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

PREPARATION AND ADMINISTRATION OF ZYNRELEF

Before you begin preparing ZYNRELEF, review the following checklist.

- ☑ Follow your facility's standard operating procedures for aseptic and sterile preparation and disposal of unused vial contents.
- ☑ It is recommended that a 2-person team prepare this product: designate a sterile person and a nonsterile person.
- ☑ If any of the components are damaged or become unusable, use only ZYNRELEF–supplied replacement components, which are individually supplied separate from the ZYNRELEF kit (vented vial spike kit, Luer lock cone-shaped applicator kit, and Luer lock syringe kit).
- ☑ Assemble 1 or 2 syringes, depending on the procedure, using only the components supplied in the ZYNRELEF kit.
- ☑ Do not mix ZYNRELEF with water, saline, or other local anesthetics. Diluting and/or mixing ZYNRELEF with bupivacaine is not needed for efficacy.
- ☑ **Do not remove the stopper from the vial or attempt to pour out its contents. The product is thick, and you will not be able to pull an effective dose from a separate container.**
- ☑ Fill syringe with 7 mL of air before attaching to vented vial spike. **Invert the vial and wait for the product to fill the neck of the vial before pushing the air in. This improves withdrawal time.** ZYNRELEF is specially formulated to coat the affected area and may take a few minutes to withdraw.
- ☑ Only withdraw the amount of ZYNRELEF needed to coat the affected tissue based on the size of the surgical site.
- ☑ Do not attempt to speed up withdrawal by diluting product.
- ☑ Do not attempt to inject ZYNRELEF or to attach a needle to the provided syringe.
- ☑ Store ZYNRELEF at controlled room temperature (20°C to 25°C or 68°F to 77°F, with excursions permitted between 15°C to 30°C or 59°F to 86°F). Keep ZYNRELEF protected from light and moisture.

To see preparation steps in more detail, frequently asked questions, and administration information, refer to the Instructions for Use in your ZYNRELEF Kit, or visit ZYNRELEF.com.

ZYNRELEF Kit Components

DO NOT substitute any of the components.

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.

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.

References: 1. ZYNRELEF [instructions for use]. San Diego, CA: Heron Therapeutics Inc; 2021.

Preparing ZYNRELEF

A Quick Reference

The following steps for preparing ZYNRELEF are abbreviated from the full version found in the Instructions for Use. Familiarize yourself with the entire preparation process before using this as a quick reference.

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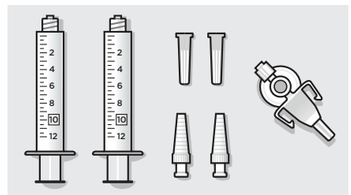
1 Prepare components.



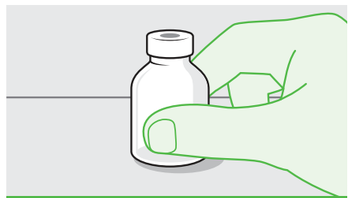
Sterile

Open all components onto sterile field.

Reminder: Prepare all syringes provided in kit. Do not substitute any components.

Note: *Vial contains overfill to account for amount that remains in the vial, vial spike, applicator, and syringe during drug withdrawal and administration.*

2 Prepare vial.

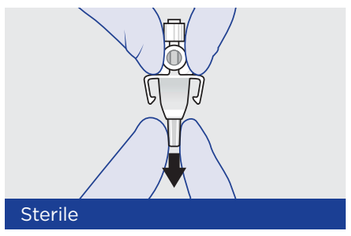


Nonsterile

A. Remove vial cap and place onto stable nonsterile surface.

B. Cleanse septum with alcohol wipe and hold vial in place.

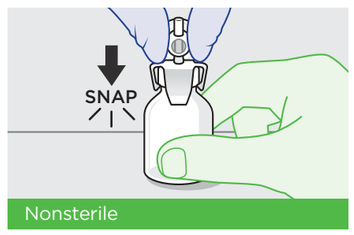
3 Remove protective sheath.



Sterile

Remove blue protective sheath and Luer cap from vented vial spike.

4 Attach vented vial spike.



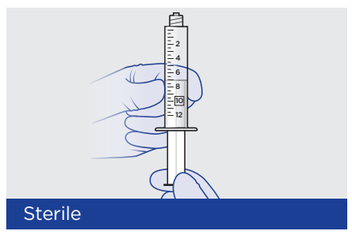
Nonsterile

Hold vial in place.

Sterile

Hold spike by adapter neck and push through septum until it "snaps" into place.

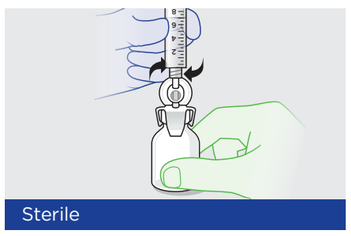
5 Prepare syringe.



Sterile

Fill syringe with 7 mL of air before attaching to the spike.

6 Prepare for withdrawal.

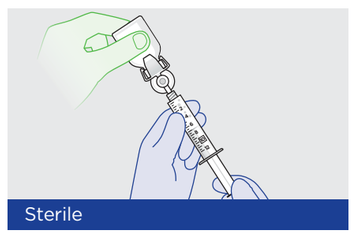


Sterile

Attach air-filled syringe to the spike.

Note: *Avoid moving plunger rod up and down during withdrawal process.*

7 Withdraw product.



Sterile

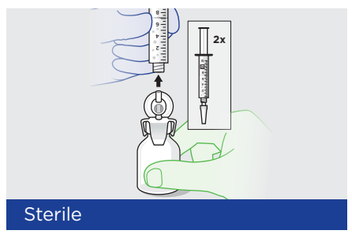
A. Invert vial using syringe.

B. **Allow product to fill neck of vial.**

C. Push air into vial and wait for air bubble to rise.

D. Withdraw 7 mL of product. Small air bubbles in syringe are normal.

8 Attach Luer lock applicator.



Sterile

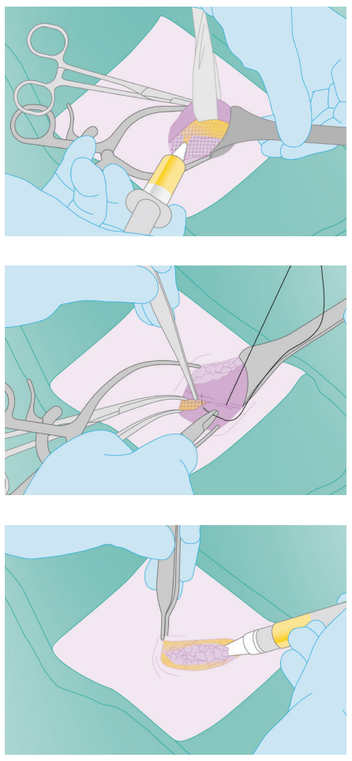
A. Return vial to a flat surface, remove syringe from vial, and attach Luer lock applicator.

B. Place syringe on sterile surface, and repeat steps 5 to 8 with second syringe (400-mg/12-mg kits only).

Administering ZYNRELEF

A single-dose application of ZYNRELEF is administered directly into the surgical site via a needle-free syringe and Luer lock applicator to coat the affected tissue prior to suturing.

ZYNRELEF should only be administered with the syringe and Luer lock cone-shaped applicator provided in the ZYNRELEF kit. Two syringes are provided to aid in application of a 400-mg/12-mg dose (14 mL of ZYNRELEF).



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1 Final irrigation and suction

ZYNRELEF is applied without a needle into the surgical site following final irrigation and suction and prior to suturing.

Only apply ZYNRELEF after final irrigation and suction of each layer before closing, if multiple tissue layers are involved.

2 ZYNRELEF application

Using the Luer lock cone-shaped applicator attached to the syringe, apply ZYNRELEF to the tissues within the surgical site that could result in pain generation.

- Use a sufficient amount to coat the tissues. For small spaces, ensure there is not an excess that could be expressed from the site during closure.
- Only apply ZYNRELEF to the tissue layers below the skin incision and not directly onto the skin.

3 Suturing

ZYNRELEF does not degrade sutures.

When using monofilament sutures, use 3 or more knots as contact with ZYNRELEF may cause a single knot to loosen or untie.

IMPORTANT INFORMATION

- **Diluting and/or mixing ZYNRELEF with bupivacaine is not needed for efficacy. ZYNRELEF cannot be mixed with water, saline, or other local anesthetics as the product will become difficult to administer.**
- If any of the kit components are damaged or become unusable, use replacement components, which are individually supplied separate from the kit.
- When ZYNRELEF comes in contact with moisture in the tissues, it becomes more viscous, allowing it to stay in place.
- **Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF. Overall local anesthetic exposure must be considered.**

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