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

VALUE PROPOSITION SUMMARY

ZYNRELEF Provides Unmatched Clinical Benefits for a Broad Set of Patients

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.

Economic Advantages

Heron has made collaboration with pharmacy departments a key priority in many areas, including ensuring the economics of ZYNRELEF support broad access for patients and healthcare providers:

- 23%-34% lower wholesale acquisition cost than Exparel®[a]
- 23%-31% lower 340B cost than Exparel[a]
- GPO and sub-WAC discounts available
- Full-line wholesaler distribution (prime vendor discounts will apply)

ZYNRELEF has favorable reimbursement. For Medicare patients, ZYNRELEF is reimbursed separately in HOPDs and ASCs through 2027.[b] Separate payment for ZYNRELEF is available for many commercial patients.

Exparel is not currently separately reimbursed in the HOPD. Pumps and generic local anesthetics like bupivacaine HCl are currently packaged across all settings of care.

Comparison vs Exparel[c]

Clinical Features

	ZYNRELEF	Exparel
Designed to Overcome Challenges of Inflammation at Surgical Site[1]	✓	✗
Greater Pain Reduction Through 72 Hours vs Bupivacaine HCl[1-4]	✓	✗
Superior Pain Reduction vs Bupivacaine HCl[1-3]	✓	✗
Greater Reduction in Severe Pain vs Bupivacaine HCl[2,3]	✓	✗
Significant Increase in Opioid-Free Patients vs Bupivacaine HCl[1-3]	✓	✗
Greater Decrease of Opioid-Related AEs vs Bupivacaine HCl[2,3]	✓	✗
Needle-Free Instillation[1]	✓	✗

Pharmacy Collaboration and Cost Savings

	ZYNRELEF	Exparel
Lower Acquisition Cost and Average Cost	✓	✗
2 SKUs and 340B Pricing at Launch[d]	✓	✗
340B Pricing	✓	✓
GPO Contracting	✓	✗
Full-Line Wholesaler Distribution (Prime Vendor Discount Will Apply)	✓	✗
Separate Reimbursement in HOPD (Medicare)[b]	✓	✗
Separate Reimbursement in ASC (Medicare)[b]	✓	✓

Real-World Evidence

In addition to Heron's clinical trials, independent third-party investigators have presented real-world evidence in total knee arthroplasty showing the benefits of ZYNRELEF versus other treatments, including Exparel and a joint cocktail.[5-7,e]

- Compared to Exparel patients, ZYNRELEF patients had 19% lower opioid consumption ($P < .04$), 38% more same-day discharges ($P < .011$[f]), and 23%[f] lower pain scores at discharge ($P < .05$)[5,6]
- Compared to joint cocktail[g] patients, ZYNRELEF[h] patients had 45% lower pain scores ($P < .001$), lower incidence of severe pain (24% vs 55%, $P = .016$), 53% lower opioid consumption ($P < .05$), and 56% shorter length of stay (25 hours shorter, $P < .05$)[7]

[a] Exparel (bupivacaine liposome injectable suspension) is a trademark of Pacira Pharmaceuticals, Inc. Cost comparisons reflect pricing as of January 1, 2023.
[b] Through March 2025, ZYNRELEF will be separately reimbursed at ASP + 6% in HOPDs and ASCs under 3-year transitional pass-through status. Separate reimbursement will continue under legislation passed in late 2022 that directs CMS to pay for certain non-opioids outside of the packaged payment for procedures in HOPDs and ASCs from January 2025 through December 2027.
[c] ZYNRELEF and Exparel have not been studied in a head-to-head trial. Cost and reimbursement comparisons do not imply safety or efficacy.
[d] Exparel added a second SKU in September 2016, approximately 5 years post launch. Exparel introduced 340B pricing in October 2022, approximately 11 years post launch.
[e] The presented efficacy data is intended to comply with the FDA Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling.
[f] Information shown in addition to that presented in the poster was obtained from investigator.
[g] Joint cocktail patients received 400 mg ropivacaine, 30 mg ketorolac, 0.6 mg epinephrine, and either 0.5 mg hydromorphone or 5 mg morphine diluted to a total volume of 100 mL as a periarticular injection.
[h] ZYNRELEF patients received ZYNRELEF 400 mg/12 mg administered via instillation plus ropivacaine 50 mg administered as a periarticular injection.

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INDICATION

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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 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.

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 ≥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.

GPO: group purchasing organization. **WAC:** wholesale acquisition cost. **HOPD:** hospital outpatient department. **ASC:** ambulatory surgical center. **AE:** adverse event. **SKU:** stock keeping unit. **Severe pain:** VAS (Visual Analog Scale) score ≥7. **ASP:** average sales price. **CMS:** Centers for Medicare & Medicaid Services.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **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.** Sah AP. Initial experience with a novel extended-release, dual-acting local topical anesthetic in TKA compared to a long-lasting bupivacaine peri-articular injection. Poster presented at: Orthopedics Today Hawaii; January 8-12, 2023; Koloa, HI. **6.** Investigator's data on file. San Diego, CA: Heron Therapeutics Inc; 2023. **7.** Warner K, Bonkowski B, Melton K, Smith C, Turner A. A retrospective review of a multi-modal analgesia protocol with bupivacaine and meloxicam (Zynrelef) local instillation vs joint cocktail (ropivacaine/ketorolac/epinephrine/hydromorphone or morphine) local infiltration in primary total knee arthroplasty. Poster presented at: Orthopedics Today Hawaii; January 8-12, 2023; Koloa, HI.

HERON THERAPEUTICS®

4242 CAMPUS POINT COURT, SUITE 200 • SAN DIEGO, CA 92121 • 858-251-4400