

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



USE CAMERA APP
TO SCAN AND WATCH
ADMINISTRATION VIDEOS

ZYNRELEF.com/TKA

ADMINISTRATION OF ZYNRELEF

ZYNRELEF is administered via a needle-free syringe directly to affected tissue.¹

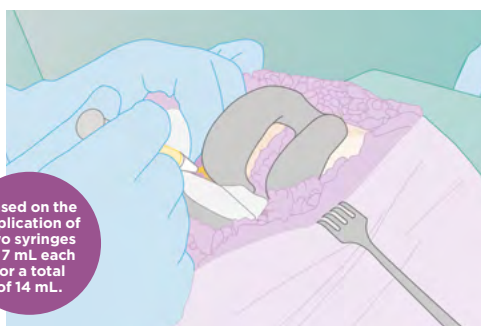
Important Information

- Recommended dose for a total knee arthroplasty: up to 400 mg/12 mg (withdraw 14 mL)¹
- Diluting and/or mixing ZYNRELEF with bupivacaine is not necessary to achieve efficacy. ZYNRELEF cannot be mixed with water, saline, or other local anesthetics as the product will become difficult to administer.¹
- Only administer with syringes and Luer lock cone-shaped applicators provided in kit²
- If any of the kit components are damaged or become unusable, use replacement components, which are individually supplied separate from the kit²
- Only apply to tissue layers below the skin if multiple tissue layers are involved, after final irrigation and suction of each layer, before closing¹
- When ZYNRELEF comes in contact with moisture in the tissues, it becomes more viscous, allowing it to stay in place
- You may use other local anesthetics before application of ZYNRELEF without causing release of the active ingredients all at once. The toxic effects of local anesthetics are additive. Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF.¹
- ZYNRELEF does not degrade sutures. If using monofilament sutures, use 3 or more knots as contact with ZYNRELEF may cause a single knot to loosen or untie.¹

Please see additional information in [Instructions for Use](#).

APPLY ZYNRELEF AFTER FINAL IRRIGATION AND SUCTION OF EACH LAYER, BEFORE CLOSING.

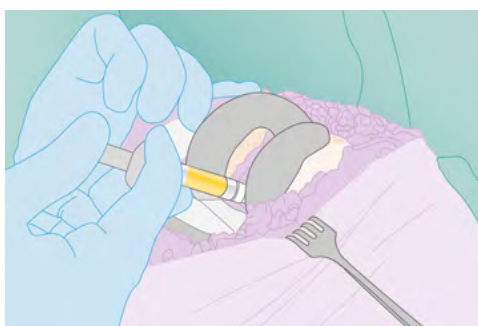
1 APPLY TO POSTERIOR CAPSULE MEDIALY AND LATERALLY.³



Based on the application of two syringes at 7 mL each for a total of 14 mL.

- Insert Luer lock cone-shaped applicator at outer base of implant and apply ~1.75 mL behind LCL and MCL
- Apply to the most posterior tissues first and work forward (anteriorly), including areas of interface where bone meets prosthesis
- **Insert applicator as far toward back of capsule as possible, ideally while knee is in flexion**

2 APPLY TO POSTERIOR CAPSULE CENTRALLY.^{3,a}



- Insert Luer lock cone-shaped applicator at inner base of implant via intercondylar notch and apply another quarter of first 7 mL syringe (~1.75 mL) laterally and medially to tissues surrounding PS post or PLC

^aCruciate retaining knee: Place Luer lock cone-shaped applicator over top of tibial spacer via intercondylar notch and apply 1.75 mL medially and laterally to tissues surrounding PCL.

3 APPLY TO MEDIAL, LATERAL, AND ANTERIOR CAPSULE.³



- Straighten knee, and then use the remaining 3.5 mL of the first syringe plus the entire second syringe to apply ~10.5 mL to inside of anterior capsule, lateral and medial gutters, and surrounding tissues as needed
- **Use applicator to spread material wherever there may be nerve endings, including peripatellar tissues**
- Do not add ZYNRELEF to dermal or subdermal layers; **if excess does express from site, clean skin surface after suturing**

Please see additional information in [Instructions for Use](#).

LCL: lateral collateral ligament. **MCL:** medial collateral ligament.
PS: posterior stabilized. **PLC:** posterolateral capsule.
PCL: posterior cruciate ligament.

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.**

Please see additional Important Safety Information on the following page and full [Prescribing Information](#), including [Boxed Warning](#).



IMPORTANT SAFETY INFORMATION (CONT)

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.

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 $\geq 10\%$) 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.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** ZYNRELEF [instructions for use]. San Diego, CA: Heron Therapeutics Inc; 2021. **3.** Data on file. Pharmacy/study manual for clinical study protocol: HTX-011-209. San Diego, CA: Heron Therapeutics Inc; 2018.

For preparation steps, please refer to the Instructions for Use in your ZYNRELEF Kit, or visit ZYNRELEF.com/admin