ZYNRELEF™
(bupivacaine and meloxicam)
extended-release solution
29.25 mg/mL and 0.88 mg/mL

ORDERING AND PRICING INFORMATION

ZYNRELEF is the first and only extended-release dual-acting local anesthetic (DALA) designed to address the challenges of pain and inflammation at the surgical site.[1-3]

Supplied and marketed by: Heron Therapeutics, Inc
Product name: ZYNRELEF
Established name: bupivacaine and meloxicam extended-release solution

- GPO, 340B, and sub-WAC pricing available
- Available through authorized wholesalers and specialty distributors
  - Prime vendor discounts apply
- ZYNRELEF is available in 2 volumes as shown below

Product Code (NDC)	Bupivacaine/ Meloxicam	Volume	WAC Price	340B Price	Kit Contents *(in addition to single-dose vial)*
47426-301-02	400 mg/12 mg	14 mL	$267.50	$203.57	1 vented vial spike, 2 x 12-mL Luer lock syringes, 2 Luer lock cone-shaped applicators, 2 syringe tip caps
47426-303-01	200 mg/6 mg	7 mL	$135.50	$103.12	1 vented vial spike, 1 x 12-mL Luer lock syringe, 1 Luer lock cone-shaped applicator, 1 syringe tip cap

Note: All kits have the same outer dimensions: 4.04" (depth) x 1.60" (height) x 7.04" (width). Minimum order quantity for each SKU is 10 kits. ZYNRELEF pricing as of May 12, 2021. Confirm current pricing with your Heron representative.

Key Product and Packaging Characteristics

- Room temperature storage (20°C to 25°C); 36-month shelf life[3,4]
- Kits are sized to fit in standard OR medication carts (eg, Pyxis™)
- ZYNRELEF is a clear, pale yellow to yellow, viscous solution
- ZYNRELEF is developed and packaged in the United States

Questions? Contact Heron Connect® at 1-844-HERON11 (1-844-437-6611) or HeronConnect.com

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL 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.**
- **ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.**
- **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.**

Contraindications

ZYNRELEF is contraindicated in patients with known hypersensitivity (eg, anaphylactic reactions and serious skin reactions) to any amide local anesthetic, NSAIDs, or other components of ZYNRELEF; with 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); undergoing obstetrical paracervical block anesthesia; or undergoing coronary artery bypass graft (CABG) surgery.

Warnings and Precautions

Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after application of ZYNRELEF. When using ZYNRELEF with other local anesthetics, overall local anesthetic exposure must be considered through 72 hours.

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

Hypertension: Patients taking some antihypertensive medication may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

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.

Please see additional Important Safety Information on the following page and full Prescribing Information, including Boxed Warning.

ZYNRELEF™ (bupivacaine and meloxicam) extended-release solution should be prepared and administered using only the components provided in the ZYNRELEF kit.

Replacement Parts

The following replacement kit components can be ordered free of charge or for $0.01 per case[a] from authorized wholesalers and specialty distributors:

- Luer lock cone-shaped applicators (GTIN 00347426902106, 10 per case)
- Vented vial spikes (GTIN 00347426903059, 5 per case)
- 12-mL Luer lock syringes (GTIN 00347426904087, 8 per case)

[a]Some distributors may charge $0.01 per case for accounting purposes.

Storage and Handling

Store ZYNRELEF kits at controlled room temperature (20°C to 25°C). Protect from moisture and light.

Drug and Kit Component Replacement

In the event the ZYNRELEF vial or another ZYNRELEF kit component is damaged or missing from a purchased kit, or if a component has a physical or mechanical defect, Heron Therapeutics, Inc will provide a replacement product kit. Contact Heron Connect at 1-844-HERON11 (1-844-437-6611) from 8 AM to 8 PM ET, Monday through Friday.

HERON CONNECT

Heron Connect offers customized support for ZYNRELEF billing and coding questions. Reimbursement Counselors are available at **1-844-HERON11 (1-844-437-6611)** from 8 AM to 8 PM ET, Monday through Friday.

For more information, visit **HeronConnect.com**

IMPORTANT SAFETY INFORMATION (CONT)

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 failure.

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

Methemoglobinemia: Cases have been reported with local anesthetic use.

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

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

Fetal Toxicity: Due to the risk of oligohydramnios/fetal renal dysfunction and premature closure of the ductus arteriosus with NSAIDS, limit use of ZYNRELEF between about 20 to 30 weeks gestation, and avoid use after about 30 weeks.

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

Drug Interactions

Drugs That Interfere with Hemostasis: Monitor patients for bleeding who are using ZYNRELEF with drugs that interfere with hemostasis (eg, warfarin, aspirin, SSRIs/SNRIs).

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

ACE Inhibitors and ARBs: 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.

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

Use in Specific Populations

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

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

Severe Renal Impairment: Not recommended.

Adverse Reactions

Most common adverse reactions (incidence ≥10%) in controlled clinical trials with ZYNRELEF are constipation, vomiting, and headache.

Report side effects to Heron at 1-844-437-6611 or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including Boxed Warning.

References: 1. Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee G-C. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: Phase III results from the randomized EPOCH 1 study. *Reg Anesth Pain Med*. 2019;44(7):700-706. doi:10.1136/rapm-2019-100531. **2.** Viscusi E, Minkowitz H, Winkle P, Ramamoorthy S, Hu J, Singla N. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in herniorrhaphy: results from the Phase 3 EPOCH 2 study. *Hernia*. 2019;23(6):1071-1080. doi:10.1007/s10029-019-02023-6. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **4.** Roca R; Center for Drug Evaluation and Research. NDA approval letter: NDA 211988 (Zynrelef). Silver Spring, MD: US Food and Drug Administration; May 12, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/211988Orig1s000ltr.pdf. Accessed May 13, 2021.

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