ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution,
for instillation use
29.25 mg/mL and 0.88 mg/mL

ZYNRELEF: A synergistic foundation for postoperative pain management

With the First and Only Extended-Release Dual-Acting Local Anesthetic[1-4]

ZYNRELEF is a synergistic foundation for postoperative pain management, providing superior pain relief for up to 72 hours, with fewer patients experiencing severe pain, and reducing or eliminating the need for opioids in many patients following surgery versus standard-of-care bupivacaine HCl solution.[1-3]

DISCOVER ZYNRELEF

Synergistic Mechanism of Action

Combines the local anesthetic bupivacaine with a low dose of the NSAID meloxicam, delivered in a proprietary Biochronomer® polymer, designed to overcome the challenges of inflammation and normalize pH at the surgical site[1-5,a]

Superior 72-Hour Pain Relief

Significantly reduced postoperative pain through 72 hours, with fewer patients experiencing severe pain[1-3,b]

Opioid Reduction and Elimination

Significantly more opioid-free patients through 72 hours, with more opioid-free patients through the 28-day recovery period[1-3]

Significantly reduced overall opioid consumption, with fewer opioid-related adverse events[1-3,b]

No callbacks for pain when combined with OTC regimen among HOPE patients undergoing open inguinal herniorrhaphy who were discharged without an opioid prescription[6,c]

Needle-Free Application

Single, needle-free application that does not require mixing with bupivacaine to achieve efficacy[1]

Broad Access Pricing and Favorable Reimbursement

2 SKUs, priced to achieve broad access, with GPO, 340B, and sub-WAC pricing available. ZYNRELEF is available through authorized wholesalers and specialty distributors.

INDICATION

ZYNRELEF is indicated in adults for instillation to produce postsurgical analgesia for up to 72 hours after soft tissue and orthopedic procedures including foot and ankle, and other procedures in which direct exposure to articular cartilage is avoided.

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.

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.**

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

[a]Synergistic increases in analgesia compared with meloxicam or bupivacaine alone were shown in preclinical and Phase 2 studies.[1,5]

[b]Clinical findings were demonstrated in Phase 3 trials for bunionectomy with osteotomy and open inguinal herniorrhaphy comparing ZYNRELEF to both placebo and bupivacaine HCl solution.[1-3]

[c]The HOPE Project collected data on opioid elimination protocols in a real-world setting. In HOPE Hernia 1, ZYNRELEF was used as the foundation of 2 different non-opioid multimodal postoperative regimens for patients undergoing open inguinal herniorrhaphy.[6]

Watch ZYNRELEF surgery application videos

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IMPORTANT SAFETY INFORMATION (CONT)

Contraindications

ZYNRELEF is contraindicated in patients with a 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 CABG.

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.

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.

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.

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

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 effects.

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 ≥5%) in controlled clinical trials with ZYNRELEF are soft tissue procedures: vomiting and orthopedic procedures: constipation 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 additional Important Safety Information on the previous page and full Prescribing Information, including Boxed Warning.

Additional resources and product information, including clinical trial results, an explanation of the product's mechanism of action, and pricing, can be found online at

ZYNRELEF.COM

For general information, contact

844-HERON11 (844-437-6611)

To report an adverse event or product complaint, contact

844-HERON11 (844-437-6611)

MEDINFO@HERONTX.COM

Heron Connect® provides support programs that meet the needs of patients and providers. Visit

HERONCONNECT.COM

GPO: group purchasing organization. **HCl:** hydrochloride. **HOPE:** Helping Opioid Prescription Elimination. **OTC:** over-the-counter. **SKU:** stock-keeping unit. **WAC:** wholesale acquisition cost.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2024. **2.** 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. **3.** 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. **4.** Lachiewicz PF, Lee G-C, Pollak R, Leiman D, Hu J, Sah A. HTX-011 reduced pain and opioid use after primary total knee arthroplasty: results of a randomized Phase 2b trial. *J Arthroplasty*. 2020;35(10):2843-2851. doi:10.1016/j.arth.2020.05.044. **5.** Ottoboni T, Quart B, Pawasauskas J, Dasta JF, Pollak RA, Viscusi ER. Mechanism of action of HTX-011: a novel, extended-release, dual-acting local anesthetic formulation for postoperative pain. *Reg Anesth Pain Med*. 2020;45(2):117-123. doi:10.1136/rapm-2019-100714. **6.** Minkowitz H, Soto R, Fanikos J, et al. Opioid-free recovery after hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting: a randomized, open-label study. *Pain Ther*. 2021;10(2):1295-1308. doi:10.1007/s40122-021-00289-2.

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