e]	202 (120)	228 (131) [h]	44 (44) [d]	69 (37) [d]
	C_{96h} (ng/mL)	7.7 (5.8) [m]	NS	158 (126) [h]	21 (23) [d]	43 (28) [l]
	C_{144h} (ng/mL)	NS	28 (37) [n]	52 (56) [k]	NS	NS

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). For spinal surgery, ZYNRELEF mean doses for single-level and multilevel surgeries are shown; individual doses ranged from 45 mg/1.4 mg to 248 mg/7.4 mg.

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

[b] N=50; [c] N=12; [d] N=11; [e] N=16; [f] N=32; [g] N=19; [h] N=18; [i] N=13; [j] N=35; [k] N=17; [l] N=10; [m] N=15; [n] N=28

NS = not sampled.

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 10 to 25 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 21 to 42 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 Inte*ractions (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.

13.2 Animal Toxicology and/or Pharmacology

Necrosis and degeneration of cartilage and chondrocytes were observed following intra-articular injection of a single dose of ZYNRELEF in the knee joint of rabbits. Cartilage degeneration was also observed following intra-articular injection of a single dose of ZYNRELEF in the knee joints of dogs.

14 CLINICAL STUDIES

The efficacy of ZYNRELEF was established in 3 double-blind, controlled studies in patients undergoing bunionectomy (Study 1), unilateral open inguinal herniorrhaphy (Study 2), and total knee arthroplasty (Study 3). Refer to 12.2 for additional supportive pharmacodynamic data for ZYNRELEF *[see Pharmacodynamics (12.2)]*.

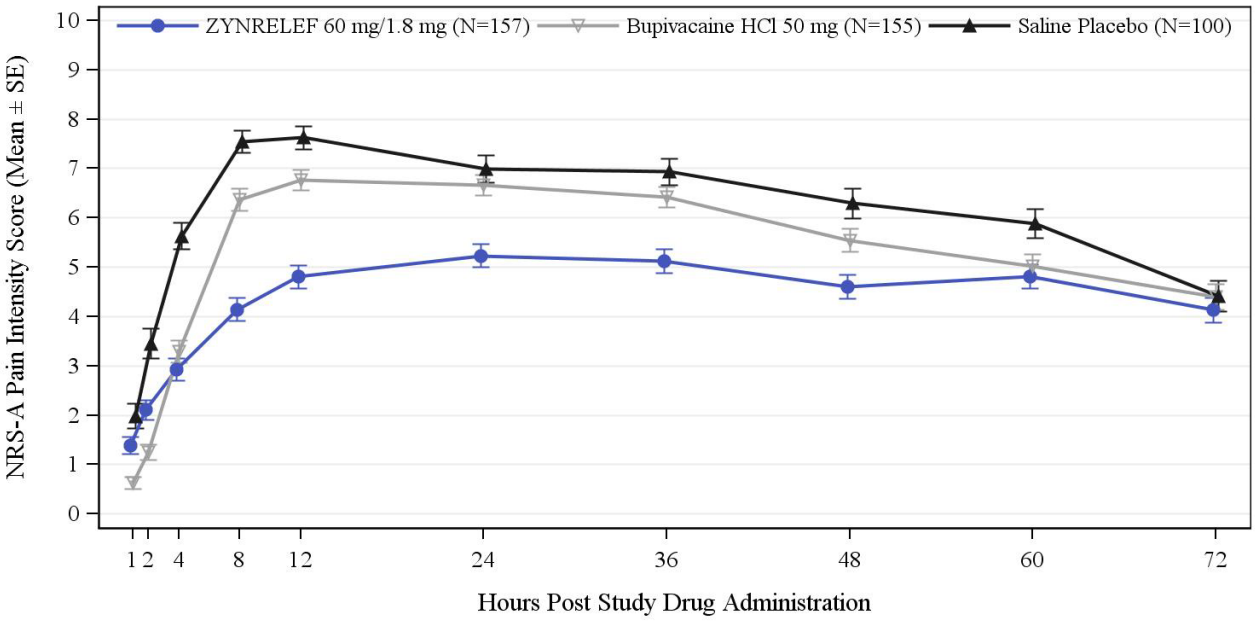
Based on the extrapolation of efficacy of ZYNRELEF across the 3 double-blind, controlled studies in patients undergoing bunionectomy, unilateral open inguinal herniorrhaphy, and total knee arthroplasty, and the pharmacokinetic profiles across surgical procedures with varied characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity, the pharmacokinetic profile and effectiveness of ZYNRELEF are not expected to be clinically significantly different when ZYNRELEF is administered at an appropriate dose in other soft tissue and orthopedic surgical procedures *[see Dosage and Administration (2.4), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

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)



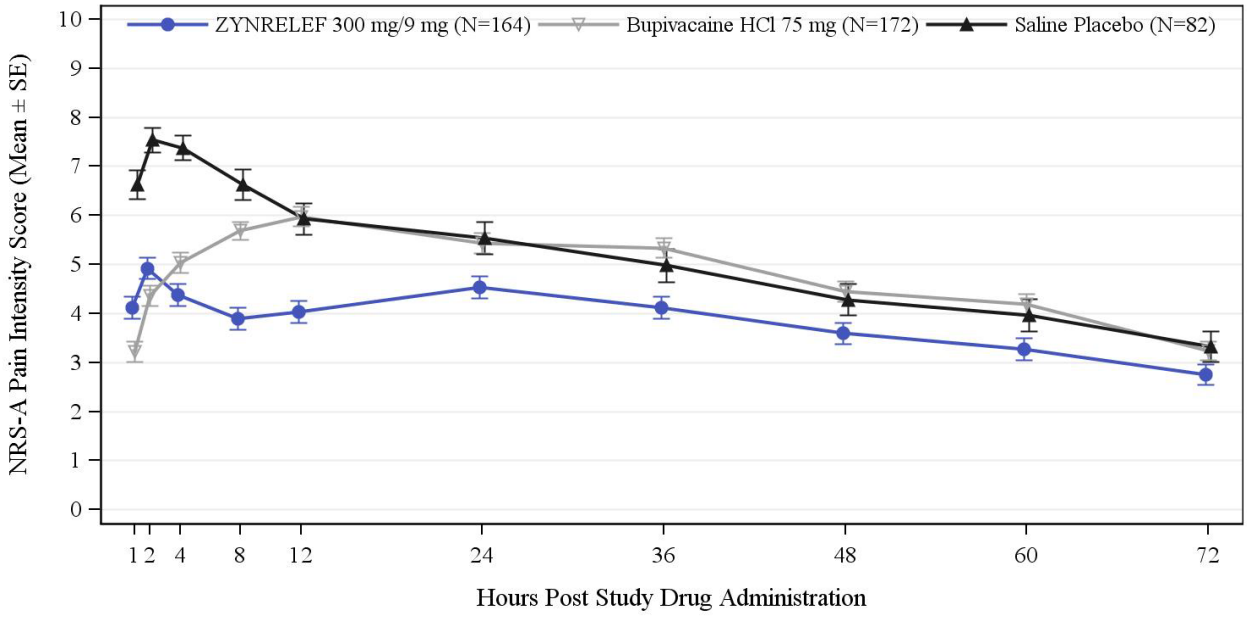
Study 2

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)



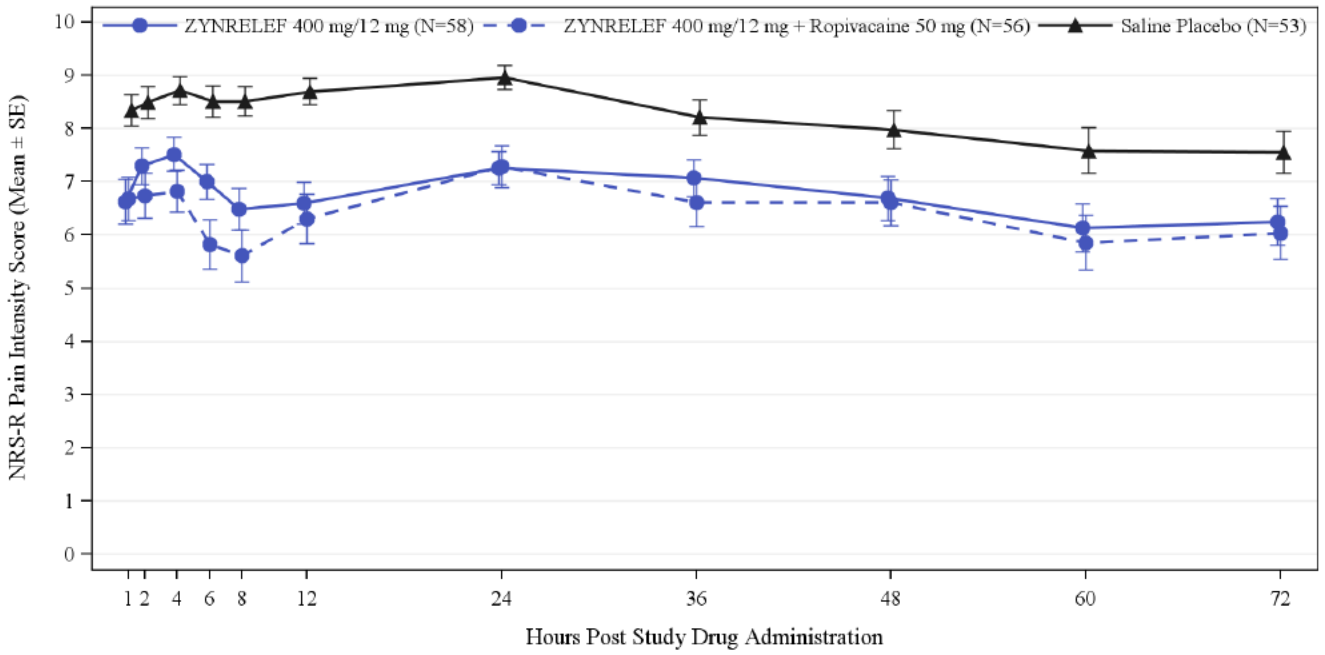
Study 3

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)



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	Net Quantity Volume*				
47426-301-02	400 mg/12 mg	14 mL	1	2 x 12 mL	2	2
47426-302-02	300 mg/9 mg	10.5 mL	1	1 x 12 mL	1	1
47426-303-01	200 mg/6 mg	7 mL	1	1 x 12 mL	1	1
47426-304-01	60 mg/1.8 mg	2.3 mL	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 (5.14, 5.15)]*.

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 (5.12)]*.

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 (5.16) 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.

Patent: https://www.herontx.com/patents/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA-211988-SUPPL-13**
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PAS (Efficacy)	12/23/2022	12/23/2022	11/29/2023	01/23/2024	12/13/2023

3. **Provides For:** To support the proposed indication for broader use of ZYNRELEF in soft tissue and orthopedic surgical procedures as follows:
   ZYNRELEF is indicated in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures.
   Limitations of Use:
   Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large (b) (4) and head and neck procedures.

4. **Review #:** 1

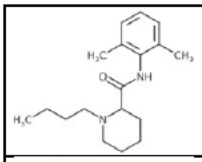
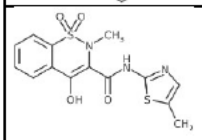
5. **Clinical Review Division**: CDER/ON/DAAP

6. **Name and Address of Applicant**:
   Name: Heron Therapeutics, Inc.
   Address: 4242 Campus Point Court
   Suite 200
   San Diego, CA 92121
   Attn: Kimberly J. Manhard, Executive Vice President, Drug Development
   Phone number: 858-251-4446

7. **Drug Product**:

Drug Name	Dosage Form	Strengths	Route of Administration	Rx or OTC	Special Product
ZYNRELEF (bupivacaine and meloxicam) extended-release solution, for soft tissue or periarticular instillation use	Extended-release solution	400 mg/12 mg, 200 mg/6 mg	For soft tissue or periarticular instillation use	Rx	No

8. Chemical Name and Structure of Drug Substance:

	**USAN:** Bupivacaine **Chemical Name:** (2RS)-1-Butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide **Molecular Formula:** $C_{18}H_{28}N_2O$ **MW**: 288.43 G/MOL
	**USAN:** Meloxicam **Chemical Name:** 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide **Molecular Formula:** $C_{14}H_{13}N_3O_4S_2$ **MW**: 351.40 G/MOL

9. Indication: ZYNRELEF is indicated in adults for (b) (4) .

10. Supporting/Relating Documents: 573 (eCTD Seq 0152)

11. Disciplines/Consults: NA

12. Executive Summary:

This supplement is managed by OND.

The applicant proposes the following change: to support the proposed indication for broader use of ZYNRELEF in soft tissue and orthopedic surgical procedures as follows: ZYNRELEF is indicated in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures.

Limitations of Use:

Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large (b) (4), and head and neck procedures.

To support the (b) (4)

(b) (4)

13. Conclusions & Recommendations:
This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Sandeep Putty, Ph.D., CMC reviewer, Branch 3, DPMAI, OLDP, OPQ

16. Secondary Reviewer:
Gurpreet Gill-Sangha, Branch Chief, Branch 3, DPMAI, OLDP, OPQ

CMC ASSESSMENT

I BACKGROUND INFORMATION

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.

II PROPOSED CHANGES

to support the proposed indication for broader use of ZYNRELEF in soft tissue and orthopedic surgical procedures as follows:

ZYNRELEF is indicated in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures.

Limitations of Use

Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large (b) (4), and head and neck procedures.

(b) (4)

(b) (4)

(b) (4)

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IFUs for 60 mg/1.8 mg

(b) (4)

Frequently Asked Questions

(b) (4)

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 mg/12 mg	14 mL	1	2 x 12 mL	2	2
47426-302-02	300 mg/9 mg	10.5 mL	1	1 x 12 mL	1	1
47426-303-01	200 mg/6 mg	7 mL	1	1 x 12 mL	1	1
47426-304-01	60 mg/1.8 mg	2.3 mL	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:

Reviewer's comment: Acceptable.

The applicant provided the updated vial label, vial carton label and kit carton label with the expanded indication for product strengths 60 mg/1.8 mg, 200 mg/6 mg, 300 mg/9 mg and 400 mg/12 mg. In this review these labels were only reproduced for 60 mg/1.8 mg strength, for the other strength labels refer to the supplement.

The applicant updated response to Frequently Asked Question 2 in the Instructions For Use from "The medication is specially formulated to coat the affected area. You should not attempt to worm or dilute this product in any way." to (b) (4)

The applicant did not propose any changes to section 3,11 and 16 in the PI, however DMEPA reviewer recommended adding the unit of measure following each numeric dose and the net quantity volume under section 16. The applicant accepted to all the recommendation suggested by DMEPA reviewer. The DMEPA reviewer have no further recommendation form the Mediation Error Prevention and Analysis perspective. Refer to DMEPA review submitted by Susan Hakeem in DARRTS on 11/21/2023.

Environment Assessment:

Heron Therapeutics, Inc. (Heron) claims a Categorical Exclusion from the requirement to prepare an Environmental Assessment for both bupivacaine and meloxicam in compliance with the categorical exclusion criteria 21 CFR Part 25.31, applicable when the FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will nonetheless be below 1 part per billion (ppb) (21 CFR Part 25.31(b)).

A claim in compliance with the Categorical Exclusion criteria 21 CFR Part 25.31(a), applicable when the FDA's approval of the application does not significantly increase the use of the active moiety, is also applicable but considered secondary.

Further, Heron claims that to the best of their knowledge no extraordinary circumstances exist that may significantly affect the quality of the human environment (21 CFR 25.21).

In compliance with 21 CFR Part 25.15(d) an Environmental Assessment is not submitted.

Applicant's categorical exclusion from the requirement to prepare an environmental assessment for bupivacaine and meloxicam is acceptable.

IV RISK ASSOCIATED WITH THE PROPOSED CHANGES AND IMPACT TO PRODUCT QUALITY AND PATIENT SAFETY

Low

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

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 REVIEW AND EVALUATION

Application number:	NDA 211988
Supporting document/s:	573, 626, 630, 656, and 679
Applicant's letter date:	12/23/2023, 4/26/2023, 5/10/2023, 7/20/2023, and 9/20/2023
CDER stamp date:	12/23/2023, 4/26/2023, 5/10/2023, 7/20/2023, and 9/20/2023
Product:	ZYNRELEF (bupivacaine and meloxicam)
Indication:	(b) (4)
Applicant:	Heron Therapeutics, Inc.
Pharm/Tox Review Division:	Division of Pharmacology Toxicology for Neuroscience
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Reviewer:	Jaime D'Agostino PhD
Supervisor/Team Leader:	Jay H. Chang, PhD
Clinical Division Director:	Rigoberto Roca, MD
Project Manager:	Sandy Truong PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211988 are owned by Heron Therapeutics, Inc. or are data for which Heron Therapeutics, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 211988 that Heron Therapeutics, Inc. 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.

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1 Executive Summary

1.1 Introduction

The Applicant, Heron Therapeutics Inc, developed a fixed-combination drug containing bupivacaine and meloxicam, which they referred to as HTX-011 during development. HTX-011 is a viscous solution that is formulated in a proprietary tri(ethylene glycol)-based poly(orthoester) polymer. HTX-011 was approved on 5/12/2021 as Zynrelef 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. On 12/8/2021, an efficacy supplement (SDN 219) was approved and the indication was updated to "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".

In this efficacy supplement (SDN 573), the Applicant is seeking to further update the indication to "indicated in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic procedures". Due to concerns for chondrolysis outlined in the labels of local anesthetics, including bupivacaine, communicated to the Applicant in previous communications (including a Type C meeting held on 9/14/2021), the Applicant conducted nonclinical intra-articular studies with their drug product in rabbits and dogs to address the potential risk.

1.2 Brief Discussion of Nonclinical Findings

In total, three GLP nonclinical studies were conducted. All three studies were single dose intra-articular injections of a formulation of Zynrelef (HTX-011-81) that is similar to the clinical formulation. The small differences in the formulation are not expected to impact the translatability of the nonclinical results to the clinical formulation. Two studies were conducted in rabbits: one with sacrifice time points 7- and 21- days post injection (Study 35-77) and a second with sacrifice time points 7- and 60- days post injection (Study 36-02). The single dog study had sacrifice time points 8- and 22- days post injection (Study 35-78).

In rabbits (Study 35-77), multiple histopathological findings were observed in the knee joint 7 days after treatment with effects on the synovium (inflammation, hyperplasia, hemorrhage, ulcer/erosion), chondrocytes (degeneration/necrosis), and cartilage of the marginal zone (degeneration). These findings were observed in almost all treated animals but not observed in the saline control knee joints of the same animals. The average severity scores of the findings were mild to moderate. A number of the histopathological findings in the joint space, including cartilage degeneration in the marginal zone, chondrocyte necrosis/degeneration, and hyperplasia/inflammation in the synovium, were still present at the 21-day sacrifice. Incidence and severity of the findings were generally similar to those in animals sacrificed 7 days after injection. Thus, the damage caused by treatment with HTX-011-81 was not completely reversible

after 21 days. It appeared that ulcer/erosion/hemorrhage of the synovium and exudate were no longer present on Day 21 or greatly reduced in severity/incidence.

The rabbit study with extended observation (Study 36-02) showed similar findings in the treated joint at Day 7 as were previously observed (Study 35-77) including degeneration/necrosis of the marginal zone cartilage, degeneration/necrosis of chondrocytes, erosion/ulceration of the synovium, synovium epithelium hyperplasia, exudate, synovial inflammation, and synovial hemorrhage. However, two additional findings were observed on Day 7 in the newer study: thrombus in the synovium and meniscus degeneration. At the extended observation timepoint (Day 60) there were still findings in the treated knee joints consisting of degeneration/necrosis of the marginal zone cartilage, degeneration/necrosis of chondrocytes, synovium epithelium hyperplasia, and synovial inflammation. The severity of the synovial findings was decreased suggesting a partial recovery compared to Day 7, although minimal to mild inflammation and hyperplasia were still present. However, the findings of degeneration and necrosis had increased severity on Day 60 and the pathology report noted that these effects extended from the marginal zones into load bearing cartilage. Thus, it appeared that the effects on chondrocytes/cartilage may be permanent effects that only become worse over time despite a partial resolution of effects in the synovium.

Dogs treated with HTX-011-81 in their knee joint (Study 35-78) also had histopathological findings at 8 days post injection; however, the response to HTX-011-81 appeared to be less pronounced in dogs compared to rabbits. Histopathological findings included inflammation in the synovium (mixed cell and mononuclear cell), an accumulation of necrotic debris (believed to be immune cells), and cartilage degeneration. Similar to the rabbit study, average severity scores of the findings were mild to moderate. It is not completely clear whether the cartilage degeneration was due to HTX-011-81 or generally due to the knee being injected with something as it was also observed in saline treated knees at a similar severity. However, the frequency of the finding was higher in HTX-011-81-treated knees (3/4 or 75%) compared to saline-treated knees (3/8 or 38%) and there were no findings of cartilage degeneration in knees injected with the comparator, Exparel (0/4). Cartilage degeneration was not present in animals sacrificed on Day 22 and findings of synovial inflammation and the presence of necrotic debris were less frequent/severe suggesting that the effects of HTX-011-81 diminished with time in dogs. However, there were new findings in the knee of animals treated with HTX-011-81 (but not saline or Exparel) on Day 22 that were not present on Day 8 such as periarticular mononuclear cell inflammation and periarticular hemorrhage. Thus, it is unclear if the effect of HTX-011-81 on the knee joint is recovering within the evaluated.

The dog study also included animals treated with Exparel (bupivacaine) as a comparator since the presence of bupivacaine in Zynrelef was the source of the initial concern for potential chondrotoxicity. Interestingly, no findings were observed in knee joints treated with Exparel. This suggests that bupivacaine may not be the cause of the findings observed with Zynrelef. However, it must be kept in mind that the concentration and absolute dose of bupivacaine in the Exparel arm (13.3 mg/mL; ~13.3 mg total dose)

was lower than in Zynrelef (29.25 mg/mL; ~20.5 mg total dose) so it is unclear if bupivacaine may be contributing to the effects caused by Zynrelef. Based on a combination of the lack of an effect with bupivacaine comparator, the prolonged response in the knee (21 days or longer), and the fact that the TEG-POE polymer is known to stay at the local tissue site for an extended period (20 days in rats, 24 days in dogs, and 18 days in humans) it is possible the findings are related to the TEG-POE polymer; however, contributions from the drug substances and other excipients cannot be ruled out.

The Applicant acknowledged their drug product (likely due to the polymer) caused synovial inflammation but they do not believe their product caused direct chondrotoxicity. They also contend that only synovial inflammation was observed in dogs (the more human relevant model) and that this finding is not clinically relevant because it likely recovers, was caused by relatively exaggerated doses in animals, and is common and not adverse in humans. In contrast, the FDA reviewer's interpretation of the nonclinical data is that treatment with HTX-011-81 leads to a robust local inflammatory reaction in the synovium (which appears to mostly recover by Day 22 in dogs and Day 60 in rabbits) and cartilage damage that appears to recover in dogs but gets worse with time in rabbits. Of note, the Applicant did not provide a convincing argument supported by data that justifies why results from either species would be more representative of humans. The effects observed in dogs and rabbits occurred with a formulation of Zynrelef that included clinically relevant concentrations of the drug product and excipients (~1x). The FDA reviewer believes that the findings in animals indicates Zynrelef may cause similar effects in humans if exposed to articular cartilage.

1.3 Recommendations

1.3.1 Approvability

The nonclinical studies identified a potential risk for Zynrelef to cause synovial inflammation and cartilage degeneration and necrosis if injected into the knee by the intra-articular route of administration. However, we recognize that there is clinical experience with Zynrelef exposure to cartilage via instillation for orthopedic surgical procedures where direct articular exposure is avoided. Therefore, Supplement-013 may be approved if the benefits of the drug outweigh the potential risks with respect to the proposed clinical use, and with appropriate labeling regarding the risk for cartilage damage from Zynrelef injection via the intra-articular route in animals. The reader is referred to the clinical review for a detailed discussion of the benefit risk profile of the drug.

1.3.2 Additional Non Clinical Recommendations

We recommend including the results of the nonclinical studies submitted with this supplement in labeling to inform prescribers of the potential risk of chondrolysis.

1.3.3 Labeling

Original Labeling (Supplement 5)	Applicant's Proposed Labeling (Supplement 13)	Recommended Changes to Proposed Labeling	Rationale for recommended changes/Comment
---------- 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).	---------- INDICATIONS AND USAGE---------- (b) (4) (b) (4)	---------- INDICATIONS AND USAGE---------- **ZYNRELEF is indicated in adults for postsurgical analgesia for up to 72 hours after:** • **soft tissue surgical procedures** • **orthopedic surgical procedures** – **foot and ankle procedures** – **other orthopedic surgical procedures in which direct exposure to articular cartilage is avoided (e.g., total joint arthroplasty) *[see Warnings and Precautions (5.10)]*** 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).	The clinical team has recommended the following indication based on excluding surgeries with exposure to articular cartilage other than those where there is clinical safety data based on the risk for cartilage damage identified in nonclinical studies.
---------- WARNINGS AND PRECAUTIONS---------- Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of	---------- WARNINGS AND PRECAUTIONS---------- (b) (4)	---------- WARNINGS AND PRECAUTIONS---------- Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs	After discussion between the clinical and nonclinical teams, a new warning/precaution is recommended based on the risk for cartilage damage identified in

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	(b) (4)	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). **Risk of Joint Cartilage Necrosis and Degeneration with Unapproved Intra-articular Use: Animal studies evaluating the effects of ZYNRELEF**	nonclinical studies. The new warning was assigned as 5.10. All warning numbered 5.1-5.9 were left the same. The previous warning numbered as 5.10 (Chondrolysis) was renumbered as 5.11 and all subsequent warnings remained the same with the numbering increased by 1.

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).	(b) (4)	**following intra-articular administration in the knee joint demonstrated cartilage necrosis and degeneration (5.10, 13.2).** Chondrolysis: Limit exposure to articular cartilage due to the potential risk of chondrolysis (**5.11**). Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use **(5.12)**. Serious Skin Reactions: NSAIDs, including meloxicam, can cause serious skin adverse reactions. If symptoms present, evaluate clinically **(5.14).** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): If symptoms are present, evaluate clinically **(5.15).** 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 (**5.16**, 8.1). Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (**5.17**).	
5 WARNINGS AND PRECAUTIONS	**5 WARNINGS AND PRECAUTIONS**	**5 WARNINGS AND PRECAUTIONS**	After discussion between the clinical

		5.10 Risk of Joint Cartilage Necrosis with Unapproved Intra-articular Use **The safety and effectiveness of intra-articular use of ZYNRELEF in orthopedic surgical procedures other than for foot and ankle procedures have not been established, and ZYNRELEF is not approved for use via other intra-articular administration routes. Animal studies evaluating the effects of ZYNRELEF following intra-articular administration in the knee joint demonstrated cartilage necrosis and degeneration *[see Nonclinical Toxicology (13.2)]*.**	and nonclinical teams a new warning/precaution is recommended based on the risk for cartilage damage identified in nonclinical studies. The new warning was assigned as 5.10. All warning numbered 5.1-5.9 were left the same. The previous warning numbered as 5.10 (Chondrolysis) was renumbered as 5.11 and all subsequent warnings remained the same with the numbering increased by 1.
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	**8.1 Pregnancy** (b) (4)	None	The Applicant made a minor update to change hydrochloride to HCl.

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	(b) (4)		

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).*	(b) (4)		

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. <u>Clinical Considerations</u> *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	(b) (4)		

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	(b) (4)		

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. <u>Data</u> *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	(b) (4)		

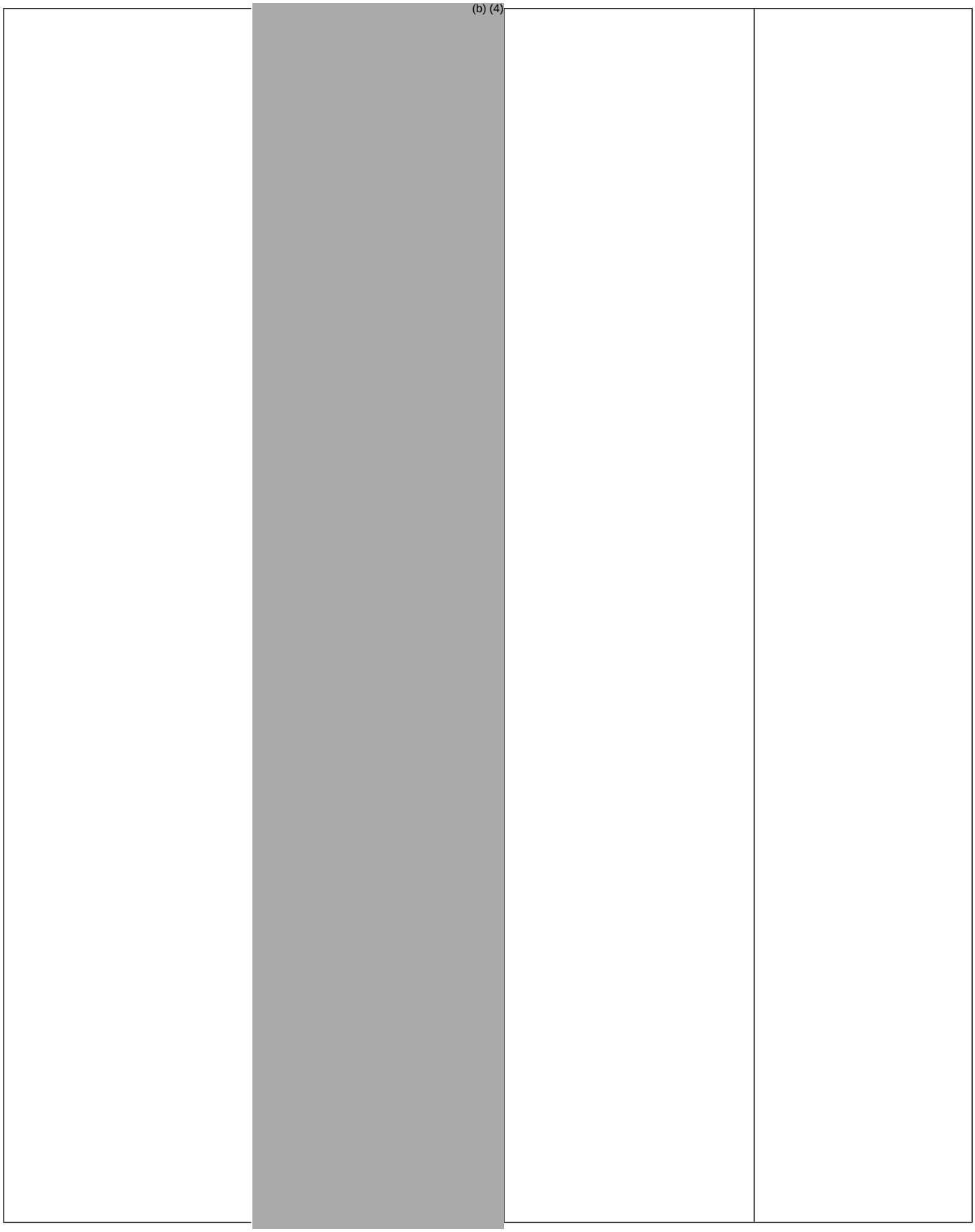
oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction 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	(b) (4)		

	(b) (4)		
Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, and 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).	(b) (4)		
8.2 Lactation <u>Risk Summary</u> 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	8.2 Lactation (b) (4)	8.2 Lactation <u>Risk Summary</u> 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	After discussion with the clinical and maternal health review teams it was decided to recommend (b) (4)

(b) (4)

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.		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.	


(b) (4)

	(b) (4)		
	8.2 Lactation (b) (4)	**8.2 Lactation** Information regarding the impact of succinylcholine on breast milk production is not known as there have been limited clinical studies conducted evaluating the effect of succinylcholine on breast milk production in breastfeeding mothers. There is no information regarding the presence of succinylcholine in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for succinylcholine and any potential adverse effects on the breastfed child from succinylcholine or from the underlying maternal condition.	Per PLLR, the (b) (4) section was appropriately changed to Section 8.2 Lactation. We defer to the clinical and maternal health review teams on the clinical language.
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. <u>Carcinogenesis</u> *Bupivacaine* Long-term studies in animals to evaluate the carcinogenic potential of ZYNRELEF or bupivacaine have not been conducted. *Meloxicam*	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility** (b) (4)	**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. <u>Carcinogenesis</u> *Bupivacaine* Long-term studies in animals to evaluate the carcinogenic potential of ZYNRELEF or bupivacaine have not been conducted. *Meloxicam*	The Applicant did not propose any changes to section 13. The nonclinical review team recommends adding the results of intra-articular nonclinical studies to assess the potential for damage to cartilage which supports the (b) (4)

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). <u>Mutagenesis</u> *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. <u>Impairment of Fertility</u> *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).	(b) (4)	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). <u>Mutagenesis</u> *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. <u>Impairment of Fertility</u> *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.	(b) (4)	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. **13.2 Animal Toxicology and/or Pharmacology** **Necrosis and degeneration of cartilage and chondrocytes were observed following intra-articular injection of a single dose of ZYNRELEF in the knee joint of rabbits. Cartilage degeneration was also observed following intra-articular injection of a single dose of ZYNRELEF in the knee joint of dogs.**	

Differences from the original label are highlighted in bold.

2 Drug Information

2.1 Drug

CAS Registry Number 38396-39-3 (bupivacaine); 71125-38-7 (meloxicam)

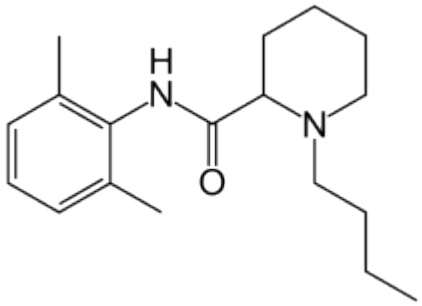
Generic Name bupivacaine (base) and meloxicam (base)

Code Name Zynrelef, HTX-011, and HTX-011-56

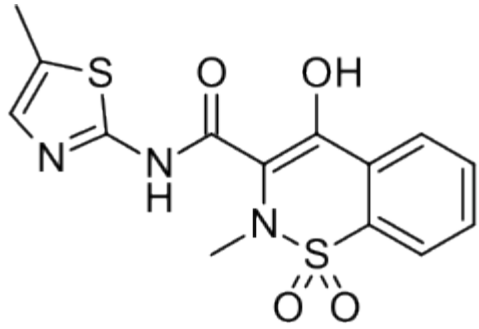
Chemical Name (RS)-1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide (bupivacaine) and 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam)

Molecular Formula/Molecular Weight $C_{18}H_{28}N_20$ / 288.43 g/mol (bupivacaine); $C_{14}H_{13}N_30_4S_2$ / 351.40 g/mol (meloxicam)

Structure or Biochemical Description



Bupivacaine



Meloxicam

Pharmacologic Class Amide local anesthetic (bupivacaine); nonsteroidal anti-inflammatory drug (meloxicam)

2.2 Relevant INDs, NDAs, BLAs and DMFs

The development program for this NDA was completed under IND 125927, originally submitted to the Agency on 5/7/2015.

The Applicant submitted the original NDA as a 505(b)(2) application referencing MARCAINE™ (bupivacaine, NDA 016964), Bupivacaine hydrochloride (NDA 18053), Sensorcaine (NDA 18304), and MOBIC® (meloxicam, NDA 020938) as the listed drugs.

2.3 Drug Formulation

HTX-011 is an extended-release solution containing a fixed-dose combination of bupivacaine and meloxicam. HTX-011 uses AP135, a highly viscous polymer to provide extended release of the active ingredients. Dimethyl sulfoxide (DMSO) and triacetin are included as (b) (4), respectively.

Table 1 Composition of Approved ZYNRELEF (aka HTX-011-56)

Component	Concentration (% w/w)	Concentration (mg/g)	Concentration (mg/mL)	Function	Reference to Quality Standard
Bupivacaine base	2.50	25.0	29.25	Active ingredient	Manufacturer
Meloxicam	0.075	0.75	0.88	Active ingredient	USP, Ph Eur
AP135	62.375	623.75	729.788	Release-controlling polymeric excipient	Manufacturer
Dimethyl sulfoxide	10.00	100	117	(b) (4)	USP, Ph Eur
Triacetin	25.00	250	292.5		USP, Ph Eur
Maleic acid	0.05	0.5	0.585		NF, Ph Eur
Totals	**100.00**	**1000.0**	**1170**		

Abbreviations: AP135, tri(ethylene glycol) poly(orthoester); USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia; NF, National Formulary

Table from page 10 of the Applicant's Drug Product Summary for HTX-011 (2.3.P)

Table 2 Composition of HTX-011-81

Test Article (Formulation #)	Bupivacaine (w/w%)	Meloxicam (w/w%)	(b) (4)	(b) (4)	Maleic Acid (w/w%)	DMSO (w/w%)	Triacetin (w/w%)
HTX-011-81	2.5	0.075			0.05	(b) (4)	(b) (4)

Table from page 16 of the Applicant's study report for Study 35-77 (4.2.3.6)

The maximum recommended human dose (MRHD) is 400 mg bupivacaine and 12 mg of meloxicam. This dose would require administration of 13.68 mL of the drug product solution.

The Applicant used HTX-011-81 in the nonclinical studies submitted with this efficacy supplement (Supplement 13; SDN 573). HTX-011-81 is a slightly modified formulation of HTX-011-56 (approved formulation) that (b) (4)

2.4 Comments on Novel Excipients

The excipients were considered qualified as part of the original NDA review in the context of the original indication (see nonclinical review dated 5/11/2021) and for the current indication that was approved as part of efficacy supplement S-05 (see nonclinical review dated 11/22/2021). (b) (4)

(b) (4)

Of note, there is an outstanding postmarketing requirement (PMR 4059-4) to conduct a study that evaluates the impact of the excipient DMSO on the developing brain to support pediatric clinical studies in children from birth to less than three years of age. As of the time of this review, the nonclinical study is ongoing.

In the context of the current submission for the newly proposed indications, a slightly different drug product was tested for potential chondrotoxicity in nonclinical studies by the intra-articular route of administration. In terms of the excipients, the drug product tested in the nonclinical studies contains an (b) (4) concentration of all excipients except triacetin (b) (4) (the drug product tested) vs. 25% in HTX-011-56 (the approved drug product); see tables above for full composition of the drug products].

In the nonclinical studies, the drug product produced synovial inflammation, cartilage damage, and chondrocyte damage in both rats and dogs (see section 6 of this review for more details). Effects in dogs were greatly reduced 22 days after treatment but in rabbits cartilage and chondrocyte damage were still present at a similar severity and incidence 60 days after treatment. Although a vehicle control group was not included in the studies to ascertain the impact of the excipients, there is evidence that the excipients contributed to the effect since no effects on chondrocytes/cartilage were observed with Exparel (bupivacaine) in dogs. The bupivacaine component in HTX-011-56 represented the original concern for chondrocyte damage as many of the local anesthetics, including bupivacaine, ropivacaine, and lidocaine, include warnings in their drug product labels describing a risk for chondrolysis based on clinical observations. However, the concentration of bupivacaine in Exparel and the total amount of bupivacaine was slightly lower than HTX-011-81 in the study and Exparel was not tested in rabbits, the more sensitive species based on the toxicity observed. Taken together, while not definitive, the data suggest a role of the excipients in the inflammatory response and resulting cartilage/chondrocyte damage.

2.5 Comments on Impurities/Degradants of Concern

The current drug substance and drug product impurities are shown below:

Table 3 Bupivacaine Drug Substance Specifications

Attribute		Acceptance Criteria	Test Method Reference
Appearance		White to off-white crystalline powder or crystals or granules	Visual
Identification	IR	Complies with reference spectrum	USP <197A>, Ph Eur 2.2.24
	Chromatographic	Complies with reference	TLC
Water content (% w/w)		(b) (4)	USP <921>, Ph Eur 2.5.12
Residue on ignition/sulfated ash (% w/w)			USP <281>, Ph Eur 2.4.14
Loss on drying (% w/w)			USP <731>, Ph Eur 2.2.32
Assay (% w/w)			Titration
Chromatographic purity (% w/w)	(b) (4)		HPLC
	Any unspecified impurity		
	Total impurities		
(b) (4)			GC
			GC
			GC
Bacterial endotoxins (EU/g)			USP <85>, Ph Eur 2.6.14
Microbiological limits (CFU/g)	Total aerobic microbial count[a]		USP <61>, Ph Eur 2.6.12
	Total combined yeasts/molds count[a]		

Abbreviations: IR, infrared; USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia; TLC, thin layer chromatography; HPLC, high performance liquid chromatography; GC, gas chromatography; % w/w, percent weight/weight; ppm, parts per million; EU, endotoxin units; CFU, colony forming units; NMT, not more than

[a] Per USP <1111> and Ph Eur 5.1.4; 10^2 is 200 CFU/g.

Table from page 1 of the Applicant's specification document (3.2.S.4.1)

Table 4 Meloxicam Drug Substance Specifications

Attribute		Acceptance Criteria	Test Method Reference
Appearance		Pale yellow powder	Visual
Identification	IR	Complies with reference spectrum	USP <197K>, Ph Eur 2.2.24
	HPLC	The retention time of the major peak of the sample corresponds to that of the reference standard	USP monograph
Loss on drying (% w/w)		NMT 0.5	USP <731>, Ph Eur 2.2.32
Residue on ignition/sulfated ash (% w/w)		NMT 0.1	USP <281>, Ph Eur 2.4.14
Assay, HPLC (% w/w on dried basis)		98.0 – 102.0	USP monograph
Assay, titration (% w/w on dried basis)		99.0 – 101.0	Ph Eur monograph
Related substances (HPLC) (% w/w)	USP related compound A and Ph Eur impurity A[a]	NMT 0.1	HPLC, USP monograph Procedure 1, Ph Eur monograph
	USP related compound B and Ph Eur impurity B[b]	NMT 0.1	
	USP methyl meloxicam and Ph Eur impurity C[c]	NMT 0.05	
	USP ethyl meloxicam and Ph Eur impurity D[d]	NMT 0.05	
	Any unspecified impurity	NMT 0.10	
	Total impurities	NMT 0.3	
Residual solvents (ppm)	[redacted] (b) (4)		GC

Attribute		Acceptance Criteria	Test Method Reference
Bacterial endotoxins (EU/g)		[redacted] (b) (4)	USP <85>, Ph Eur 2.6.14
Microbial limits (CFU/g)	Total aerobic microbial count		USP <61>, Ph Eur 2.6.12
	Total combined yeasts/molds count		

Abbreviations: IR, infrared; USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia; HPLC, high performance liquid chromatography; GC, gas chromatography; % w/w, percent weight/weight; ppm, parts per million; NMT, not more than; EU, endotoxin units; CFU, colony forming units

[redacted] (b) (4)

Table from page 1 of the Applicant's specification document (3.2.S.4.1)

Table 5 Zynrelef Drug Product Specifications

Attribute	Acceptance Criteria	Method Reference
Appearance (Visual)	(b) (4)	
Dynamic Viscosity at 25°C		
Molecular Mass Distribution (GPC)		
Particulate Matter by Light Obscuration		
Identification of Bupivacaine and Meloxicam by HILIC[a]		
Identification of Bupivacaine and Meloxicam by HPLC[a]		
Bupivacaine Assay (HPLC)		
Bupivacaine Related Substances (Area % by HPLC)		
Bupivacaine Dose Uniformity[a]		
Meloxicam Assay (HPLC)		

Attribute	Acceptance Criteria	Method Reference
Meloxicam Related Substances (Area % by HPLC)	(b) (4)	
Meloxicam Dose Uniformity[a]		
In Vitro Release (see Table 2 for additional Level 2 and Level 3 acceptance criteria)		
(b) (4)		
Container Closure Integrity (Dye Ingress)[b]		
Bacterial Endotoxins		
Sterility[a]		
Extractable Volume[a]		

Abbreviations: BHT, butylated hydroxytoluene; CHDEA, cyclohexyldiethanolamine; GPC, gel permeation chromatography; GC, gas chromatography; HPLC, high performance liquid chromatography; M_w, weight average molecular weight; M_n, number average molecular weight; LMW, low molecular weight; LC, label claim; NMT, not more than; NA, not applicable; AV, acceptance value; HILIC, hydrophilic interaction liquid chromatography; NLT, not less than; ppm, parts per million; USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia

[a] Tested on release only
[b] Tested on stability only

The impurities and degradants were considered qualified as part of the original NDA review in the context of the original indication (see nonclinical review dated 5/11/2021) and for the current indication that was approved as part of efficacy supplement S-05 (see nonclinical review dated 11/22/2021). (b) (4)

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The Sponsor is proposing a general indication of "in adults for (b) (4)

The dose varies depending on the surgical procedure Zynrelef is being used for. The maximum dose is 14 mL (400 mg bupivacaine and 12 mg meloxicam).

2.7 Regulatory Background

NDA 211988 was originally approved on 5/21/2021 with an indication "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". On 9/14/2021, the Applicant and FDA had a Type C meeting to discuss expansion of the indication to additional surgeries. It was communicated to the Applicant that additional nonclinical data would be needed to support orthopedic surgical procedures in which articular cartilage would be exposed due to the potential for local anesthetics to cause chondrolysis, which has been observed clinically.

Shortly after the Type C meeting (9/29/2021), the Applicant submitted an efficacy supplement (efficacy supplement #5; SDN 219) to broaden the indication to "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". This efficacy supplement was approved on 12/8/2021. While there was still a concern regarding the risk of chondrolysis to exposed articular cartilage and the Applicant did not provide any nonclinical data to assess the potential risk as described in the Type C meeting, it was determined that the risk was low for the surgical procedures sought in the indication. However, since the risk may not be negligible, a warning was added to the label to "limit exposure to articular cartilage due to the potential risk of chondrolysis." In addition, a new post-marketing requirement (PMR; 4059-5) was issued to 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.

The Applicant submitted the current efficacy supplement (efficacy supplement #13; SDN 573) on 12/23/2022 to broaden the indication even further to (b) (4) To address the potential for chondrolysis to articular cartilage, the Applicant included nonclinical studies assessing chondrotoxicity following intra-articular injection in rabbits and dogs.

3 Studies Submitted

3.1 Studies Reviewed

- 35-77: A GLP 7- and 21-day local toxicity evaluation of a single intra-articular injection in a rabbit model

- 35-78: A GLP 7- and 21-day local toxicity evaluation of a single intra-articular injection in Beagle dogs

- 36-02: 36-02: A GLP 7- and 60-day local toxicity evaluation of a single articular injection in a rabbit model

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

This review focuses on the newly submitted nonclinical data submitted to address the potential for chondrocyte toxicity. For review of nonclinical data relating to other aspects of the NDA the reader is referred to the following reviews:

Table 6 Nonclinical Reviews Referenced

Submission	SDN	Date	Nonclinical Review
Original NDA	1	9/21/2018	4/17/2019, 6/12/2020, and 5/11/2021
Efficacy Supplement S-05	219	9/29/2021	11/22/2021

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: HTX-011: A GLP 7- and 21-day local toxicity evaluation of a single intra-articular injection in a rabbit model

Study no.:	35-77
Study report location:	4.2.3.6 Local tolerance; \\CDSESUB1\EVSPROD\ind125927\0279\m4\42-stud-rep\423-tox\4236-loc-tol\35-77\35-77.pdf
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	1/25/2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HTX-011-81, Lot# 120221, N/A

Key Study Findings

Methods

Doses:	HTX-011-81 0.25 (7.3 mg bupivacaine and 0.2 mg meloxicam) or 0.5 mL (14.6 mg bupivacaine and 0.4 mg meloxicam) to the right knee Saline control 0.25 or 0.5 mL to the left knee HTX-011-81 contains 29.35 mg/mL bupivacaine and 0.88 mg/mL meloxicam
Frequency of dosing:	Single dose
Route of administration:	Intra-articular injection
Dose volume:	0.25 or 0.5 mL
Formulation/Vehicle:	HTX-011-81/none
Species/Strain:	New Zealand White rabbit
Number/Sex/Group:	4 males/group
Age:	7-9 months
Weight:	3.5-4.3 kg
Satellite groups:	None
Unique study design:	Each animal served as its own control. Test article was injected into the right knee and saline was injected into the left knee
Deviation from study protocol:	There were a few minor deviations that did not impact the integrity of the study.

Experimental Design

Table 7 Study 35-77 Experimental Design

Study Group	Material to be Injected	Hindlimb (knee joint)	Dose Volume (mL)	Description
Group 1	HTX-011	Right	0.25	Extended-release soluton of bupivacaine and meloxicam
Group 2			0.50	
Group 3	Saline	Left	0.25	0.9% sterile sodium chloride solution
Group 4			0.50	

Table from page 21 of the Applicant's study report for 35-77 (section 4.2.3.6)

Observations and Results

Mortality

Checks for mortality/moribundity were performed at least twice daily.

All treated animals survived to scheduled termination.

Clinical Signs

Detailed clinical observations were performed weekly.

No clinical signs observed were associated with HTX-011 administration. The animals were considered to be in good overall health condition throughout the study.

Body Weights

Body weights were measured weekly.

There was no significant difference in body weight following treatment. Only a single animal (21-day cohort) displayed a large decrease in body weight following treatment (~9% loss in body weight).

Food Consumption

Food consumption was measured daily.

Food consumption was decreased on the day of dosing and the day after dosing in the majority of the animals. Food consumption returned to near pre-dosing levels after that. The decrease in food consumption did not appear to affect the overall body weight of the animals.

Gross Pathology

Limited necropsies were performed on the treated sites and surrounding tissues.

The only gross finding was dark foci in animals on Day 7. The injection volume did not appear to have a major impact on the finding. The dark foci were observed on the medial aspect and correlated with hemorrhage in the synovium microscopically. The dark foci were not seen in animals sacrificed on Day 21 suggesting the finding completely recovered.

Table 8 Gross Pathology Findings

N = 4	Day 7 (0.25 mL)	Day 21 (0.25 mL	Day 7 (0.5 mL)	Day 21 (0.5 mL)
Dark Focus	4	0	2	0

Histopathology

Adequate Battery

Yes. Histopathological analysis was limited to the femorotibial joints and draining lymph nodes. This is considered acceptable since the study is focused on addressing the potential for chondrotoxicity.

Peer Review
Yes.

Histological Findings
Following treatment with saline, the left knee joint was relatively unaffected with the major finding being multifocal cartilage degeneration. This finding was also observed in a similar frequency and severity in HTX-011 treated right knees. The finding had a similar incidence and severity on Day 7 and 21.

Multiple histopathological findings were observed in the joints of animals treated with HTX-011 and sacrificed on Day 7 that were not observed with saline including: cartilage degeneration in the marginal zone, chondrocyte necrosis and degeneration, ulcers and erosion of the synovium, hyperplasia of the synovium epithelium, exudate, synovium inflammation, and synovium hemorrhage. The overall incidence and severity of the findings appeared to be similar between the two injection volumes used (0.25 mL and 0.5 mL) with a slight increased severity for a few findings with the 0.5 mL volume. Animals sacrificed on Day 21 had similar incidences and severity scores for cartilage degeneration and chondrocyte necrosis/degeneration suggesting these effects lasted at least 21 days. Other findings appeared to have reduced incidences and severity scores on Day 21 suggesting these effects were at least partially reversible over 21 days.

Table 9 Histopathological Changes Observed in Animals Receiving 0.25 mL

N = 4	Saline Day 7	HTX-011 Day 7	HTX-011 Day 21
Cartilage degeneration (multifocal)	4 (1.3)	4 (1.2)	4 (1.3)
Cartilage degeneration (marginal zone)	0	3 (2.7)	3 (2.7)
Chondrocyte degeneration/necrosis	0	4 (2.7)	3 (2.7)
Synovium ulcer/erosion	1 (1)	4 (1.8)	0
Synovium epithelium hyperplasia	0	4 (1.5)	2 (1)
Exudate	1 (1)	4 (2.3)	0
Synovium inflammation	0	4 (3)	4 (1.8)
Synovium hemorrhage	0	4 (2)	1 (1)

Values in () = average severity score. 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Table 10 Histopathological Changes Observed in Animals Receiving 0.5 mL

N = 4	Saline Day 7	HTX-011 Day 7	HTX-011 Day 21
Cartilage degeneration (multifocal)	4 (1)	3 (1.7)	4 (1.3)
Cartilage degeneration (marginal zone)	0	4 (3)	4 (2.5)
Chondrocyte degeneration/necrosis	0	4 (1.8)	3 (2.3)
Synovium ulcer/erosion	0	4 (2.5)	2 (1.5)
Synovium epithelium hyperplasia	0	4 (1.8)	3 (1.7)
Exudate	0	4 (2.8)	2 (1.5)
Synovium inflammation	0	4 (3.3)	4 (2.5)

Synovium hemorrhage	0	4 (2)	0

Values in () = average severity score. 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Dosing Solution Analysis

Stability was also tested on samples that were exposed to room temperature for the longest time that any sample was left at room temperature during the study. All three parameters measured (viscosity, DMSO content, (b) (4)) where within the acceptance criterion of +/- 10% of the initial value.

Table 11 Dosing Solution Analysis

N = 4	Initial	55 days 2-8 degrees C	84 days 2-8 degrees C
Viscosity	(b) (4)		
DMSO			
(b) (4)			

In addition, certificates of analysis were provided for the lot. Bupivacaine and meloxicam content were measured and compared to the label claim. Samples were analyzed on two separate days. Bupivacaine levels were 102 and 101.0% of label claim and meloxicam levels were 100.6 and 100.9% of label claim.

Study title: HTX-011: A GLP 7- and 21-day local toxicity evaluation of a single intra-articular injection of HTX-011 or comparator Exparel in beagle dogs

Study no.:	35-78
Study report location:	4.2.3.6 Local tolerance; \\CDSESUB1\EVSPROD\ind125927\0279\m4\42-stud-rep\423-tox\4236-loc-tol\35-78\35-78.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	3/21/2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HTX-011-81, Lot# 120221, N/A

Key Study Findings

Methods

Doses:	HTX-011-81 0.7 mL (20.5 mg bupivacaine and 0.6 mg meloxicam) to the left knee Exparel (13.3 mg bupivacaine) 1 mL to the left knee Saline control 0.7 or 1 mL to the right knee HTX-011-81 contains 29.35 mg/mL bupivacaine and 0.88 mg/mL meloxicam Exparel contains 13.3 mg/mL bupivacaine and 0 mg/mL meloxicam
Frequency of dosing:	Single dose
Route of administration:	Intra-articular injection
Dose volume:	0.7 or 1 mL
Formulation/Vehicle:	HTX-011-81/none
Species/Strain:	Beagle Dog
Number/Sex/Group:	4 males/group
Age:	13-17 months
Weight:	12-13.9 kg
Satellite groups:	None
Unique study design:	Each animal served as its own control. HTX-011-81 or the comparator was injected into the left knee and saline was injected into the right knee
Deviation from study protocol:	There were a few minor deviations that did not impact the integrity of the study.

Experimental Design

Table 12 Study 35-78 Experimental Design

Group	Number and Sex of Animals		Route	Dose	Dose Location	Dose Conc. (mg/mL) [A]	Dose Volume (mL/animal)
	7-Day Cohort	21-Day Cohort					
1	4 Males	4 Males	Intra-articular injection	HTX-011	Dose Site 1	29.25	0.7
				Saline	Dose Site 2	0	0.7
2	4 Males	4 Males		Exparel®	Dose Site 1	13.3	1
				Saline	Dose Site 2	0	1

[A] Dose concentration of bupivacaine within the test article
Note: Conc. = Concentration
Table from page 12 of the Applicant's study report for 35-78 (section 4.2.3.6)

Observations and Results

Mortality

Checks for mortality/moribundity were performed at least twice daily.

All treated animals survived to scheduled termination.

Clinical Signs

Detailed clinical observations were performed weekly.

Mild erythema at the injection site was a common finding in the study. Erythema appeared to be slightly more common with HTX-011-81 and Exparel compared to saline. Erythema was observed in all animals that received HTX-011-81 or Exparel, while it was observed in 10/16 animals injected with saline.

Body Weights

Body weights were measured weekly.

There was no significant difference in body weight following treatment. Animals either maintained or had slight increases in body weight following treatment. There were no differences in body weights between Exparel-treated and HTX-011-81-treated animals.

Food Consumption

Food consumption was measured daily.

Food consumption was decreased on the day of dosing and the day after dosing in animals receiving HTX-011-81. Food consumption returned to near pre-dosing levels after that. A similar decrease was observed in animals receiving Exparel, although it appeared that these animals recovered quicker as all animals consumed near pre-dosing levels on the day after dosing while some of the HTX-011-81 treated animals were still eating less than before treatment. The decrease in food consumption did not appear to affect the overall body weight of the animals.

Gross Pathology

Limited necropsies were performed on the main body cavity, treated sites and surrounding tissues.

Gross injection site findings were observed in a few animals in all treatment groups. Based on the sporadic findings there was no indication that treatment with HTX-011 resulted in a more severe response than saline or Exparel.

Table 13 Gross Pathology Findings

Day 8	Saline (n = 8)	Exparel (n = 4)	HTX-011 (n =4)
Abnormal shape	0	0	1
Red discoloration	0	0	1

Abnormal content	1	0	0
Accumulation of fluid	1	0	0

Day 22	Saline (n = 8)	Exparel (n = 4)	HTX-011 (n =4)
Red discoloration	0	0	1
Pink discoloration	1	1	0
Abnormal surface	1	0	0

Histopathology

Adequate Battery

Yes. Histopathological analysis was limited to the left and right stifle joints. This is considered acceptable since the study is focused on addressing the potential for chondrotoxicity.

Peer Review
Yes.

Histological Findings
Following treatment with saline, the right knee joint was relatively unaffected with the major finding being cartilage degeneration in 3 out of 8 animals.

Histopathological findings were observed in the joints of animals treated with HTX-011 and sacrificed on Day 8 and included: mixed cell synovial inflammation, mononuclear synovial inflammation, accumulation of necrotic debris (which was believed to be immune cells), and cartilage degeneration. The synovial inflammation was at an increased incidence and severity as compared to saline control animals. While cartilage degeneration of a similar severity was observed in saline control animals, the incidence was elevated in the HTX-011-81 treated knees.

No histopathological findings were observed in knee joints injected with Exparel.

On the Day 22 sacrifice, knees injected with HTX-011-81 did not show evidence of cartilage degeneration and had reduced incidences and severity of necrotic debris and synovial inflammation. However, two new findings were observed: periarticular mononuclear cell inflammation and periarticular hemorrhage.

Table 14 Histopathological Findings on Day 8

Day 8	Saline (n =8)	Exparel (n = 4)	HTX-011 (n = 4)

Synovial mixed cell inflammation	1 (1)	0	2 (3.5)
Synovial mononuclear cell inflammation	1 (1)	0	2 (3)
Accumulation of necrotic debris	0	0	4 (2.3)
Cartilage degeneration	3 (2)	0	3 (2)

Values in () = average severity score. 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Table 15 Histopathological Findings on Day 8 vs. Day 22

	HTX-011 Day 8 (n = 4)	HTX-011 Day 22 (n = 4)
Synovial mixed cell inflammation	2 (3.5)	0
Synovial mononuclear cell inflammation	2 (3)	1 (2)
Periarticular mononuclear cell inflammation	0	2 (2.5)
Accumulation of necrotic debris	4 (2.3)	1 (2)
Periarticular hemorrhage	0	2 (2)
Cartilage degeneration	3 (2)	0

Values in () = average severity score. 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Dosing Solution Analysis

The lot of HTX-011-81 used in the study was tested for stability. The samples were allowed to reach ambient temperature for 30 minutes and then shipped on wet ice/ice packs for characterization. Samples were also tested after being stored for 55 and 84 days at 2-8 degrees C beforehand. All three parameters measured (viscosity, DMSO content, (b) (4)) were within the acceptance criterion of +/- 10% of the initial value.

Table 16 Dosing Solution Analysis

N = 4	Initial	55 days 2-8 degrees C	84 days 2-8 degrees C
Viscosity	(b) (4)		
DMSO			
(b) (4)			

Certificates of analysis were provided for the lot. Bupivacaine and meloxicam content were measured and compared to the label claim. Bupivacaine levels were 101.0% of label claim and meloxicam levels were 100.9% of label claim.

Study title: HTX-011: A GLP 7- and 60-day local toxicity evaluation of a single intra-articular injection in a rabbit model

Study no.:	36-02
Study report location:	4.2.3.6 Local tolerance; \\CDSESUB1\EVSPROD\nda211988\0178\m4\42-stud-rep\423-tox\4236-loc-tol\36-02\36-02.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1/12/2023
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HTX-011-81, Lot# 120822, N/A

Key Study Findings

Methods

Doses:	HTX-011-81 0.5 mL (14.6 mg bupivacaine and 0.4 mg meloxicam) to the right knee Saline control 0.5 mL to the left knee HTX-011-81 contains 29.35 mg/mL bupivacaine and 0.88 mg/mL meloxicam
Frequency of dosing:	Single dose
Route of administration:	Intra-articular injection
Dose volume:	0.5 mL
Formulation/Vehicle:	HTX-011-81/none
Species/Strain:	New Zealand White rabbit
Number/Sex/Group:	2 males and 2 females/group
Age:	9.4-16.2 months
Weight:	2.9-4.2 kg
Satellite groups:	None
Unique study design:	Each animal served as its own control. Test article was injected into the right knee and saline was injected into the left knee
Deviation from study protocol:	There were a few minor deviations that did not impact the integrity of the study.

Experimental Design

Table 17 Study 36-02 Experimental Design

Number of Animals		Route	Material to be Injected	Hindlimb (Knee joint)	Dose Volume (mL)
7 Day Cohort	60 Day Cohort				
4	4	Intra-articular injection	Test: (HTX-011-81) Extended-release solution of bupivacaine and meloxicam	Right	0.5
			Control: (Saline) 0.9% sterile sodium chloride solution	Left	0.5

Table from page 19 of the Applicant's study report for 36-02 (section 4.2.3.6)

Observations and Results

Mortality

Checks for mortality/moribundity were performed at least twice daily.

All treated animals survived to scheduled termination.

Clinical Signs

Detailed clinical observations were performed weekly. Cage side observations were made twice daily.

The animals were considered to be in good overall health condition throughout the study. However, a few clinical signs were observed during the study.

Lameness of the right hindlimb (HTX-001 injected) was observed 3 days after treatment which was believed to be associated with a broken nail tip or possibly a sprain/strain. Lameness improved 3 days after a treatment with buprenorphine by SC injection. This animal underwent scheduled sacrifice on Day 7. Lameness was also reported in a few other animals on the day of dosing. Almost all animals showed decreased activity after dosing. Abnormal appetite was reported in a few animals.

Body Weights

Body weights were measured weekly.

There was a slight decrease in body weight during the first week of treatment but this was not considered a significant decrease. In animals that were not sacrificed on Day 7, body weight gradually increased throughout the remainder of the study.

Food Consumption

Food consumption was measured daily.

Food consumption was decreased during the first week (corresponding to the body weight decreases observed) but gradually increased in animals that were not sacrificed on Day 7.

Gross Pathology

Limited necropsies were performed on the treated sites and surrounding tissues.

The only gross findings were pale, yellowish foci on the medial aspect of the right (HTX-011 treated) femoro-tibial joint in a single animal and dark foci on the medial and lateral aspect of both the right and left femoro-tibial joint in the same animals as the yellowish focus.

Histopathology

Adequate Battery

Yes. Histopathological analysis was limited to the femoro-tibial joints and the iliac and popliteal lymph nodes. This is considered acceptable since the study was focused on addressing the potential for chondrotoxicity.

Peer Review
Yes.

Histological Findings
Multiple histopathological findings were observed in the knee joints of treated animals.

In saline-treated knees, the only finding was minimal cartilage degeneration. This was also seen in HTX-011-treated knees of both Day 7 and Day 60 animals at a similar incidence. The average severity score was slightly increased in HTX-011-treated knees.

Multiple findings that were not observed in saline-treated knees were observed in HTX-011 treated knees on Day 7 including degeneration/necrosis of cartilage, degeneration/necrosis of chondrocytes, erosion/ulcer of the synovium, synovium epithelial hyperplasia, exudate, synovium inflammation, synovium hyperplasia, vascular inflammation of the synovium, thrombus in the synovium, and meniscus degeneration. Some findings appeared to recover as they were no longer observed on Day 60 (erosion/ulcer of the synovium, vascular inflammation of the synovium, and thrombus of the synovium). A number of findings were still present after 60 days, suggesting the damage due to HTX-011 was long lasting. Some of these findings had a decreased incidence and/or severity (synovium epithelium hyperplasia, synovium inflammation, synovium hemorrhage, and meniscus degeneration) suggesting potential partial recovery. Degeneration/necrosis of cartilage and degeneration/necrosis of chondrocytes both had similar or increased severity at Day 60 with a similar incidence, indicating these changes persist and even worsen after the synovial inflammation reverses.

Table 18 Histopathological Findings

N = 4	Saline Day 7	HTX-011 Day 7	HTX-011 Day 60
Cartilage Degeneration	4 (1)	4 (1.5)	4 (1.7)
Degeneration/necrosis of cartilage (marginal zone)	0	4 (2.3)	3 (3.8)
Degeneration/necrosis of chondrocytes	0	4 (2.5)	4 (2.75)
Erosion/ulcer of synovium	0	4 (2.5)	0
Synovium epithelium hyperplasia	0	4 (2)	3 (1.3)
Exudate	0	3 (2.7)	1 (1)
Synovium inflammation	1 (1)	4 (3.5)	4 (1.5)
Synovium hemorrhage	0	4 (2.3)	1 (1)
Vascular inflammation of the synovium	0	2 (1)	0

Thrombus of the synovium	0	2 (1)	0
Meniscus degeneration	0	3 (2)	1 (2)

Values in () = average severity score. 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Dosing Solution Analysis

Stability was also tested on samples that were exposed to room temperature for the longest time that any sample was left at room temperature during the study. All three parameters measured (viscosity, DMSO content, (b) (4)) where within the acceptance criterion of +/- 10% of the initial value.

Table 19 Dosing Solution Analysis

N = 4	Initial	55 days 2-8 degrees C	84 days 2-8 degrees C
Viscosity	(b) (4)		
DMSO			
(b) (4)			

In addition, certificates of analysis were provided for the lot. Bupivacaine and meloxicam content were measured and compared to the label claim. Samples were analyzed on two separate days. Bupivacaine levels were 102 and 101.0% of label claim and meloxicam levels were 100.6 and 100.9% of label claim.

11 Integrated Summary and Safety Evaluation

The Applicant initially submitted efficacy supplement S-13 (SDN 573; 12/23/2022) with rabbit (Study 35-77) and dog (Study 35-78) single intra-articular injection toxicity studies, both with 7- and 21-day observation periods.

In rabbits (Study 35-77), multiple histopathological findings were observed in the knee joint 7 days after HTX-011-81 treatment with effects on the synovium (inflammation, hyperplasia, hemorrhage, ulcer/erosion), chondrocytes (degeneration/necrosis), and cartilage of the marginal zone (degeneration). These findings were observed in almost all HTX-011-81-treated knee joints but not observed in the saline control knee joints of the same animals. The average severity scores of the findings were mild to moderate. The Applicant claimed that findings in animals that received the larger injection volume of HTX-011-81 (0.5 mL vs. 0.25 mL) were more severe but in the FDA reviewer's opinion, the severity scores were similar regardless of the dose volume injected into the joint.

In rabbits sacrificed 21 days after injection there were still a number of histopathological findings in the joint space, including cartilage degeneration in the marginal zone, chondrocyte necrosis/degeneration, and hyperplasia/inflammation in the synovium. Incidence and severity of the findings were generally similar to those in animals sacrificed 7 days after injection. It appeared that ulcer/erosion/hemorrhage of the synovium and exudate were no longer present on Day 21 or greatly reduced in severity/incidence. Since some of the findings were less frequent/severe after 21 days, it is not clear if the remaining findings represent permanent damage or would improve given longer time. Regardless it is concerning that the damage to cartilage and chondrocytes is still present 21 days after injection. Thus, the damage caused by treatment with HTX-011-81 was not completely reversible after 21 days.

Dogs treated with HTX-011-81 in their knee joint (Study 35-78) also had histopathological findings at 8 days post injection; however, the response to HTX-011-81 appeared to be less pronounced. Histopathological findings included inflammation in the synovium (mixed cell and mononuclear cell), an accumulation of necrotic debris (believed to be immune cells), and cartilage degeneration. Similar to the rabbit study, average severity scores of the findings were mild to moderate. It is not completely clear whether the cartilage degeneration was due to HTX-011-81 or generally due to the knee being injected with something as it was also observed in saline treated knees at a similar severity. However, the frequency of the finding was higher in HTX-011-81 treated knees (3/4 or 75%) compared to saline treated knees (3/8 or 38%) and there were no findings of cartilage degeneration in knees injected with Exparel (0/4). Cartilage degeneration was not present in animals sacrificed on Day 22 and findings of synovial inflammation and the presence of necrotic debris were less frequent/severe suggesting that the effects of HTX-011-81 diminished with time in dogs. However, there were new findings in the knee of animals treated with HTX-011-81 (but not saline or Exparel) on Day 22 that were not present on Day 8 such as periarticular mononuclear cell inflammation and periarticular hemorrhage. Thus, it is unclear if the damage to the knee joint by HTX-011-81 is fully recovering by 22 days post injection.

The dog study also included animals treated with Exparel (bupivacaine) as a comparator since the presence of bupivacaine in Zynrelef was the source of the initial concern for potential chondrotoxicity. Interestingly, no findings were observed in knee joints treated with Exparel. This suggests that bupivacaine is not likely the cause of the findings observed with Zynrelef. However, it must be kept in mind that the concentration and absolute dose of bupivacaine (13.3 mg/mL; ~13.3 mg total dose) in the comparator arm was lower than in Zynrelef (29.25 mg/mL; ~20.5 mg total dose) so it is not a perfect comparison.

It is reasonable that the excipients in Zynrelef could have contributed to the findings in the knee based on the results of studies submitted to support the original NDA approval. Following subcutaneous injection in animal studies, HTX-011-56 caused a robust inflammatory response that was consistent with a foreign body reaction and primarily characterized by persistent chronic inflammation that was still present after 28 days. Further, the reaction with HTX-011-56 appeared to be primarily due to the TEG-POE

polymer as similar findings were seen with AP18A in other studies conducted by the Applicant, which is a similar polymer that is 80% AP135 (the TEG-POE polymer in Zynrelef). Similar to the inflammation observed following subcutaneous injection, synovial inflammation was observed following IA injection in both rabbits and dogs which lasted for at least 21 days. Based on the results, the response in the knee is likely driven by the TEG-POE polymer, although a contribution from the other excipients or drug substances cannot be ruled out at this time.

Due to the concern regarding the findings in the cartilage in Studies 35-77 (cartilage degeneration and chondrocyte degeneration/necrosis at Day 7, with marginal to no improvement noted at Day 21 post-injection) and 35-78 (cartilage degeneration and the accumulation of necrotic debris at a higher incidence than with saline injection at Day 8 post-injection with improvement at Day 22) an information request was sent to the Applicant requesting further justification to support the safety of Zynrelef for orthopedic surgeries in which exposure to articular cartilage could be high. The information request was sent on 4/12/2023 and the Applicant provided a response on 4/26/2023.

The Applicant did not believe that the nonclinical data does not alter Zynrelef's positive benefit-risk assessment as Zynrelef did not cause direct chondrotoxicity (likely secondary to the synovial inflammation), clinical data in bunionectomy did not show evidence of chondrolysis despite exposure to the first metacarpal joint, and there are no post-marketing reports of chondrolysis or other cartilage-related events to date. Further the Applicant believed that there was only cartilage degeneration in the rabbit but not dog, the cartilage damage was isolated to the marginal zone and therefore not clinically meaningful, and that dogs represented a more human-relevant model. These points will be further discussed later in this section.

The Applicant further noted that the synovial inflammation represents a reaction to the polymer of Zynrelef and that the synovial inflammation would resolve once the polymer fully degrades. They speculated that since the polymer is detectable microscopically for approximately 20 days in rats and 24 days in dogs, and presumably similarly in rabbits, this would explain why there may have been some residual effects in rabbits on Day 21 as some polymer may still be present. To support this, the Applicant informed us that they were conducting an additional study in rabbits with a longer sacrifice timepoint (Day 60) post IA injection to demonstrate full recovery of the synovial inflammation and that the study would be submitted within the review cycle. The study (Study 36-02) was received on 7/20/2023. The final report of the nonclinical data was considered a major amendment, and the Applicant was informed on 7/30/2023 that the goal date would be extended by three months to provide time for a full review of the submission.

The rabbit IA study with extended observation (Study 36-02) showed similar findings in the treated joint at Day 7 as were previously observed (Study 35-77) including degeneration/necrosis of the marginal zone cartilage, degeneration/necrosis of chondrocytes, erosion/ulceration of the synovium, synovium epithelium hyperplasia, exudate, synovial inflammation, and synovial hemorrhage. However, two additional findings were observed on Day 7 in the newer study: thrombus in the synovium and

meniscus degeneration. At the extended observation timepoint (Day 60) there were still findings in the HTX-011-81-treated knee joints consisting of degeneration/necrosis of the marginal zone cartilage, degeneration/necrosis of chondrocytes, synovium epithelium hyperplasia, and synovial inflammation. The severity of the synovial findings was decreased suggesting a partial recovery compared to Day 7, although some minimal to mild inflammation and hyperplasia were still present. However, the findings of degeneration and necrosis had increased severity on Day 60 and the pathology report noted that these effects extended from the marginal zones into load bearing cartilage. Thus, it appeared that the effects on chondrocytes/cartilage may be permanent effects that only become worse over time despite a partial resolution of effects in the synovium. This data is in contrast to the Applicant's initial view that the effects of Zynrelef would recover once the polymer fully degrades from the knee joint.

As mentioned earlier, the Applicant outlined a number of reasons why they believed that the nonclinical data does not alter the positive benefit-risk assessment for orthopedic procedures, including those with expected high exposure of Zynrelef to articular cartilage. First, the Applicant believed that Zynrelef does not cause direct chondrotoxicity. Instead, they note that synovitis was observed in both rabbits and dogs and that chondrocyte toxicity was only observed in rabbits, likely secondary to the observed synovitis. However, the lack of cartilage degeneration in the dog was questionable since there was an increased frequency (75% of animals) of the finding in HTX-011-81-treated joints compared to the saline control (38% of animals) and Exparel (0% of animals)-treated joints. Historical control data was not available to put the findings into context. The FDA reviewer feels that there was evidence of HTX-011-81-mediated cartilage degeneration in dogs since the frequency of cartilage degeneration exceeded both groups (saline and Exparel) injected with something other than HTX-011-81. The Applicant contended that the adverse cartilage changes were secondary to synovial inflammation. Whether the cartilage effects are a result of direct toxicity by the drug or occurs secondary to inflammation, the resulting cartilage damage would be a potential concern for humans. The Applicant did provide some safety data in humans to support that cartilage damage is not occurring with their drug product; therefore, the nonclinical team defers to the clinical team in regard to the ability of the human data to support that the risk identified in the nonclinical studies may not be relevant to the indications proposed.

The Applicant argued that the dog is the more relevant model for humans and thus the results from rabbit studies have less clinical significance. In the Applicant's view the dog indicates that the only response would be synovial inflammation that would resolve after the polymer is cleared and would not be of clinical significance to humans. However, as noted above, the FDA reviewer does not agree that there were no effects on the cartilage in dogs. When comparing the rabbit and dog, the local response in the knee joint to Zynrelef is less severe in dogs and appears to recover as opposed to the lack of recovery seen in rabbits, even after 60 days. However, it should be noted that there are some new effects observed on Day 22 (periarticular inflammation and hemorrhage) in dogs and longer-term data were not provided to evaluate what would happen beyond Day 22.

The FDA reviewer does not agree that the dog is a more relevant species for IA injection or that the results in rabbits (irreversible cartilage damage that expands to the load bearing zones with time) should carry less weight. The FDA reviewer discussed the findings with a nonclinical pathologist in the Agency who has experience evaluating knee pathology, and they also did not believe that there was any reason to believe that the rabbit model was not human relevant or that the dog would be more human relevant as compared to the rabbit. At this time, the Applicant has not provided convincing evidence to suggest that the results from either species would be more predictive of what could occur in humans following exposure of Zynrelef to articular cartilage.

The Applicant also noted that the nonclinical studies are exaggerated in that the relative amount injected per the surface area of cartilage is higher in the nonclinical studies as compared to what would occur clinically. In that regard they claimed that the dose/surface area was 1.8 times higher than in humans (the Applicant did not provide their calculations or references and did not calculate a value for rabbits). The reviewer calculated a dose/cartilage volume based on internal references and determined that the dog was ~1.9x higher than in humans which is a similar result. Cartilage volume data was not available for rabbits to make a similar comparison. It is unclear what the dose volume/cartilage volume ratio would be for every surgery that Zynrelef could be used for if approved for the proposed broad indication in this efficacy supplement and thus the ratio may not be exaggerated for all potential surgeries. It is also unclear if the higher ratio of dose volume/cartilage volume played a major role in the findings as the Applicant did not identify a dose volume that would not cause any effects. Furthermore, two dose volumes were tested in the rabbit study with a 21-day sacrifice and there did not appear to be a significant difference in the incidence or severity of findings with the 0.25 mL dose volume as compared to the 0.5 mL dose volume.

The Applicant further stated that the exaggerated volume used in the rabbit study with a 60-day observation period displaced the synovial fluid in the small volume of the rabbit stifle joint capsule interrupting chondrocyte access to the required oxygen and nutrients in the synovial fluid. In that regard, the volumes injected by the Applicant in the nonclinical studies are similar to the volume of the knees which contains the synovial fluid. However, the idea that this caused a lack of required oxygen and nutrients seems unlikely since a similar volume of saline was used in the control knees yet extensive cartilage and chondrocyte damage was only seen in the HTX-011-treated knees.

In terms of the dose volumes used in the nonclinical studies, they are generally considered reasonable for the species chosen and from the nonclinical perspective the volumes used in the nonclinical studies are not considered exaggerated. Clinical relevance of the dose volumes for IA administration is often evaluated by comparing the dose volume to knee volume with that of clinical dosing (Human knee volumes = Heilmann et al., 1996 and Kraus et al., 2007; Rabbit knee volume = Matsuzaka et al., 2002; dog knee volumes = Sawyer 1963 and Wehr 2007). In this case, the dose volume to knee volume ratios for the rabbit (0.5-1x) and dog (0.4-2.2x) study are similar to that of humans assuming 9 mL in the joint space (the dose used in total knee arthroplasty

(TKA); clinical study #HTX-011-209). It should be noted that the drug product is delivered by infiltration and not injection into the joint space as is the case for IA administration and thus the comparison of dose volume to knee volume is not a direct comparison but should be a reasonable approximation. However, as noted earlier for cartilage volume, it is unclear what the dose volume/total volume of the surgical space would be for every surgery that Zynrelef could be used for if approved for the proposed broad indication in this efficacy supplement and may not be representative of all potential surgeries.

In summary, the Applicant believes their drug product (likely due to the polymer) causes synovial inflammation but not direct chondrotoxicity and that only synovial inflammation was observed in dogs, which they contend is the more human relevant model. The Applicant also believes that synovial inflammation is not a clinically relevant finding as it likely recovers, it was caused by relatively high doses in animals, and synovial inflammation is common and not adverse in humans. The FDA reviewer disagrees with a number of the Applicant's positions as outlined in the discussion above. Instead, the FDA reviewer's interpretation of the nonclinical data is that treatment with HTX-011-81 leads to a robust local inflammation reaction in the synovium (which appears to recover by Day 22 in dogs and Day 60 in rabbits) and cartilage damage that appears to recover in dogs but gets worse with time in rabbits. This occurred with a formulation of Zynrelef that included clinically relevant concentrations of the drug product and excipients (~1x). The FDA reviewer believes that the data indicates a potential for Zynrelef to cause similar findings if exposed to articular cartilage in humans and defers to the clinical team in regard to the clinical relevance if the findings were to occur in humans and impact on the proposed surgical indications, especially in light of the human experience cited by the Applicant.

12 Appendix/Attachments

Literature cited:

Heilmann HH, Lindenhayn K, Walther HU (1996) Volume of synovial fluid in normal and osteoarthritic human knee joints. Z Orthop Ihre Grenzgeb (German) 134, 144-148.

Kraus VB, Stabler TV, Kong SY, Varju G, McDaniel G (2007) Measurement of synovial fluid volume using urea. Osteoarthritis Cartilage 15, 1217-1220.

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/s/

JAIME R D'AGOSTINO
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JAY H CHANG
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Number	NDA 211988 SDN 659
Supplement Number	13
Related IND Number	IND 125927
Drug Name	Zynrelef® (Bupivacaine and Meloxicam) Extended-Release Solution
Indication(s)	For Soft Tissue or Periarticular Instillation Use Efficacy Supplement for Expanded Indication for Soft Tissue and Orthopedic Surgical Procedures
Applicant	Heron Therapeutics
Date(s)	Response to Information Request Submission: July 26, 2023
Review Priority	Standard
Biometrics Division	Division of Biometric I
Statistical Reviewer	Jing Han, PhD, Mathematical Statistician
Concurring Reviewer	Xinyu Tang, PhD, Team Lead
	Sue Jane Wang, PhD, Deputy Director
Medical Division	Division of Anesthesiology, Addition Medicine, and Pain Medicine
Clinical Team	Mu Yang, MD, Medical Officer
	Alla Bazini, MD, Associate Director
Project Manager	Sandy Truong, PharmD, Senior Regulatory Health Project Manager

The Applicant submitted a response to the Information Request (IR) dated July 18, 2023 related to abdominoplasty data included in efficacy supplement S-13 submitted on December 23, 2022.

The clinical team sent an IR on July 18, 2023 to the Applicant asking about how the data from Studies 203 and 401 Cohort 2, which appeared to demonstrate that treatment with Zynrelef was possibly less efficacious than bupivacaine, could support the analgesic benefit of Zynrelef for use in abdominoplasties and other large soft tissue procedures. The Applicant responded on July 26, 2023, stating "the efficacy/PD results of both Study 203 instillation-only cohort and Study 401 Cohort 2, where the 95% CIs of the differences in mean pain scores contain the null, indicate no difference between ZYNRELEF and bupivacaine HCl groups in these studies" and thus, "it would be inappropriate to conclude that the results demonstrate inferiority of Zynrelef compared with bupivacaine HCl." The clinical team requested statistical team's input regarding the Sponsor's statistical arguments that both studies are sound and that we should not be making the presumption that Zynrelef is less efficacious than bupivacaine in the abdominoplasty surgical model based on these results.

The statistical team discussed the results from the two studies with the clinical team and emailed the following comments to the clinical team on August 25, 2023:

> It seems that Studies 203 and 401 Cohort 2 are designed for PK and safety data, not for efficacy comparison. Based on the efficacy results from these two studies, where the 95% CIs of the differences in mean pain scores contain the null, we could not conclude that the difference between YNRELEF and bupivacaine HCl groups is statistically significant. The conclusion is different from what the sponsor's statement of no difference between ZYNRELEF and bupivacaine HCl groups in these studies. The no difference statement is not appropriate because it requires a test for equivalence instead of the test for difference that the sponsor used for those two studies.

The statistical team does not have comments to be conveyed to the sponsor.

References

- Information Request(IR) dated July 18, 2023 https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806e0dd3
- Response dated July 26, 2023 to the above IR \\CDSESUB1\evsprod\NDA211988\0180\m1\us
- Statistical Filling Review dated February 22, 2023 https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806b442a

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/s/

JING HAN
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XINYU TANG
11/02/2023 04:41:43 PM

SUE JANE WANG
11/06/2023 11:09:02 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA:	211988; Efficacy Supplement 013
Submission Date:	12/23/2022
Link to EDR	\\CDSESUB1\evsprod\NDA211988\0152
Relevant IND(s):	IND 125927
Brand Name:	Zynrelef
Generic Name:	Bupivacaine (2.5% bupivacaine base) and Meloxicam (0.075%)
Formulation; Strength(s):	ER solution; bupivacaine (2.5% bupivacaine base) and meloxicam (0.075%)
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Neuropsychiatric Pharmacology
OND Division:	Division of Anesthesiology, Addiction Medicine, Pain Medicine
Sponsor:	Heron Therapeutics, Inc.
Dosage Regimen:	Single dose by instillation
Approved 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.
Proposed Expanded Indication	ZYNRELEF is indicated in adults fo (b) (4) [redacted] Limitations of Use: Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large (b) (4) [redacted] spinal, and head and neck procedures.

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1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Neuropsychiatric pharmacology (OCP/DNP) has reviewed the information submitted on 12/23/2022 in the current supplemental application NDA 211988 S-013 for the proposed expanded indication for in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures for Zynrelef. From a clinical pharmacology perspective, the information submitted in this supplemental NDA is acceptable. Labeling negotiations are ongoing as of 12/11/2023.

1.2 Regulatory Background

The NDA 211988 for bupivacaine and meloxicam extended-release solution under the tradename ZYNRELEF was initially approved on May 12, 2021, for use 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, with a limitation of use for highly vascular procedures such as intrathoracic, large multilevel spinal, and head and neck procedures.

A supplemental NDA (sNDA), S-005 was approved on December 8, 2021, in which the indication for ZYNRELEF was expanded to 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. In S-005 submission, the applicant updated the safety information, with no new clinical or nonclinical studies.

In this current sNDA, S-013 submitted on December 23, 2022, applicant proposed for broader use of ZYNRELEF in soft tissue and orthopedic surgical procedures. To support the broad indications, four new studies (in addition to those submitted with original NDA) were submitted. The details of the studies submitted with this submission and the data provided for each of the procedures and the studies submitted with original NDA is shown in the below Table 1.

Table 1: Studies conducted in Zynrelef NDA and sNDA, S-013 (new studies are bolded and italicized) to support broad indication for soft tissue and orthopedic surgical procedures.

Proposed Indication for	Studied Surgical Procedures	Phase (study #)	Data Provided	Surgery Type (Location, Size, Vascularity)
Soft Tissue	Open inguinal herniorrhaphy	Phase 3 (302)	Efficacy, PK (spare) & safety	Abdomen, Small to Medium, Moderate
		Phase 2 (202)	Efficacy, PK (rich) & safety	
	Augmentation mammoplasty	Phase 2 (211)	Efficacy, PK (rich) & safety	Thorax, Large, High
	Abdominoplasty	Phase 2 (203)	Efficacy, PK (rich) & safety	Abdomen, Large, Moderate
	Abdominoplasty	***Phase 4 (New Study 401)***	***PK (rich), safety & PD***	***Abdomen, Large, Moderate***
	C-Section	***Phase 2 (New Study 220)***	***PK (rich), safety & PD***	***Abdomen/pelvis, Medium, Moderate***
Orthopedic	Bunionectomy	Phase 3 (301)	Efficacy, PK (spare) & safety	Lower Extremity, Small, Low
		Phase 2 (208)	Efficacy, PK (rich) & safety	
	Total Knee Arthroplasty	Phase 2 (209)	Efficacy, PK (rich) & safety	Lower Extremity, Large, Moderate to High
	Total Shoulder Arthroplasty	***Phase 4 (New Study 401)***	***PK (rich), safety & PD***	***Upper Extremity, Medium to Large, Moderate***
	Spinal Surgery	***Phase 2 (New Study 221)***	***PK (rich), safety & PD***	***Spine, Small to Medium, Moderate to High***

PD endpoints: In the new studies, the applicant obtained exploratory PD data for efficacy, the mean AUC of NRS-R (rest) pain scores and postoperative opioid consumption through 72h, which were not designed or powered for treatment comparison. The clinical team reviewed these endpoints, for details, refer to the clinical teams' review.

1.3 Summary of Clinical Pharmacology Findings

Review Focus:

In this submission, the applicant evaluated Zynrelef in two soft tissue procedures, namely, abdominoplasty and C-Section and two orthopedic procedures, namely, total shoulder arthroplasty and spinal surgery. Rich PK was collected in all four new studies. The review focus of the PK data in these studies is:

1. To inform systemic safety of bupivacaine and meloxicam based on the systemic exposures.
2. To identify if the subjects had bupivacaine concentrations significantly higher than 1000 ng/mL (threshold for toxic concentrations of bupivacaine).

3. For C-Section (Study 220) where Zynrelef was administered to postpartum women, is to evaluate for bupivacaine and meloxicam (active moieties):
    a. milk/plasma AUC ratios
    b. mean estimated infant oral doses
    c. relative infant doses compared to maternal dose on mg/kg basis and
    d. last time point of measurable concentrations in breast milk.

Systemic Exposure Comparison:

Bupivacaine:

For systemic exposure, the PK parameters (Cmax and AUC) of bupivacaine component of Zynrelef obtained in the newly submitted studies were compared to the PK parameters obtained in the studies conducted in the original NDA submission (Table 2). If the systemic exposure of bupivacaine these new studies is lower compared to the studies submitted in original NDA, then the systemic exposure is covered based on the safety information evaluated in the NDA studies.

- **Cmax:** In the studies submitted in original NDA, the highest mean Cmax value of 710 ng/mL is obtained in augmentation mammoplasty procedure (Study 211). However, this procedure was not approved in the original NDA and its PK information was not included to the label because it was evaluated as a Phase 2 study with limited number of subjects via instillation route of administration (n=50); thereby have limited data supporting efficacy. In this submission, along with other soft tissue procedures, the augmentation mammoplasty procedure is being approved; and the Applicant included its PK parameters in the label. In the original NDA, the highest Cmax approved in the label was 695 ng/mL for total knee arthroplasty. The mean Cmax value of all new studies (Table 3) in the current supplement is lower compared to 695 of total knee arthroplasty or 710 ng/mL of augmentation mammoplasty (Table 2).
- **AUCinf:** In the NDA studies, the highest mean AUCinf value, 38173 h.ng/mL is obtained in total knee arthroplasty (Study 209). This study was approved and the AUCinf value was included in the label. The mean AUCinf value of all new studies (Table 3) in the current supplement are lower than 38173 h.ng/mL (Table 2).

Meloxicam:

For meloxicam component of Zynrelef, the PK parameters of new studies were compared to the Mobic label (Table 2), as was done for the NDA studies[1]. Based on the Mobic label, the observed Cmax and estimated AUCinf values of meloxicam are 1050 ng/mL and 142045 h.ng/mL. The obtained Cmax and AUCinf values of meloxicam in the new studies is lower than the Mobic label.

[1] NDA ClinPharm review, DARRTS dated 04/10/2019.

Table 2: Highest mean PK parameters in the NDA studies

Highest mean PK values from original NDA studies / listed drug (Mobic for meloxicam)			
Bupivacaine		**Meloxicam**	
Cmax	**AUCinf**	**Cmax**	**AUCinf**
710 ng/mL (Augmentation mammoplasty- Study 211) [a] 695 ng/mL (Total Knee Arthroplasty- Study 209) [b]	38173 h.ng/mL (Total Knee Arthroplasty- Study 209) [b]	1050 ng/mL [c]	142045 h.ng/mL [d]

[a] Study was conducted in the original NDA; however, it was not approved in the original NDA due to limited data supporting efficacy (a Phase 2 study) and hence its PK information was not included to the label. Since this procedure is being approved in this submission along with other soft tissue procedures, the Applicant added the PK parameters in the label with this submission.

[b] Study was conducted in the original NDA and the value is included in the approved label.

[c] Maximum Cmax value from Mobic label

[d] Meloxicam AUCinf calculations for Mobic were based AUCtau of oral Meloxicam (for details, refer to ClinPharm review in DARRTS dated 04/10/2019)

Table 3: Mean PK parameters in the new studies from this supplement.

Procedure (Study)	**New Studies, mean PK values ***			
	Bupivacaine		**Meloxicam**	
	Cmax (ng/mL)	**AUCinf (h.ng/mL)**	**Cmax (ng/mL)**	**AUCinf (h.ng/mL)**
Abdominoplasty (Study 401, Cohort 2)	382	24400	116	8500
C-Section (Study 220)	291	17500	114	9620
Total Shoulder Arthroplasty (Study 401, Cohort 1)	372	20500	248	23900
Spinal Surgery (Study 221)	163	8430	90	7060

*PK values are arithmetic mean. The dose of Zynrelef was 400 mg /12 mg, expect for spinal surgery where the dose was 191 mg/5.7 mg.

Bupivacaine Maximum Observed Concentrations:

With regards to the subjects with bupivacaine concentrations more than 1000 ng/mL in the new studies, it is noted that two subjects had >1000 ng/mL (maximum value of 1150 ng/mL), in the active comparator, Bupivacaine HCl treatment arm, while none of the subjects in the Zynrelef treatment arm had bupivacaine concentrations more than 1000 ng/mL. The details are in individual studies review below. Overall, the observed bupivacaine concentrations in Bupivacaine HCl or Zynrelef treatment arms are not significantly higher than that was observed in the other previously submitted NDA studies.

PK Conclusions from C-Section Study (study 220):

Study 220 was an open-label, two cohort study that evaluated the PK in expressed breast milk and plasma and safety of ZYNRELEF in women undergoing a planned C-section who chose prospectively not to breastfeed their newborn. Two doses of Zynrelef 300 mg/9 mg and 400 mg/12mg was evaluated in cohort 1, n=14 and Cohort 2, n=11 subjects, respectively. For the highest dose, 400 mg/12mg below are the PK conclusions:

- Cmax of bupivacaine and meloxicam in milk were ~ 14% and 3%, respectively of maternal plasma Cmax.
- The milk/plasma AUCt ratio for bupivacaine and meloxicam were 0.101 and 0.016, respectively.
- Mean estimated infant oral dose (assuming a standardized milk consumption of 200 mL/kg/day) for bupivacaine and meloxicam were 0.01 mg/kg (~ 30 micrograms for a 3 kg infant) and 0.001 mg/kg (~ 3 micrograms for a 3 kg infant), respectively.
- The relative infant dose of bupivacaine and meloxicam were 0.3 % and 1 %, respectively compared to maternal dose in a mg/kg basis.
- The last measurable concentrations in breast milk were at 6 days post-dose for bupivacaine and 8 days post-dose for meloxicam.
- The study did not evaluate the effects of ZYNRELEF on milk production.
- Since infants did not receive breast milk, the effects of ZYNRELEF on the breastfed infant is not known.

1.3 Individual Studies Review:

Study 220, Caesarean-Section

- A phase 2, open-label study of the pharmacokinetics and safety of Zynrelef administered postpartum to women undergoing a planned caesarean section.

The study was conducted in two cohorts.

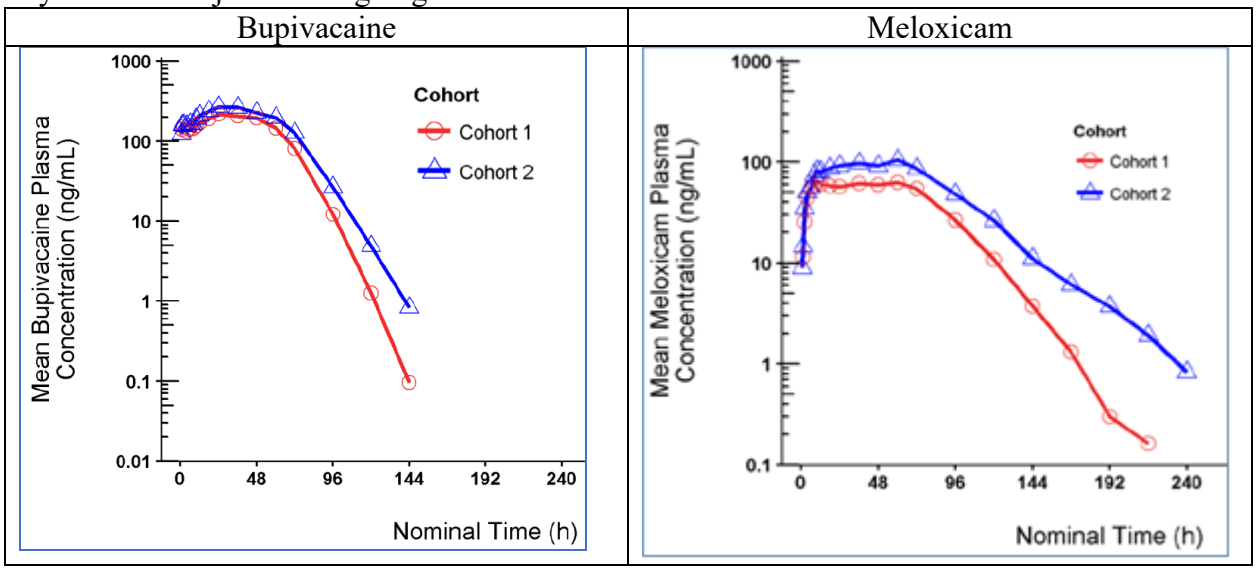
- Cohort 1: Zynrelef 300 mg/9 mg (N=13)
    - Eligible subjects enrolled underwent a C-section under ropivacaine spinal anesthesia on Day 1. In addition to ropivacaine spinal anesthesia, management of intraoperative anesthesia was in accordance with the prevailing institutional practice/anesthesiologist's preference as long as it did not include bupivacaine or meloxicam. After delivery of the newborn baby, all subjects received a single dose of ZYNRELEF 300 mg/9 mg (bupivacaine/meloxicam) administered via instillation into the surgical site.
- Cohort 2: Zynrelef 400 mg/12 mg and a scheduled, non-opioid MMA regimen (N=11)
    - On the day of surgery (Day 1), each subject was administered oral (PO) acetaminophen 975 mg to 1 g approximately 2 hours prior to the start of anesthesia. Subjects underwent a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal morphine sulfate injection (Duramorph) 50 µg, and intrathecal fentanyl 20 µg. After delivery of the newborn baby, each subject received a single dose of Zynrelef 400 mg/12 mg administered via

instillation into the surgical site. Following surgery, subjects received a scheduled, non-opioid MMA regimen while awake during the first 5 days after surgery consisting of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours so that an analgesic was taken approximately every 3 hours while the subject was awake.

The PK (in expressed breast milk and plasma), safety, and efficacy were assessed in Cohorts 1 and 2. The concentrations of bupivacaine, meloxicam, DMSO, and Zynrelef TEG POE water-soluble end products [redacted] (b) (4) in expressed breast milk and in plasma were analyzed in all subjects. In this review, the PK of active ingredients, bupivacaine and meloxicam were evaluated. For inactive ingredients evaluation, refer to the non-clinical team's review.

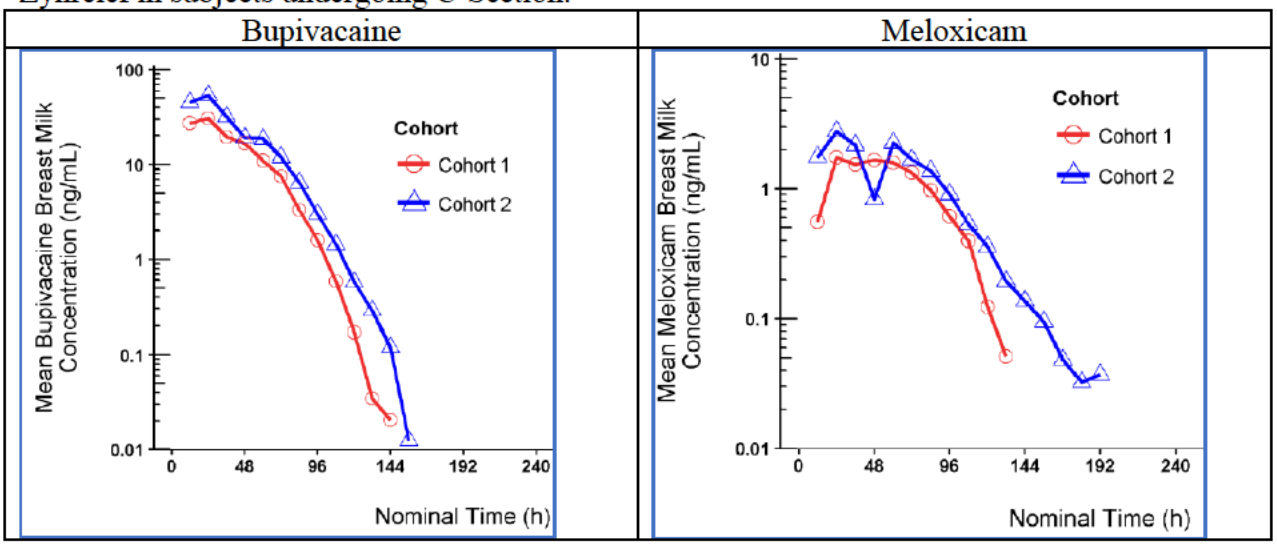
The PK profiles of bupivacaine and meloxicam in plasma and milk in Study 220 are shown in Figure 1 and Figure 2, respectively. The PK parameters of bupivacaine and meloxicam in plasma and milk are shown in Table 4 and Table 5, respectively.

Figure 1: Plasma PK profiles of bupivacaine and meloxicam following a single dose of Zynrelef in subjects undergoing C-Section.



Cohort 1: Zynrelef 300 mg/9 mg (N=13); Cohort 2: Zynrelef 400 mg/12 mg (N=11)

Figure 2: Breast milk PK profiles of bupivacaine and meloxicam following a single dose of Zynrelef in subjects undergoing C-Section.



Cohort 1: Zynrelef 300 mg/9 mg (N=13); Cohort 2: Zynrelef 400 mg/12 mg (N=11)

Table 4: Plasma PK parameters of bupivacaine and meloxicam following a single dose of Zynrelef in subjects undergoing C-Section.

Plasma PK Parameter [$]	**Bupivacaine**		**Meloxicam**	
	Cohort 1	**Cohort 2**	**Cohort 1**	**Cohort 2**
	Zynrelef 300 mg/9 mg (N=13)	**Zynrelef 400 mg/12 mg + MMA (N=11)**	**Zynrelef 300 mg/9 mg (N=14)**	**Zynrelef 400 mg/12 mg + MMA (N=11)**
Tmax (h)	24 [4, 49]	24 [1, 48]	36 [10, 73]	60 [9, 73]
Tlast (h)	99 [73, 145]	122 [97, 149]	146 [122, 224]	215 [121, 243]
Cmax (ng/mL)	238 (59.5)	291 (69.6)	75.2 (31.7)	114 (48.6)
Cavg (ng/mL)	124 (23.3)	140 (30.9)	36.5 (14.3)	47.4 (14.6)
AUClast (h·ng/mL)	13200 (3340)	17400 (4810)	5660 (2380)	9550 (4510)
AUCinf (h·ng/mL)	13300 (3220)	17500 (4810)	5940 (2320) [a]	9620 (4540)
t½ (h)	10 (3)	10 (2)	18 (6) [a]	20 (8)

[$] PK parameters values are arithmetic mean (standard deviation), except for Tmax and Tlast where it is median (minimum, maximum)
Cavg, average plasma concentration from Time 0 up to Time t of the last measured concentration
[a] N=12

Table 5: Breast milk PK parameters following a single dose of Zynrelef in subjects undergoing C-section.

Breast Milk PK Parameter [$]	Bupivacaine		Meloxicam	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
	Zynrelef 300 mg/9 mg (N=14)	Zynrelef 400 mg/12 mg + MMA (N=11)	Zynrelef 300 mg/9 mg (N=14)	Zynrelef 400 mg/12 mg + MMA (N=11)
Tmax (h)	44 [10, 106]	24 [10, 60]	59 [21, 106]	58 [12, 84]
Tlast (h)	118 [94, 142]	142 [96, 152]	102 [84, 132]	119 [72, 192]
Cmax (ng/mL)	21.1 (12.4)	40.1 (25.4)	1.92 (1.00)	3.06 (2.70)
AUClast (h·ng/mL)	769 (532)	1600 (1040)	86.7 (59.8)	161 (186)
AUClast Milk /Plasma ratio [b]	0.059 (0.036) [a] [0.000602, 0.114]	0.101 (0.080) [0.0170, 0.265]	0.015 (0.006) [a] [0.00517, 0.0250]	0.016 (0.011) [0.00480, 0.0424]
EIDtotal (mg/kg) [c]	0.00671 (0.00446)	0.0133 (0.00864)	0.000753 (0.000505)	0.00134 (0.00155)
RIDtotal (%) [d]	0.18 (0.106)	0.32 (0.170)	0.68 (0.375)	1.0 (0.997)

[$] PK parameters values are arithmetic mean (SD), except for Tmax and Tlast where it is median (minimum, maximum)

[a] N=13

[b] AUClast Milk /Plasma ratio: $AUClast_{Milk}$/ $AUClast_{Plasma}$

[c] Estimated infant dose, EIDtotal (mg/kg) = Milk /Plasma AUCt ratio x average maternal plasma concentration x 200 mL/kg/day (infant breast milk intake volume)

[d] Relative infant dose, RID_{total} (%) = infant dosage (mg/kg)/maternal dosage (mg/kg) multiplied by 100.

In this study, none of the subjects had bupivacaine concentrations >1000 ng/mL.

PK Conclusions from C-Section Study (study 220):

- Bupivacaine and meloxicam milk Cmax were approximately 14% and 3%, respectively of maternal plasma Cmax.
- Milk/Plasma AUCt ratio:
  - Bupivacaine: 0.101
  - Meloxicam: 0.016
- Mean estimated infant oral dose (assuming a standardized milk consumption of 200 mL/kg/day):
  - Bupivacaine: 0.01 mg/kg
  - Meloxicam: 0.001 mg/kg
- Relative infant dose compared to maternal dose on a mg/kg basis:
  - Bupivacaine: 0.3 %
  - Meloxicam: 1 %
- Last measurable concentrations in breast milk were at 6 days post-dose for bupivacaine and 8 days post-dose for meloxicam.

- Study did not evaluate the effects of ZYNRELEF on milk production.
- Since infants did not receive breast milk obtained following ZYNRELEF administration; therefore, the effects of ZYNRELEF on the breastfed infant is not known.

Comments:

- The obtained plasma Cmax and AUCinf values of bupivacaine or meloxicam in this C-section study are lower than the other surgical procedures submitted in original NDA studies.

Study 401 Cohort 2- Abdominoplasty (Soft Tissue Surgical Procedure):

- A Phase 4, randomized, blinded, active-controlled study of Zynrelef in subjects undergoing different surgical procedures. The Cohort 2 of the study conducted in subjects undergoing abdominoplasty. Approximately 30 subjects were to be randomized in a 2:1 ratio to HTX-011 400 mg/12 mg or bupivacaine HCl 125 mg, respectively. All subjects also received a scheduled postoperative non-opioid multimodal analgesic regimen. In this study, rich PK sampling was conducted from pre-dose to 144h post-dose.

The PK profiles and PK parameters of bupivacaine and meloxicam in plasma in Study 401 Cohort 2 are shown in Figure 3 and Table 6, respectively.

Figure 3: Plasma PK profiles of bupivacaine and meloxicam following a single dose of Zynrelef in subjects undergoing abdominoplasty.

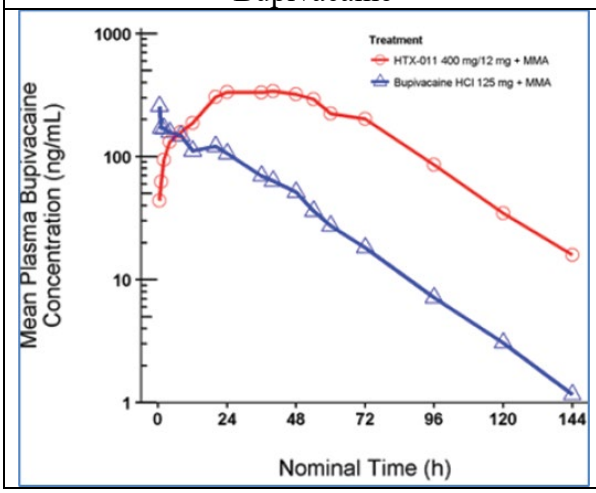
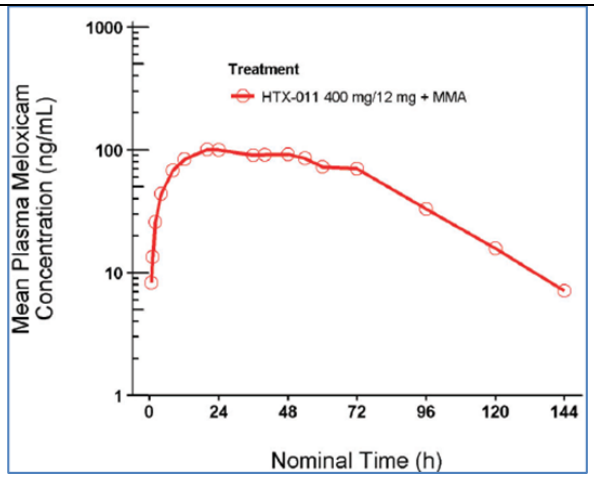
Bupivacaine	Meloxicam
	

Table 6: Plasma PK parameters of bupivacaine and meloxicam following a single dose of Zynrelef or Bupivacaine HCl in subjects undergoing abdominoplasty.

PK Parameter [$]	Zynrelef 400 mg/12 mg (N=22)		Bupivacaine HCl 125 mg (N=12)
	Bupivacaine	Meloxicam	Bupivacaine
Tmax (h)	31 [20, 54]	24 [4, 72]	19 [0.5, 48]
Tlast (h)	144 [119, 166]	143 [97, 150]	121 [70, 147]
Cmax (ng/mL)	382 (149)	116 (62)	290 (369)
AUClast (h·ng/mL)	23900 (9660)	7820 (4160)	6000 (3110)
AUCinf (h·ng/mL)	24400 (9700)	8500 (4270)	6050 (3100)
t½ (h)	20 (8)	21 (9)	17 (6)

In this study, one subject (010-0015) in Bupivacaine HCl treatment had bupivacaine concentrations >1000 ng/mL. The value is 1150 ng/mL at 0.5 and 1h.

Comments:
The obtained Cmax and AUCinf values of bupivacaine or meloxicam in this abdominoplasty study are lower than the other original NDA studies.

Study 401 Cohort 1 -Total Shoulder Arthroplasty (Orthopedic Surgical Procedure):

- Phase 4, randomized, blinded, active-controlled, multicohort study to evaluate Zynrelef compared with bupivacaine HCl in subjects undergoing different surgical procedures. Cohort 1 was conducted in subjects undergoing total shoulder arthroplasty. Approximately 30 subjects were to be randomized in a 2:1 ratio to HTX-011 400 mg/12 mg or bupivacaine HCl 100 mg, respectively. All subjects received a scheduled postoperative non-opioid multimodal analgesic regimen. In this study, rich PK sampling was conducted from pre-dose to 144h post-dose.

The PK profiles and PK parameters of bupivacaine and meloxicam in plasma in Study 401 Cohort 1 are shown in Figure 4 and Table 7, respectively.

Figure 4: Plasma PK profiles of bupivacaine and meloxicam following a single dose of Zynrelef in subjects undergoing total shoulder arthroplasty.

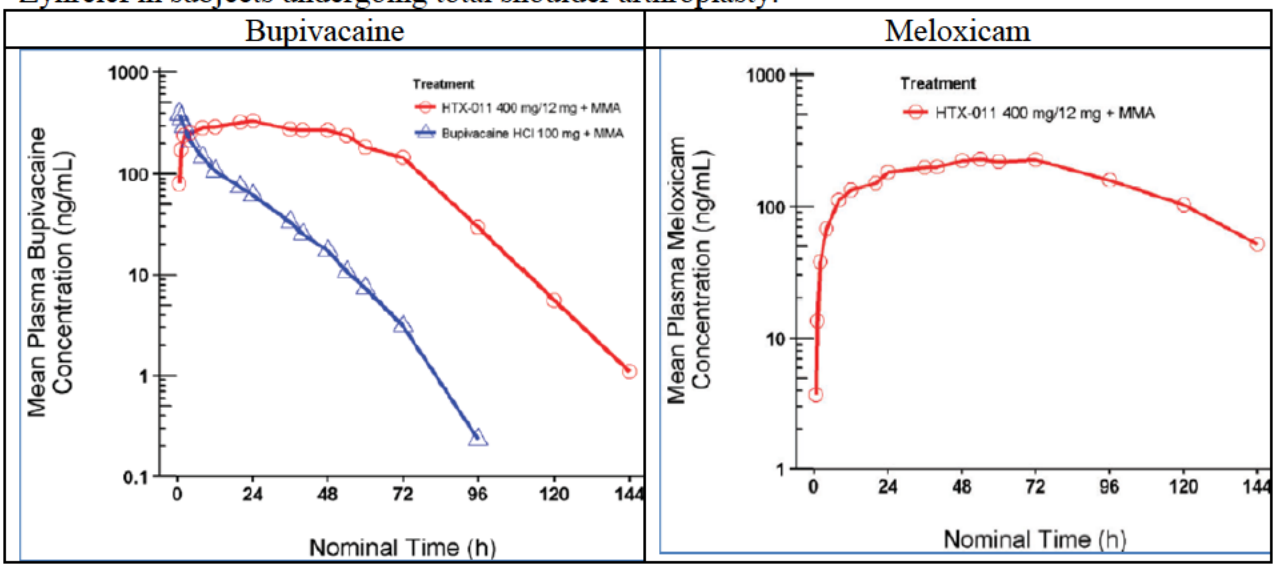


Table 7: Plasma PK parameters of bupivacaine and meloxicam following a single dose of Zynrelef or Bupivacaine HCl in subjects undergoing total shoulder arthroplasty.

PK Parameter [$]	Zynrelef 400 mg/12 mg (N=20)		Bupivacaine HCl 100 mg (N=9)
	Bupivacaine	Meloxicam (n=18[b])	Bupivacaine
Tmax (h)	20 [2, 48]	57 [12, 72]	0.6 [0.5, 3]
Tlast (h)	119 [71, 145]	144 [115, 165]	70 [24, 97]
Cmax (ng/mL)	372 (165)	248 (125)	398 (288)
AUClast (h·ng/mL)	20500 (11900)	22100 (12200)	4280 (1820)
AUCinf (h·ng/mL)	20500 (11900)	23900 (15300)	4320 (1820)
t½ (h)	10 (3)	29 (11)	8 (3)

[b] Subjects 010-0026 and 144-0006 were excluded due to a predose plasma concentration greater than 5% Cmax

In this study, one subject (144-0006) in Bupivacaine HCl treatment had bupivacaine concentrations >1000 ng/mL. The value is 1070 ng/mL at 0.5h.

Comments: The obtained Cmax and AUCinf values of bupivacaine or meloxicam in this total shoulder arthroplasty study are lower than the other original NDA studies.

Study 221- Spinal Surgery (Orthopedic Surgical Procedure):

- Phase 2, 2-part, multicenter study in subjects undergoing open lumbar spinal decompression surgery. Part A was open-label and included 3 cohorts: a bupivacaine HCl cohort and 2 Zynrelef cohorts. The purpose of Part A was to establish reference results with standard-of-care bupivacaine HCl and to evaluate Zynrelef in subjects undergoing either 1-level or 2- or 3-level lumbar spinal decompression surgery. Part B was optional. As per applicant, a decision to conduct Part B had not been made at the time of this clinical study report.

- Up to 34 subjects were to be enrolled and dosed in 1 of the following 3 cohorts:
  - Cohort 1: Bupivacaine HCl without epinephrine 100 mg administered via injection into the surgical site (6 subjects).
  - Cohort 2: Single individualized Zynrelef dose up to 200 mg/6 mg for 1-level lumbar spinal decompression surgery administered via application into the surgical site (13 subjects).
  - Cohort 3: Single individualized Zynrelef dose up to 200 mg/6 mg for 2- to 3-level lumbar spinal decompression surgery administered via application into the surgical site (13 subjects).

The PK profiles parameters of bupivacaine and meloxicam in plasma in Study 221, spinal surgery procedure is shown in Figure 5. The PK parameters of bupivacaine and meloxicam in plasma in Study 221, spinal surgery procedure is shown in Table 8 and Table 9, respectively.

Figure 5: Plasma PK profiles of bupivacaine and meloxicam following a single dose of Zynrelef in subjects undergoing spinal surgery.

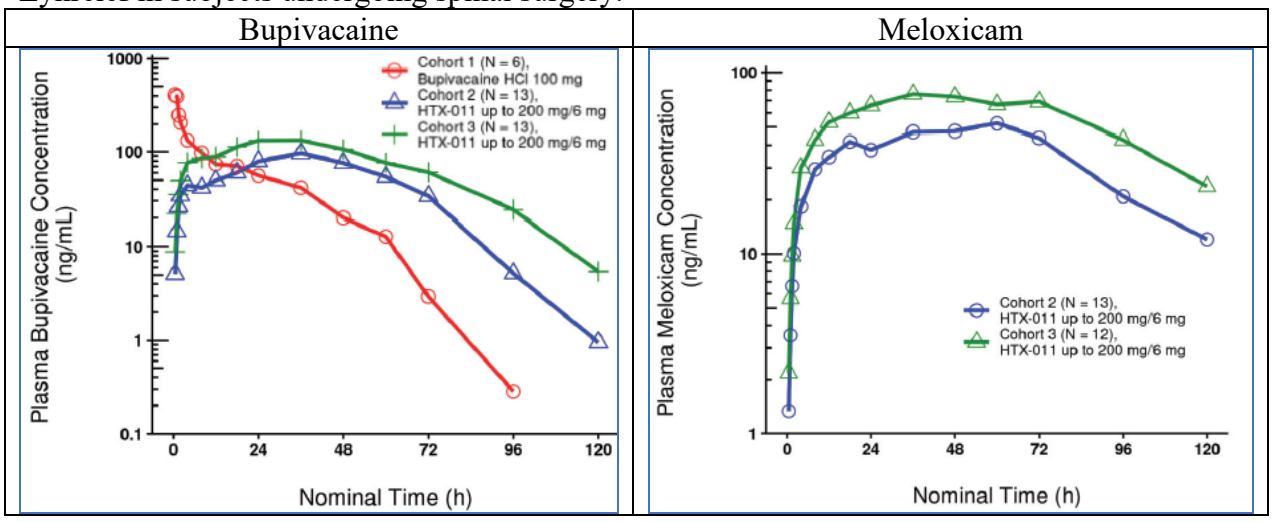


Table 8: Plasma PK parameters of bupivacaine following a single dose of Zynrelef or Bupivacaine HCl in subjects undergoing spinal surgery.

Bupivacaine PK Parameter [$]	Cohort 1	Cohort 2	Cohort 3
	Bupivacaine HCl 100 mg (N=6)	Zynrelef up to 200 mg/6 mg (N=13) Mean dose 92 mg/2.8 mg	Zynrelef up to 200 mg/6 mg (N=13) Mean dose 191 mg/5.7 mg
Tmax (h)	0.6[0.5, 2]	23 [2, 38]	24 [4, 69]
Tlast (h)	59 [46, 96]	97 [51, 123]	116 [73, 122]
Cmax (ng/mL)	387 (273)	95 (105)	163 (67)
AUClast (h·ng/mL)	3660 (1190)	4300 (4940)	8270 (4010)
AUCinf (h·ng/mL)	3620 (1330)	5740 (6550)	8430 (4230)
t½ (h)	10 (4)	19 (16)	14 (5)

Table 9: Plasma PK parameters of meloxicam following a single dose of Zynrelef in subjects undergoing spinal surgery.

Meloxicam PK Parameter [$]	Cohort 2	Cohort 3
	Zynrelef up to 200 mg/6 mg (N=13) Mean dose, 92 mg/2.8 mg	Zynrelef up to 200 mg/6 mg (N=13) Mean dose, 191 mg/5.7 mg
Tmax (h)	18 [12, 72]	43 [24, 69]
Tlast (h)	120[51, 123]	120 [73, 125]
Cmax (ng/mL)	53 (41)	90 (36)
AUClast (h·ng/mL)	3520 (2670)	6230 (3130)
AUCinf (h·ng/mL)	NR	7060 (4860)
t½ (h)	32 (13)	32 (14)

In this study, none of the subjects had bupivacaine concentrations >1000 ng/mL.

Comments:
The obtained Cmax and AUCinf values of bupivacaine or meloxicam in this spinal surgery are lower than the other original NDA studies.

1.4 Bioanalysis:

The plasma concentrations of bupivacaine and meloxicam were analyzed using validated HPLC-MS/MS.

Clinical facility: Multiple clinical hospital sites
Bio-analytical Facilities:

(b) (4)

Study 220

Milk

- Range of calibrators:
  - Meloxicam: 0.250 – 50.0 ng/mL
  - Bupivacaine: 0.100 – 20.0 ng/mL
- QCs:
  - Meloxicam: 0.750, 15.0, 37.5, 100 (dilution QC) ng/mL
  - Bupivacaine: 0.300, 6.00, 15.0, 40.0 (dilution QC) ng/mL

Study 220, Study 401 Cohort 1, Study 401 Cohort 2, and Study 221

Plasma

- Range of calibrators: Meloxicam and Bupivacaine: 1 – 1000 ng/mL
- QCs: Meloxicam and Bupivacaine: 1, 3, 50, 500 and 800 (dilution QC) ng/mL

- Accuracy and Precision of the range:
  - Accuracy (expressed as % bias): < ± 15%
  - Precision (expressed as % CV): < 15%
- Internal standards:
  - Bupivacaine: D_9
  - Meloxicam: ^{13}C, d_3 Meloxicam
- Stability: PK samples were analyzed within established frozen-storage stability for all studies.

1.5 Labeling Comments

When this review is documented in DARRTS, the labeling changes are ongoing. The applicant has added the information for Section 8.2, Lactation (based on C-section Study 220) and Section 12.3 (based on new studies).

Section 8.2, Lactation:

Since some of the results of non-clinical studies for excipients are still awaited, the labeling language for this section is not being updated in this cycle.

Section 12.3:

In this section, the applicant added descriptive statistics of PK parameters of augmentation mammoplasty (original NDA study) and new studies, abdominoplasty, C-Section, total shoulder arthroplasty and spinal surgery. Applicant separated the PK parameters of soft tissue and orthopedic surgical procedures into two separate tables as shown below. The applicant's PK parameter calculations matches to the reviewer's analysis and hence no changes are proposed.

Table 6. Summary of Pharmacokinetic Parameters for Bupivacaine and Meloxicam After Single Dose Administration of ZYNRELEF by Instillation for Soft Tissue Surgical Procedures

Active Ingredient	Parameter	Herniorrhaphy: 300 mg/9 mg ZYNRELEF (N=16)	Abdominoplasty: 400 mg/12 mg ZYNRELEF (N=22)	Augmentation Mammoplasty: 400 mg/12 mg ZYNRELEF (N=49)	Cesarean Section: 400 mg/12 mg ZYNRELEF (N=11)
Bupivacaine	C_{max} (ng/mL)	271 (147)	382 (149)	710 (246)	291 (70)
	T_{max} (h)	18 (3, 30)	31 (20, 54)	3.6 (1.3, 35)	24 (1.1, 48)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	15174 (8545)	24411 (10072)	27363 (9227)	17923 (5069)
	$AUC_{(inf)}$ (h×ng/mL)	15524 (8921)	24930 (10105)	31072 (17998)	17983 (5065)
	$t_{½}$ (h)	16 (9)	20 (8)	25 (20)	10 (2)
	C_{72h} (ng/mL)	96 (75)	202 (118)	149 (68) [b]	127 (56)
	C_{96h} (ng/mL)	37 (43)	86 (52) [c]	NS	27 (16)
	C_{144h} (ng/mL)	NS	16 (11) [c]	NS	0.8 (1.0) [d]
Meloxicam	C_{max} (ng/mL)	225 (96)	116 (62)	527 (149)	114 (49)
	T_{max} (h)	54 (24, 96)	24 (4.0, 72)	20 (5.6, 49)	60 (8.5, 73)
	$AUC_{(0-t)}$ (h×ng/mL)	18721 (7923)	7924 (4197)	30499 (9460)	9710 (4560)
	$AUC_{(inf)}$ (h×ng/mL)	NR	8304 (4422)	41809 (38414)	9778 (4592)
	$t_{½}$ (h)	NR	21 (9)	42 (70)	21 (9)
	C_{72h} (ng/mL)	197 (95)	70 (44)	214 (105) [b]	86 (43)
	C_{96h} (ng/mL)	146 (86)	33 (25) [c]	NS	48 (32)
	C_{144h} (ng/mL)	NS	7.1 (10) [c]	NS	11 (12) [d]

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 herniorrhaphy, augmentation mammoplasty, and Cesarean section; 0 to 144 h post-dose for abdominoplasty.

[b] N=48; [c] N=21; [d] N=10

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

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

Active Ingredient	Parameter	Bunionectomy: 60 mg/1.8 mg ZYNRELEF (N=17)	Total Knee Arthroplasty: 400 mg/12 mg ZYNRELEF (N=53)	Total Shoulder Arthroplasty: 400 mg/12 mg ZYNRELEF (N=20)	1-Level Spinal Surgery: 92 mg/2.8 mg ZYNRELEF (N=13)	2- or 3-Level Spinal Surgery: 191 mg/5.7 mg ZYNRELEF (N=13)
Bupivacaine	C_{max} (ng/mL)	54 (33)	695 (411)	372 (165)	95 (105)	163 (67)
	T_{max} (h)	3.0 (1.6, 24)	21 (4, 59)	20 (1.8, 48)	23 (1.9, 38)	24 (4.1, 69)
	$AUC_{(0-t)}$ [a] (h×ng/mL)	1681 (1154)	35889 (28399)	21132 (12331)	4467 (4977)	8488 (4086)
	$AUC_{(inf)}$ (h×ng/mL)	1718 (1211)	38173 (29401) [b]	21193 (12329)	5535 (6091) [c]	8659 (4288) [d]
	$t_{½}$ (h)	15 (8)	17 (7) [b]	10 (3)	25 (25) [c]	14 (5) [d]
	C_{72h} (ng/mL)	5.0 (5.3)	227 (283)	145 (117)	34 (48) [d]	61 (49) [c]
	C_{96h} (ng/mL)	1.7 (2.9) [e]	NS	30 (32)	5.2 (7.3) [d]	24 (27) [d]
	C_{144h} (ng/mL)	NS	5.3 (21) [f]	1.1 (2.2) [g]	NS	NS
Meloxicam	C_{max} (ng/mL)	26 (14) [e]	275 (134)	248 (125) [h]	53 (41) [i]	90 (36) [c]
	T_{max} (h)	18 (8, 60) [e]	36 (12, 72)	57 (12, 72) [h]	18 (12, 72) [i]	43 (23, 69) [c]
	$AUC_{(0-t)}$ (h×ng/mL)	1621 (927) [e]	19525 (12259)	22292 (12250) [h]	3556 (2665)	6269 (3133) [c]
	$AUC_{(inf)}$ (h×ng/mL)	2079 (1631) [e]	25673 (17666) [j]	24133 (15285) [k]	3826 (3890) [d]	8265 (5874) [l]
	$t_{½}$ (h)	33 (36) [e]	42 (37) [j]	29 (11) [k]	35 (15) [d]	38 (22) [l]
	C_{72h} (ng/mL)	13 (9) [e]	202 (120)	228 (131) [h]	44 (44) [d]	69 (37) [d]
	C_{96h} (ng/mL)	7.7 (5.8) [m]	NS	158 (126) [h]	21 (23) [d]	43 (28) [l]
	C_{144h} (ng/mL)	NS	28 (37) [n]	52 (56) [k]	NS	NS

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). For spinal surgery, ZYNRELEF mean doses for single-level and multilevel surgeries are shown; individual doses ranged from 45 mg/1.4 mg to 248 mg/7.4 mg.

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

[b] N=50; [c] N=12; [d] N=11; [e] N=16; [f] N=32; [g] N=19; [h] N=18; [i] N=13; [j] N=35; [k] N=17; [l] N=10; [m] N=15; [n] N=28

NS = not sampled.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

OTHER REVIEW(S)

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

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

Memorandum

Date: December 21, 2023

To: Mu Yang, Clinical Reviewer, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Sandy Truong, Senior Regulatory Project Manager, Division of Regulatory Operations – Neuroscience (DRO-N)

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

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZYNRELEF (bupivacaine and meloxicam) extended-release solution, for soft tissue or periarticular instillation use

NDA: 211988/S-013

Background:

In response to DAAP's consult request dated February 6, 2023, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for supplement 13 for ZYNRELEF (bupivacaine and meloxicam) extended-release solution, for soft tissue or periarticular instillation use. This supplement proposes expanding the indication in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on December 11, 2023 and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on November 17, 2023, and we do not have any comments at this time.

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

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

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/s/

PHILLIP A WILLIAMS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Disease, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatrics and Maternal Health Brief Memo

Date: 12/18/2023 **Date Consulted:** 2/9/2023

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Yip Wang, Regulatory Project Manager (RPM)
Rigo Roca, MD, Director
Division of Anesthesiology, Addiction, and Pain Medicine (DAAP)

NDA: 211988/S-013 (Efficacy supplement)

IND: 125927

Drug: Zynrelef (bupivacaine and meloxicam) extended-release solution, for soft tissue or periarticular installation use

Approved Indication: 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 joint arthroplasty surgical procedures.

Proposed Indication: Indicated in adults for instillation prior to postsurgical analgesia for up to 72 hours after surgical procedures.

Applicant: Heron Therapeutics, Inc.

Subject: Clinical Lactation Final Study Report (HTX-011-220) and applicant's proposed updated lactation labeling language in subsection 8.2.

Materials Reviewed:

- Applicant's submission of Zynrelef final lactation study report dated 12/23/22, "A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned C-section (Study HTX-011-220)."
- DPMH review of PLLR labeling for Zynrelef NDA 211988 dated 4/9/19, DARRTS reference ID: 4416766.
- DPMH review of draft lactation protocol (Study HTX-011-220) for Zynrelef NDA 211988, by Kristie Baisden, DO, dated 3/8/19, DARRTS Reference ID: 4401183.
- DPMH review of final lactation protocol ((Study HTX-011-220) for Zynrelef NDA 211988, by Kristie Baisden, DO, dated 5/13/19, DARRTS Reference ID: 4433034.
- DPMH review of protocol amendment (Study HTX-011-220) for Zynrelef NDA 211988 by Jeanine Best, MN, RN, PNP, Senior Clinical Analyst, dated 3/20/20, DARRTS Reference ID: 4583446.
- DAAP Type C Written Response Only (WRO) Letter by Rita K. Joshi, PharmD, dated 6/16/22, DARRTs Reference ID: 5000145.
- Applicant's response to DPMH Information Request (IR) submitted on 6/30/22.
- Applicant's response to DAAP Nonclinical IR submitted on 9/20/23.

Consult Question: "DAAP requests whether DPMH agrees the reported lactation data from Study 220 would support the proposed labeling updates in Section 8.2."

INTRODUCTION

On February 9, 2023, the Division of Anesthesiology, Addiction, and Pain Medicine (DAAP) consulted the Division of Pediatrics and Maternal Health (DPMH) to provide input on applicant's proposed updates to labeling subsection 8.2 based on the findings from Study HTX-011-220: "A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned C-section."

BACKGROUND

Regulatory History

- On May 12, 2021, Zynrelef (bupivacaine and meloxicam) NDA 211988 received initial FDA approval in adults for soft tissue or periarticular instillation use to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.
- On December 8, 2021, an efficacy supplement was approved 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.

- On June 16, 2022, DAAP issued Type C Guidance Written Response Only (WRO) Letter to the applicant which included comments from DPMH regarding the applicant's proposed lactation labeling updates related to Study 220 results.[1]
- On December 23, 2022, the applicant submitted an efficacy supplement proposing an expanded indication for Zynrelef use in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic surgical procedures. The applicant also submitted final study report for Study 220 which contains clinical lactation data to support proposed labeling changes in Section 8.2.
- On June 16, 2023, the Agency sent the applicant an IR for any relevant lactation pharmacovigilance cases and a review of published literature regarding Zynrelef (including active pharmaceutical ingredients and excipients) use in lactating women.
- On June 30, 2023, the applicant submitted their response which was found to be adequate for review.

Product Description[2,3]

- Each mL of the HTX-011 solution contains active ingredients bupivacaine 29.25 mg and meloxicam 0.88 mg and inactive ingredients tri(ethylene glycol) poly(orthoester) (TEG-POE) polymer (730 mg), triacetin (293 mg), dimethyl sulfoxide (DMSO; 117 mg), and maleic acid 0.59 mg). (b) (4)
- *Dose and administration:* intended for single-dose administration only; prepared and administered with the components provided in the Zynrelef kit; applied without a needle into the surgical site following final irrigation and suction and prior to suturing; recommended dose is up to a maximum of dose of 400mg/12 mg (14 mL).

Currently Approved Lactation Labeling[3]

Approved Zynrelef labeling is in the Pregnancy and Lactation Labeling Rule (PLLR) format and includes the following information related to use during 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.

[1] DAAP Type C Written Response Only (WRO) Letter by Rita K. Joshi, PharmD, dated 6/16/22, DARRTs Reference ID: 5000145.
[2] Source: Applicant's Final Study Report HTX-011-200 submitted 12/23/22.
[3] Zynrelef NDA 211988 currently approved labeling dated 12/13/2022, drugs@fda.

(b) (4)

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.

(b) (4) Data

Animal Data:

Following administration of Zynrelef to lactating pigs, bupivacaine and meloxicam were detected in milk, but only bupivacaine was detected in 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.

REVIEW OF SUBMISSION

Final Clinical Study Report HTX-011-220

Brief Study Description

The primary objective of this Phase 2, open-label study was to characterize the pharmacokinetics (PK) of bupivacaine, meloxicam, DMSO, and HTX-011 TEG-POE water-soluble end products in expressed breast milk and plasma from women undergoing a planned C-section who were administered a single dose of HTX-011 postpartum alone or as part of a scheduled, non-opioid multimodal analgesic (MMA) regimen. The study also assessed HTX-011safety and analgesic activity. The study did not evaluate effects of HTX-011 on the breastfed infant.

The study consisted of a 28-day screening period, C-section surgery on Day 1, a 72-hour inpatient postoperative observation period, and a follow-up period from discharge through Day 28. A single dose of HTX-011 was to be administered into the surgical site using a custom Luer lock applicator after delivery of the newborn baby. A dose of 300 mg/9 mg was administered in Cohort 1 (n=14) and 400 mg/12 mg was administered in Cohort 2 (n=11).

Blood and expressed breast milk samples were collected from subjects in Cohorts 1 and 2 to assess the PK profiles of bupivacaine, meloxicam, DMSO, and HTX-011 TEG-POE polymer water-soluble end products (b) (4)). Concentrations in breast milk were determined using validated assays. In addition, the plasma PK of the other HTX-011 excipients, maleic acid and triacetin, were evaluated as an exploratory analysis. Concentrations of maleic acid and triacetin were not determined in breast milk because levels of both excipients in breastmilk were expected to be very low based on the low plasma levels observed in the study.

Results[4]

- Refer to applicant's Figure 5 and Figure 6 below[5] demonstrating mean breast milk concentrations of HTX-011 components over time following a single dose of 300mg/9mg and 400mg/12mg, respectively.
- For the highest dose, 400mg/12 mg:

[4] Source: Clinical Pharmacology Slides from Suresh Naraharisetti, PharmD, as presented at the internal DAAP wrap up meeting on 12/6/23 for Zynrelef NDA

[5] Source: Applicant's Final Study Report HTX-011-200 submitted 12/23/22.

- Breast milk Cmax of bupivacaine and meloxicam were ~14% and 3%, respectively, of maternal plasma Cmax.
- Milk/plasma AUC_t ratio for bupivacaine and meloxicam were 0.01 and 0.016, respectively.
- Mean estimated infant oral dose (assuming a standardized milk consumption of 200 mL/kg/day) for bupivacaine and meloxicam were 0.01 mg/kg (~30 µg for a 3 kg infant) and 0.001 mg/kg (~30 µg for a 3 kg infant), respectively.
- Relative infant dose (RID) of bupivacaine and meloxicam were 0.3% and 1%, respectively, compared to maternal dose on a mg/kg basis.
- Last measurable concentrations in breast milk post dose: 6 days-bupivacaine and 8 days-meloxicam.
- The (b) (4)

(b) (4)

Reviewer's Comment
The applicant submitted the final study report for Study HTX-011-220 with proposed updates to labeling subsection 8.2 related to measured concentrations of only the active ingredients (bupivacaine and meloxicam) in breast milk. However, the applicant also measured levels of excipients in milk and did not provide a full lactational safety assessment to support the proposed updates in labeling. Therefore, DPMH defers a full review of the final report for Study HTX-011-220 and labeling recommendations for subsection 8.2 until additional information is submitted by the applicant as outlined below. A high-level of summary of the lactation study findings is provided herein as above and the reader is also referred to the Clinical Pharmacology review by Suresh Naraharisetti, PharmD, Nonclinical Review by Jaime D'Agostino, PhD, and Clinical Review by Mu Yang, MD, for additional information.

DISCUSSION

DPMH sent the applicant an IR to request any relevant clinical data from published literature or their pharmacovigilance database to evaluate the safety of components of Zynrelef in breastmilk considering infants were not exposed to Zynrelef in Study 220. The applicant's IR response dated 6/30/23, included a cumulative review of their pharmacovigilance database through 6/28/23, which noted that no breastfed infants have been exposed to Zynrelef via lactation in any clinical study and no postmarketing cases regarding have been reported involving lactation women or their infants. The applicant also performed a cumulative published literature review through 6/26/23, noting no relevant human data had been identified to inform the safety of

exposure of the breastfed infant through lactation to bupivacaine, meloxicam, DMSO, maleic acid, triacetin, or TEG-POE polymer water-soluble end products (b) (4)

DPMH attended several internal meetings with the DAAP review team from 2/2023 to 12/2023 to discuss the applicant's proposed lactation labeling updates and uncertainty regarding the clinical significance of the findings. The team acknowledged the applicant's position that levels detected in breastmilk for all Zynrelef components are low (RID <10%). However, the DAAP Nonclinical Review team noted there are ongoing juvenile animal studies for meloxicam, bupivacaine, (b) (4). On 9/8/23, the Nonclinical Review Team sent the applicant an IR noting a risk assessment for the levels of bupivacaine, meloxicam, excipients, and polymer metabolites detected in breast milk was not included in the submission to inform safety with respect the breastfeeding. On 9/22/23, the applicant responded "a lactation risk assessment for Zynrelef was not included in this efficacy supplement because its completion is partially dependent upon ongoing nonclinical postmarketing requirement studies." The applicant acknowledged DAAP's position and noted that the recommended information (breastfeeding risk assessment based on information from clinical Study 220, information from nonclinical juvenile PMR studies, and an updated nonclinical and clinical literature review) will be provided in a separate, future efficacy supplement to support the use of Zynrelef in nursing mothers.

DPMH discussed the applicant's response with the DAAP Review Team at the Wrap-up Meeting on 12/6/2023 and the decision was made not to make any labeling updates to subsection 8.2 with the current efficacy supplement given that submission of additional clinical and nonclinical data are pending.

DPMH RECOMMENDATIONS

DPMH recommends DAAP defer any updates to lactation labeling with this efficacy supplement. Instead, Zynrelef labeling subsection 8.2 should be updated when the applicant submits additional information that is pending at this time. DPMH notes the applicant's IR response dated 9/22/23 which indicates a plan to submit a full lactation risk assessment for Zynrelef (breastfeeding risk assessment based on information from clinical Study 220, information from nonclinical juvenile PMR studies, and an updated nonclinical and clinical literature review) with a future efficacy supplement to support use in breastfeeding.

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/s/

KRISTIE W BAISDEN
12/18/2023 11:06:54 AM

TAMARA N JOHNSON
12/18/2023 02:46:18 PM

LYNNE P YAO
12/18/2023 02:49:57 PM

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:	November 21, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988/S-013
Product Name, Dosage Form, 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* *Each strength is a concentration of 29.25 mg/mL bupivacaine and 0.088 mg/mL meloxicam
Applicant/Sponsor Name:	Heron Therapeutics, Inc.
TTT ID #:	2023-3542-1
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling and instructions for use (IFU) received on November 17, 2023 for Zynrelef. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels, carton labeling, and IFU for Zynrelef (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Hakeem, S. Label and Labeling Review for Zynrelef (NDA 211988/S-013). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 OCT 26. TTT ID No.: 2023-3542.

2 CONCLUSION

The Applicant addressed all of our recommendations and we have no additional recommendations at this time.

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/s/

SUSAN HAKEEM
11/21/2023 01:34:47 PM

VALERIE S VAUGHAN
11/21/2023 02:02:06 PM

LABEL AND LABELING REVIEW

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)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 26, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988/S-013
Product Name, Dosage Form, 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* *Each strength is a concentration of 29.25 mg/mL bupivacaine and 0.088 mg/mL meloxicam
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics, Inc.
FDA Received Date:	December 23, 2022
TTT ID #:	2023-3542
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 REASON FOR REVIEW

Heron Therapeutics, Inc. submitted a prior approval efficacy supplement for Zynrelef (bupivacaine and meloxicam) extended-release solution to propose changes to the labeling. Subsequently, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Zynrelef prescribing information (PI), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 211988 for Zynrelef (bupivacaine and meloxicam) extended-release solution was approved on May 12, 2021. Heron is submitting this prior approval efficacy supplement for NDA 211988/S-013 to support the proposed indication for broader use of Zynrelef in soft tissue and orthopedic surgical procedures.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C—N/A
FDA Adverse Event Reporting System (FAERS)*	D—N/A
Other	E—N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Heron Therapeutics, Inc.

4 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented in the *Dosage and Administration* section, the route of administration is missing.	Missing route of administration statement could pose risk of product administration errors.	Add the route of administration statement without the use of abbreviations.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented in the table within subsection 2.2, the units of measure are not presented immediately following the numeric dose of both bupivacaine and meloxicam or the volume to be withdrawn.	Omission of the units of measure following each numeric dose and the volume to be withdrawn may lead to misinterpretation and medication error.	We recommend including the unit of measure following each numeric dose and the volume to be withdrawn. For example, revise "60/1.8" to "60 mg/1.8 mg" and "2.3" to "2.3 mL," respectively.
2.	The warning statement [redacted] (b) (4)	Post-marketing reports have shown that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpreted as an affirmative action.	Consider underlining or bolding the word "not" to help mitigate wrong route of administration errors. Furthermore, we recommend reiterating the intended route of administration preceding the statement of routes to avoid. For example, revise to: "Administer ZYNRELEF via instillation only. ZYNRELEF should not be administered via the following routes:…" See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize*

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Medication Errors (May 2022).[a]
3.	As currently presented, (b) (4) .	(b) (4) could pose risk of product administration errors.	(b) (4) For example, we recommend revising the first bulleted point of Subsection 2.1 *Important Dosage and Administration Information* to: "ZYNRELEF is intended for single-dose instillation administration only."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented in the table within section 16, (b) (4)	(b) (4) may lead to misinterpretation and medication error.	We recommend including the unit of measure following each numeric dose and the net quantity volume. For example, revise "400/12" to "400 mg/12 mg" and "14" to "14 mL," respectively.

[a] Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022). Available from: https://www.fda.gov/media/158522/download.

5 RECOMMENDATIONS FOR HERON THERAPEUTICS, INC.

Table 3. Identified Issues and Recommendations for Heron Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The statement (b) (4)	Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 2.0 mL is seen as 20 mL).	We recommend revising the statement (b) (4) to remove the trailing zero. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*[a]
2.	The warning statement (b) (4) .	Post-marketing reports have shown that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpreted as an affirmative action.	Consider presenting the word "not" in all capital letters to help mitigate wrong route of administration errors. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*[a]
3.	The statement, (b) (4) is missing in the storage statement.	(b) (4) " may result in loss of strength or potency, or destructive alteration of the product's characteristics.	We recommend (b) (4) "protect from light and moisture" on the container label and carton labeling in alignment with the storage and handling listed in the Prescribing Information.
Instructions for Use			
1.	(b) (4)	If the syringe image does not accurately depict the co-packaged syringe, users may misunderstand the instructions or question whether they received the right dosing device.	Revise the syringe image used in the IFU to align with the syringe size that is co-packaged with the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Zynrelef that Heron Therapeutics, Inc. submitted on December 23, 2022.

Table 4. Relevant Product Information for Zynrelef	
Initial Approval Date	May 12, 2021
Active Ingredient	Bupivacaine and meloxicam
Indication	ZYNRELEF is indicated in adults for [redacted] (b) (4)
Route of Administration	[redacted] (b) (4)
Dosage Form	Extended-release solution
Strength	60 mg bupivacaine/1.8 mg meloxicam* [redacted] (b) (4)) 200 mg bupivacaine/6 mg meloxicam* 300 mg bupivacaine/9 mg meloxicam* [redacted] (b) (4)) 400 mg bupivacaine/12 mg meloxicam* *Each strength is a concentration of 29.25 mg/mL bupivacaine and 0.088 mg/mL meloxicam
Dose and Frequency	As a general guidance in selecting the proper dosing of ZYNRELEF, the following examples of dosing are provided: • For soft tissue surgical procedures, such as: - open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam - abdominoplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam - Cesarean section: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam - augmentation mammoplasty: up to 7 mL per side to deliver total of 400 mg of bupivacaine and 12 mg of meloxicam • For orthopedic surgical procedures, such as: - bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam - total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam

<table>
<tr><td></td><td>
- total shoulder arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam
- 1- to 3-level spinal surgery: up to 7 mL to deliver 200 mg bupivacaine and 6 mg meloxicam
</td></tr>
<tr><td>How Supplied</td><td>
Clear, pale-yellow to yellow viscous liquid available in four presentations. Each single-dose glass vial is filled with a solution of 29.25 mg/mL bupivacaine and 0.088 mg/mL meloxicam. Each presentation is supplied in the Zynrelef kit containing a vial (packaged in an individual carton) along with sterile, individually packaged components for administration
<table>
<tr><th colspan="3">Product Presentation</th><th rowspan="2">Vented Vial Spike Provided</th><th rowspan="2">Luer Lock Syringe(s) Provided</th><th rowspan="2">Luer Lock Applicator(s) Provided</th><th rowspan="2">Syringe Tip Cap(s) Provided</th></tr>
<tr><th>NDC</th><th>Bupivacaine/ Meloxicam (mg/mg)</th><th>Net Quantity Volume* (mL)</th></tr>
<tr><td>47426-301-02</td><td>400 mg/12 mg</td><td>14 mL</td><td>1</td><td>2 x 12 mL</td><td>2</td><td>2</td></tr>
<tr><td>47426-302-02</td><td>300 mg/9 mg</td><td>10.5 mL</td><td>1</td><td>1 x 12 mL</td><td>1</td><td>1</td></tr>
<tr><td>47426-303-01</td><td>200 mg/6 mg</td><td>7 mL</td><td>1</td><td>1 x 12 mL</td><td>1</td><td>1</td></tr>
<tr><td>47426-304-01</td><td>60 mg/1.8 mg</td><td>2.3 mL</td><td>1</td><td>1 x 3 mL</td><td>1</td><td>1</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>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</td></tr>
<tr><td>Container Closure</td><td>(b) (4) clear glass vials with a 20 mm opening. The vials are closed with 20 mm (b) (4) coated with (b) (4) and capped with 20 mm aluminum overseals.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 15, 2023, we searched for previous DMEPA reviews relevant to this current review since our review completed on October 12, 2022[b], using the terms, Zynrelef and NDA 211988. Our search identified one additional previous review[c], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Birkemeier D. Label and Labeling Review for Zynrelef (NDA 211988/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 12. TTT ID No.: 2022-1380.

[c] Birkemeier D. Label and Labeling Review Memo for Zynrelef (NDA 211988/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 18. TTT ID No.: 2022-1380-1.

APPENDIX C. —N/A

APPENDIX D. —N/A

APPENDIX E. —N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Zynrelef labels and labeling submitted by Heron Therapeutics, Inc..

- Container label(s) received on December 23, 2022.
- Carton labeling received on December 23, 2022.
- Instructions for Use received on December 23, 2022, available from:
    - 60 mg/1.8 mg: \\CDSESUB1\EVSPROD\nda211988\0152\m1\us\draft-ifu-60-soft-tissue-ortho-proc.pdf.
    - 200 mg/6 mg: \\CDSESUB1\EVSPROD\nda211988\0152\m1\us\draft-ifu-200-soft-tissue-ortho-proc.pdf.
    - 300 mg/9 mg: \\CDSESUB1\EVSPROD\nda211988\0152\m1\us\draft-ifu-300-soft-tissue-ortho-proc.pdf.
    - 400 mg/12 mg: \\CDSESUB1\EVSPROD\nda211988\0152\m1\us\draft-ifu-400-soft-tissue-ortho-proc.pdf.
- Prescribing Information (Image not shown) received on December 23, 2022., available from \\CDSESUB1\EVSPROD\nda211988\0152\m1\us\draft-pi-expand-soft-tissue-ortho-proc.pdf.

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SUSAN HAKEEM
10/26/2023 11:38:27 AM

VALERIE S VAUGHAN
10/26/2023 11:47:42 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 211988/S-013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211988

NDA ACKNOWLEDGMENT

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

Attention: Lynley Thinnes
Executive Director, Regulatory Affairs

Dear Ms. Thinnes:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug: Zynrelef (bupivacaine and meloxicam) Extended Release Solution 60 mg/1.8 mg, 200 mg/6 mg, 400 mg/12 mg

Date of Application: October 30, 2018

Date of Receipt: October 30, 2018

Our Reference Number: NDA 211988

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 December 29, 2018, 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Cite the NDA reference number at the top of each page of any submission related to this marketing application.

SUBMISSION REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact me, at 240-402-8807.

Sincerely,

{See appended electronic signature page}

Ogochukwu Ogoegbunam, PharmD, BCGP
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

OGOCHUKWU U OGOEGBUNAM
11/02/2018