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

PRODUCT MONOGRAPH

INDICATION AND USAGE

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.**

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EXECUTIVE SUMMARY[1-5]

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.

ZYNRELEF is the first and only extended-release dual-acting local anesthetic (DALA), delivering a fixed-dose combination of the local anesthetic bupivacaine and a low dose of nonsteroidal anti-inflammatory drug (NSAID) meloxicam in a proprietary Biochronomer® polymer. It is also the only local anesthetic considered by FDA to be extended-release, based on superiority to bupivacaine through 72 hours.

The approval of ZYNRELEF in the United States is supported by randomized, double-blind, bupivacaine- and placebo-controlled studies across multiple surgical models. In Phase 3 trials versus bupivacaine HCl solution, ZYNRELEF demonstrated significant reduction in pain intensity, fewer patients with severe pain, significant reduction in opioid use, and a significantly greater proportion of patients requiring no opioids through the first 72 hours following surgery, making ZYNRELEF the first and only product to demonstrate superiority over bupivacaine HCl solution in Phase 3 studies. In a pivotal Phase 2b trial in total knee arthroplasty, ZYNRELEF also demonstrated a greater reduction in pain intensity compared with saline placebo and bupivacaine HCl solution for the 72-hour postoperative period.

The safety of ZYNRELEF was evaluated in over 1,500 patients undergoing various surgical procedures in clinical trials. In patient data included in the ZYNRELEF NDA, the most common adverse reactions (incidence greater than or equal to 10% and higher than saline placebo) following ZYNRELEF administration were constipation, vomiting, and headache.

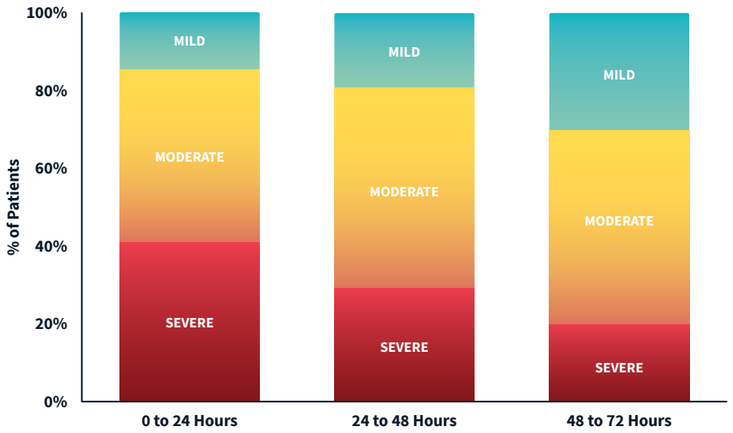
ZYNRELEF is contraindicated in patients with a known hypersensitivity (eg, anaphylactic reactions and serious skin reactions) to any amide local anesthetic, NSAIDs, or other components of ZYNRELEF; with history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (severe, sometimes fatal, anaphylactic reactions to NSAIDS have been reported in such patients); undergoing obstetrical paracervical block anesthesia; or undergoing coronary artery bypass graft (CABG) surgery.

BACKGROUND AND UNMET NEED

Postoperative Pain and Inflammation

The first 72 hours after surgery are the most painful. In a study of patients aged 16 to 79 years who underwent a variety of elective surgical procedures, 88% experienced moderate to severe pain in the first 24 hours. For 72% of patients, pain remained moderate to severe through the 48- to 72-hour window (Figure 1).[6]

Figure 1. Physiologic responses to surgical injury coincide with the first 72 hours after surgery, when pain is most severe[6]

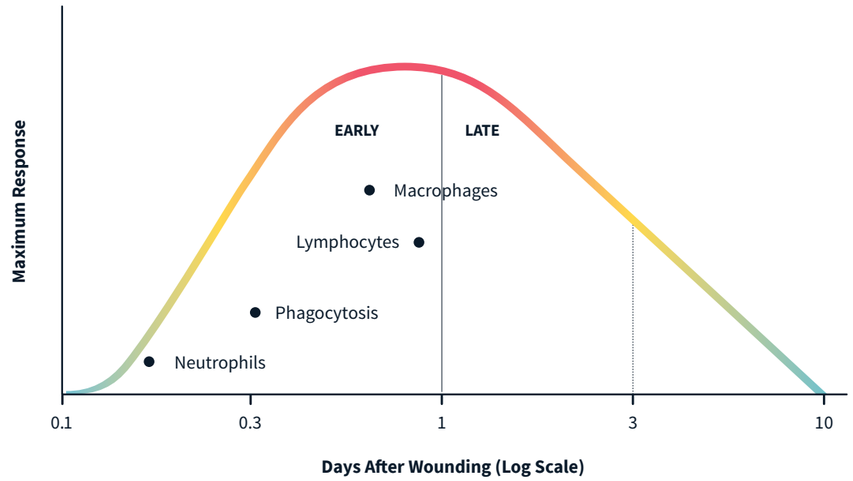


Adapted from Svensson I. *J Pain Symptom Manage*. 2000;20(3):193-201.

VAS mm	Pain Intensity
≥80 ≤100	Severe pain
≥40 <80	Moderate pain
≥0 <40	Mild or no pain

When local tissue damage activates nociceptor cells, inflammatory mediators are released.[7,8] Inflammation can modify the activity of the central nervous system's (CNS) pathways, dramatically increasing transmission of pain and reducing the pain threshold (otherwise known as *hyperalgesia*).[8] Inflammation peaks around 24 hours postoperatively and remains high through the first **72 hours** (Figure 2)—and it is also a significant component of postoperative pain.[8,9]

Figure 2. Inflammation is most active during the first 72 hours following surgery[9]

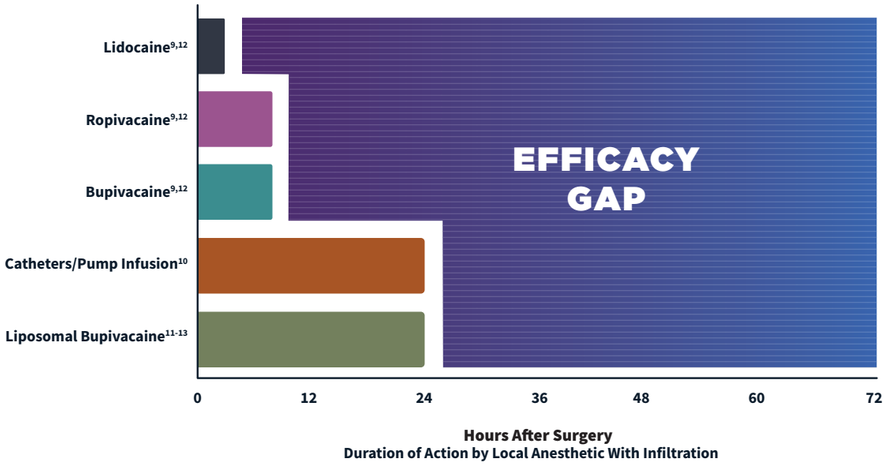


BACKGROUND & UNMET NEED

CURRENT EFFICACY GAP AND OVERRELIANCE ON OPIOIDS

The limitations of most local anesthetics have created an efficacy gap in postoperative pain management. Most local anesthetics inconsistently provide pain relief beyond 12 to 24 hours (Figure 3).[10-14] With severe pain often lasting through 72 hours, physicians rely on opioids to pick up where local anesthetics leave off.[6,15,16]

Figure 3. Efficacy gap showing points at which most local anesthetics struggle to consistently provide pain relief[10-14]



10. Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. *Miller's Anesthesia*. Vol 1. 8th ed. Philadelphia, PA: Saunders; 2015:1028-1054.e4.

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12. Kim J, Burke SM, Kryzanski JT, et al. The role of liposomal bupivacaine in reduction of postoperative pain after transforaminal lumbar interbody fusion: a clinical study. *World Neurosurg*. 2016;91:460-467. doi:10.1016/j. wneu.2016.04.058.

13. Data on file. DRG physician survey. San Diego, CA: Heron Therapeutics Inc; 2017.

14. Exparel [package insert]. San Diego, CA: Pacira Pharmaceuticals Inc; 2021.

The limitations of most local anesthetics to manage pain past 24 hours have contributed to the extensive use of opioids.[10-15]

Opioids mask pain centrally (at the brain), which can reduce the sensation of pain, but they do not block transmission of the pain signals at the source.[17] Opioids can cause serious adverse reactions, including respiratory depression. Other common adverse reactions include nausea, vomiting, pruritus, somnolence, urinary retention, and constipation.[18] Opioid-naive patients prescribed opioids after surgery have up to 61% higher total healthcare costs than those without an opioid prescription in the first year following surgery. These patients are also 7.5x more likely to experience persistent postoperative pain during the 90 days following surgery, account for 1.8x more emergency room (ER) visits, and use 1.4x more ambulance/paramedic services in the first year following surgery.[19] Previously opioid-naive patients who become persistent opioid users after a major surgery may also have up to 2.5x higher healthcare costs in the year after surgery.[20]

>50 MILLION
surgeries in the US each year[16]

>33 MILLION
opioid Rx each year[16,21]

67%
of patients filled an opioid prescription associated with their surgery[21,a]

>2 MILLION
may become persistent opioid users annually after surgery[16,21]

80%
of patients report unused opioid tablets[22]

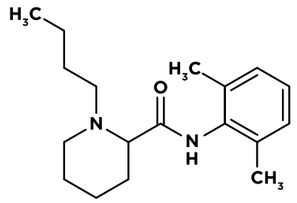
[a]Between 30 days before through 14 days after surgery.

PRODUCT DESCRIPTION

ZYNRELEF contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID). ZYNRELEF is the first and only extended-release dual-acting local anesthetic (DALA), with a novel mechanism of action that delivers postoperative pain relief for up to 72 hours. ZYNRELEF is applied without a needle into the surgical site following final irrigation and suction and prior to suturing.[1-4,23]

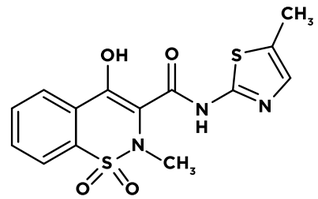
Bupivacaine

Bupivacaine comes in the form of white to off-white crystalline powder, crystals, or granules. The chemical name for bupivacaine is (±)-1-butyl-*N*-(2,6-dimethylphenyl) piperidine-2-carboxamide, and its empirical formula is $C_{18}H_{28}N_2O$. The pKa of bupivacaine is 8.1. The molecular weight of bupivacaine is 288.4. Bupivacaine is sparingly soluble in water and freely soluble in alcohol. Bupivacaine has a log P_{ow} of 1.82 and a pKa of 8.1. The structural formula of bupivacaine is shown to the right.[1]



Meloxicam

Meloxicam is a pale yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P)$_{app}$ = 0.1 in *n*-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2. Meloxicam is chemically designated as 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is $C_{14}H_{13}N_3O_4S_2$, and the structural formula is shown to the right.[1]



ZYNRELEF

ZYNRELEF is a sterile, clear, pale yellow to yellow, viscous liquid provided in single-dose vials (10 mL or 20 mL) for instillation into the surgical site. Each mL of the solution contains active ingredients bupivacaine 29.25 mg and meloxicam 0.88 mg; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg), triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg).[1]

Biochronomer® Polymer Technology

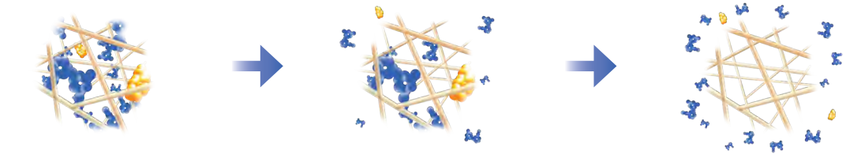
ZYNRELEF's formulation is delivered via a novel controlled-diffusion polymer technology called Biochronomer, which is designed to provide 72-hour postoperative analgesia (Figure 4).[1,23] Due to the novel properties of the Biochronomer polymer, other local anesthetics can be administered before ZYNRELEF without causing release of the active ingredients all at once.[1,2,4]

The Biochronomer polymer technology is in a product that has been used approximately 300,000 times[a] for chemotherapy-induced nausea and vomiting (CINV) patients; it has been applied in over 1,500 patients during ZYNRELEF trials.[1,5,24]

[a]Based on units distributed.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Figure 4. The formulation of ZYNRELEF is designed for 72-hour postoperative analgesia[1,23]



- The active ingredients are contained in a novel and proprietary controlled-diffusion polymer called Biochronomer[1,23]
- The ratio of bupivacaine to meloxicam is 33:1[1]

- The Biochronomer polymer is designed for consistently regulated delivery of both active ingredients for 72 hours after surgery[1,23,a]
- Release rates of active ingredients[25]:
  - 0 to 24 hours: 52% of bupivacaine 44% of meloxicam
  - 0 to 48 hours: 81% of bupivacaine 81% of meloxicam
  - 0 to 72 hours: 93% of bupivacaine 95% of meloxicam

- As the active components are released from the formulation, the polymer hydrolyzes into benign, water-soluble end products, which are eliminated from the body via the kidneys[23]

Bupivacaine Meloxicam Polymer

[a]Reflects in vitro release rates of active ingredients.

IMPORTANT SAFETY INFORMATION

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.

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INDICATION AND USAGE

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 has not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.

DOSAGE AND ADMINISTRATION

ZYNRELEF is a sterile, clear, pale-yellow to yellow, viscous liquid in a single-dose vial containing 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam and is available in the following 2 presentations (Figure 5)[1]:

- 400 mg bupivacaine and 12 mg meloxicam (14 mL in a 20-mL single-dose glass vial)
- 200 mg bupivacaine and 6 mg meloxicam (7 mL in a 10-mL single-dose glass vial)

ZYNRELEF spreads easily and covers a large area. The 14-mL dose volume is sufficient to cover total knee arthroplasty (TKA), a large surgical procedure. The recommended dose of ZYNRELEF, based on clinical trials, is up to a maximum total volume of 14 mL to deliver 400 mg/12 mg using the following surgical procedures as guidance:

- For foot and ankle surgical procedures, such as bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam
- For small-to-medium open abdominal surgical procedures, such as open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam
- For lower extremity total joint arthroplasty surgical procedures, such as total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Figure 5. Two vial sizes are available[1,26]

14-mL Vial Size

Example procedures

- Appendectomy (Open)
- Herniorrhaphy[a] (Open)
- Hysterectomy (Open)
- Total Hip Arthroplasty
- Total Knee Arthroplasty

7-mL Vial Size

Example procedures

- Bunionectomy and Phalangectomy
- Fracture - Foot & Ankle
- Female Sterilization
- Pelvic Floor Reconstruction
- Stoma Closure/Creation
- Suburethral Sling
- Total Ankle Arthroplasty

Small-to-medium laparoscopic extraction site[b] example procedures

- Appendectomy
- Colon and Small Bowel Resection
- Cholecystectomy
- Gastrectomy
- Hysterectomy
- Prostatectomy
- Roux-en-Y Gastric Bypass

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

Note: Not all procedures listed under each vial size require full contents to cover affected tissues.

[a]Includes small-to-medium open hernia repair.
[b]Extraction site is considered a small-to-medium open abdominal procedure.

IMPORTANT SAFETY INFORMATION

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.

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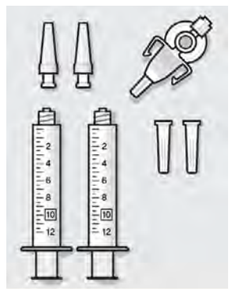
Preparation[27]

It is recommended that a 2-person team prepare this product: 1 sterile person and 1 nonsterile person. If product is prepared in advance of surgery, syringe tip caps may be used to cap the syringe until ready for application. Before administration, remove the syringe tip cap and attach the Luer lock applicator.[27]

The contents of the ZYNRELEF vial are sterile. The vial exterior is not sterile. Follow your facility's standard operating procedures regarding aseptic and sterile preparation.[27]

Figure 6. Instructions for Use for ZYNRELEF 400-mg/12-mg kit[27]

1 Prepare components.



STERILE

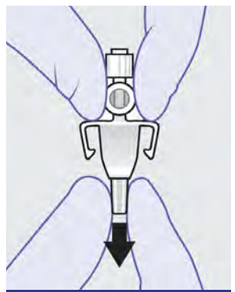
Open all components onto sterile field.
Note: Prepare all syringes provided in kit.
⚠ **Do not** substitute any of the components.
⚠ Only withdraw 7 mL of ZYNRELEF into each syringe.
Note: Vial contains overfill to account for amount that remains in the vial, vial spike, applicator, and syringe during drug withdrawal and administration.

2 Prepare vial.

NONSTERILE

A. Flip cap off of vial and place onto stable nonsterile surface.
B. Cleanse septum with alcohol wipe.
C. Hold the vial in place for the sterile person to safely insert the vented vial spike.
⚠ **Do not** remove the stopper or attempt to pour the vial contents.

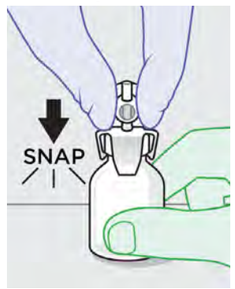
3 Remove protective sheath.



STERILE

A. Remove blue protective sheath from vented vial spike.
B. Remove Luer cap.

4 Attach vented vial spike.



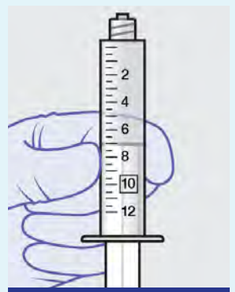
STERILE

Push the spike through the septum of the vial until it "snaps" into place.
⚠ Hold the vented vial spike by the adapter neck to maintain sterility of the vented vial spike and sterile person.

NONSTERILE

Hold the vial in place while sterile person attaches spike.
Note: Place the vial on a firm, flat surface and hold in place while the sterile person attaches the spike.

5 Prepare syringe.



STERILE

Fill the syringe with 7 mL of air before attaching to the vented vial spike.
⚠ **Air from syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial.**

6 Prepare for withdrawal.

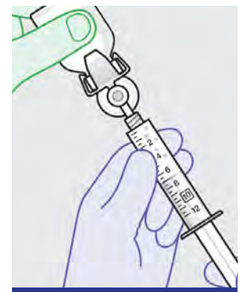
STERILE

Attach the air-filled syringe to the vented vial spike.
Note: Avoid pushing or pumping the plunger rod up and down at any point in the withdrawal process.

NONSTERILE

Hold the vial in place until the syringe is attached.

7 Withdraw product.



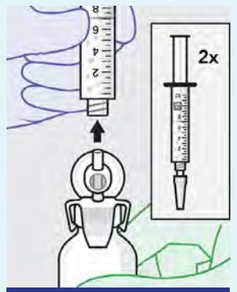
STERILE

A. Invert the vial using the syringe.
B. Allow product to fill the neck of the vial.
C. Push air into vial and wait for the air bubble to rise.
D. Withdraw 7 mL of product. It is normal for there to be small air bubbles in the syringe.
Note: Product is very thick. It may take a few minutes to withdraw.

NONSTERILE

You may assist the sterile person with inverting the vial if necessary by holding the nonsterile vial.

8 Repeat with second syringe.



STERILE

A. Return vial to nonsterile surface.
B. Remove syringe from vial and attach Luer lock applicator.
C. Place syringe on sterile surface.
D. Repeat steps 5–8 with second syringe *(400-mg/12-mg kits only)*.

NONSTERILE

Hold the vial in place for attachment of second syringe *(400-mg/12-mg kits only)*.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

To see videos on how to prepare ZYNRELEF, visit **ZYNRELEF.com/admin.**

DOSAGE | ADMINISTRATION

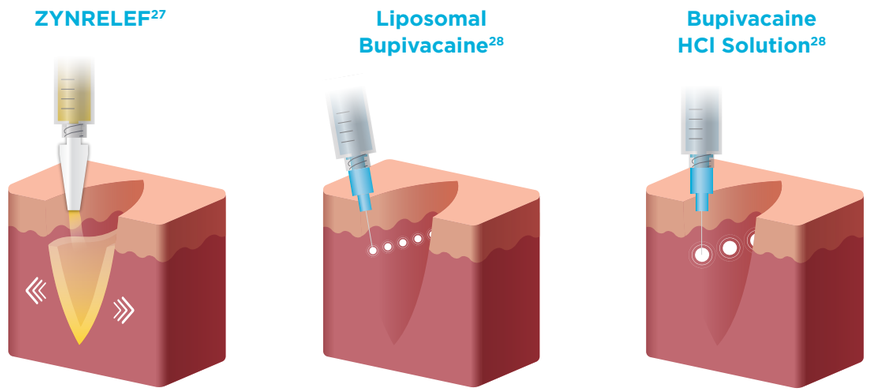
Administration

ZYNRELEF is a viscous solution administered as a single-dose, needle-free instillation to directly coat the affected tissue within the surgical site prior to suturing. ZYNRELEF becomes more viscous when it comes into contact with moisture at the surgical site, allowing it to stay where it is placed.[27] The active ingredients are released from the polymer and diffuse throughout the affected tissue.[23]

No mixing with bupivacaine is required to achieve efficacy. ZYNRELEF should not be diluted. In contrast with some longer-acting local anesthetics, ZYNRELEF does not require expansion with bupivacaine, large numbers of injections, or specialized training for administration (Figure 7).[27]

Other local anesthetics can be administered before 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.[1,2,4]

Figure 7. ZYNRELEF is applied into the surgical site, without a needle, following irrigation and suction[27]



To see administration videos for ZYNRELEF, visit **ZYNRELEF.com/admin**.

Important Administration Information[27]

- 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.
- Using the Luer lock 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.
- 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.
- The amount of ZYNRELEF required depends upon the surgical area of tissue to be treated.
- ZYNRELEF spreads easily and covers a large area.
- Diluting ZYNRELEF is not needed for efficacy.
  - ZYNRELEF cannot be mixed with water, saline, or other local anesthetics as the product will become very viscous and difficult to administer.
- 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.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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.

Compatibility Considerations[1]

- **Do not dilute ZYNRELEF.**
- ZYNRELEF is a nonaqueous solution. It cannot be mixed with water, saline, or other local anesthetics as the product will become more viscous and difficult to administer
- Other local anesthetics can be administered before ZYNRELEF without causing release of the active ingredients all at once[1,2,4]
  - The toxic effects of local anesthetics are additive. Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF.
- When a topical antiseptic such as povidone iodine (eg, Betadine®) is applied, the site should be allowed to dry before a local anesthetic, including ZYNRELEF, is administered into the site
- When administered in recommended doses and concentrations, bupivacaine HCl solution does not ordinarily produce irritation or tissue damage

ZYNRELEF is compatible with:

- All components of the ZYNRELEF kit, including syringes, Luer lock cone-shaped applicator, vented vial spike, and syringe tip caps.
- Surgical mesh materials: polypropylene (Prolene®), Gore-Tex, and polyester
- Silicone membranes
- Bone cement
- Metal alloys used in surgical implants

Packaging, Storage, and Handling[1,27]

ZYNRELEF is stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F). There are 2 different SKUs, each with different product volumes for different surgery requirements (Table 1). All outer packages and/or kits have the same dimensions, and SKUs are identifiable by different colors on the package. Each kit includes a single-dose glass vial with sterile contents, sterile Luer lock syringe(s), sterile vented vial spike, sterile Luer lock cone-shaped applicator(s), and sterile syringe tip cap(s). The kits are sized to fit in standard operating room medication carts (eg, Pyxis™) and are developed and packaged in the United States. Replacement kit components (vented vial spikes, Luer lock syringes, and Luer lock cone-shaped applicators) are available for order.

Table 1. Available product presentations[1]

Product Presentation				Vented Vial Spike Provided	Luer Lock Syringe(s) Provided	Luer Lock Cone-Shaped Applicator(s) Provided	Syringe Tip Cap(s) Provided
NDC	Bupivacaine/ Meloxicam	Volume	Vial Size				
47426-301-02	400 mg/ 12 mg	14 mL	20 mL	1	2 x 12 mL	2	2
47426-303-01	200 mg/ 6 mg	7 mL	10 mL	1	1 x 12 mL	1	1

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

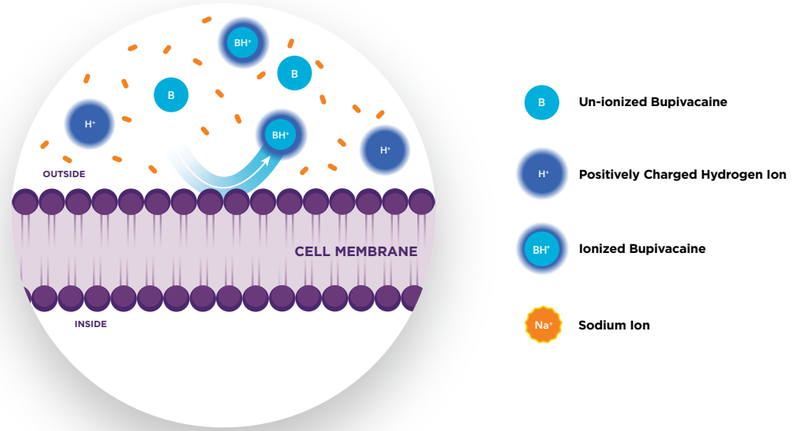
MECHANISM OF ACTION

Limitations of Other Currently Available Local Anesthetics

MOST LOCAL ANESTHETICS HAVE NOT CONSISTENTLY DEMONSTRATED EFFICACY BEYOND 12 TO 24 HOURS AFTER SURGERY[10-14]

Local anesthetics can be a strong foundation and first line of defense against postoperative pain. Local anesthetics, like bupivacaine, block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. To prevent a pain signal from propagating along a nerve cell, bupivacaine must diffuse through the nerve cell membrane and block voltage-gated sodium ion channels from inside the nerve cell (Figure 8).[10,29,30]

Figure 8. To stop pain signals, bupivacaine must diffuse through the nerve cell membrane and block the voltage-gated sodium ion channels from inside the cell[10,29,30]



IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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.

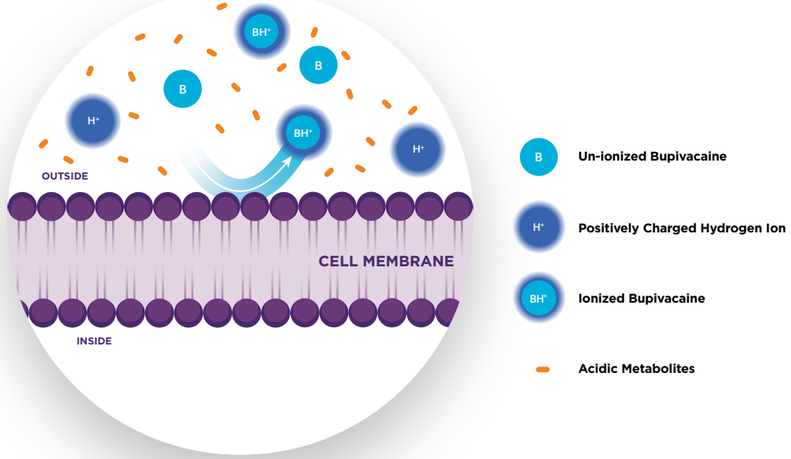
Hematologic Toxicity: Monitor hemoglobin and hematocrit in patients with any signs or symptoms of anemia.

ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution

Mechanism of Action (cont)

Inflammation can limit the efficacy of local anesthetics.[29,30] The inflammatory process associated with acute surgical injury makes it more difficult for local anesthetics to penetrate the nerve cell membrane and reach the intended site of action. As the inflammatory process unfolds in the first 24 hours after surgery, the wound site becomes more acidic. This acidic microenvironment causes bupivacaine to become ionized, preventing it from entering the nerve cell membrane (Figure 9) and blocking pain signals to the brain. Generic local anesthetics are not designed to provide pain relief beyond 8 to 12 hours.[10,13] Longer-acting local anesthetics, including liposomal bupivacaine and formulations delivered via wound infiltration catheters or pumps, exhibit limited and inconsistent efficacy beyond 12 to 24 hours in part because the inflammatory process inhibits their ability to penetrate the nerve cell membrane.[11-14,29,30]

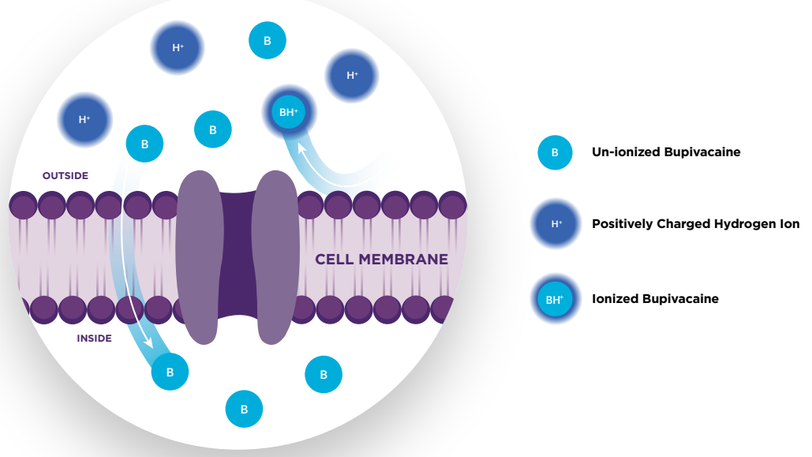
Figure 9. Inflammation causes the wound site to become more acidic, resulting in a greater portion of bupivacaine becoming ionized outside the cell; ionized bupivacaine cannot easily penetrate the nerve cell membrane and therefore cannot block pain signals[29,30]



ZYNRELEF is the first and only extended-release dual-acting local anesthetic (DALA).[1-4] ZYNRELEF has a novel, synergistic mechanism of action that combines bupivacaine with low-dose meloxicam. It was designed to overcome the challenges of inflammation at the surgical site.[1,23] Inflammation resulting from a surgical incision causes the affected tissues to become acidotic (lower pH), which reduces the penetration of local anesthetics into the nerves.[27,28] It is thought that the presence of meloxicam in ZYNRELEF inhibits the acidotic effect caused by inflammation, reducing the concentration of hydrogen ions in the environment, normalizing the pH at the surgical site, and allowing more bupivacaine to penetrate the nerve cell membrane, so that it can provide continued pain relief in the critical 72-hour window, when pain is most severe (Figure 10).[6,23]

In animal studies, wound-site administration of ZYNRELEF resulted in decreased tissue acidity (pH 6.87) versus the control group (pH 5.77) at 48 hours after incision, **which resulted in considerably more un-ionized bupivacaine available to enter nerve cells**.[23,31]

Figure 10. ZYNRELEF proposed mechanism of action[1,23]



IMPORTANT SAFETY INFORMATION

Drug Interactions

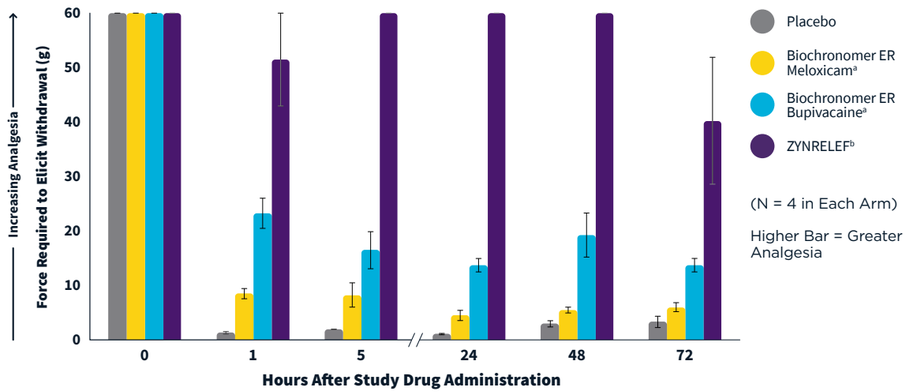
Drugs That Interfere with Hemostasis: Monitor patients for bleeding who are using ZYNRELEF with drugs that interfere with hemostasis (eg, warfarin, aspirin, SSRIs/SNRIs).

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

Mechanism of Action (cont)

In animal studies, the extended-release (ER) formulation of bupivacaine and meloxicam in the proprietary Biochronomer® polymer resulted in synergistic increases in analgesia through 72 hours compared with an extended-release formulation of either bupivacaine or meloxicam alone, or the sum of the 2 individual components, in the same Biochronomer polymer (Figure 11).[23] This finding was confirmed in 2 clinical studies (Figures 12 and 13).[1,32,33]

Figure 11. The synergistic effects of ZYNRELEF in a preclinical animal model[34]



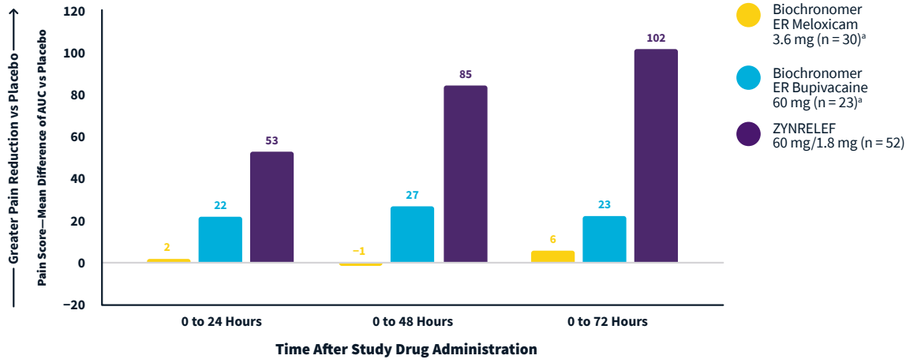
[a]Investigational products not approved by FDA; used to evaluate the activity of each component of ZYNRELEF in the polymer.

[b]Preclinical data based on an early investigational formulation.

Note: The synergistic analgesic effects of ZYNRELEF were tested in pigs. The clinical significance of these data for use in humans is unknown.

After the preclinical findings, Heron's next step was to confirm synergy through Phase 2 human studies, which also showed the synergistic effect of ZYNRELEF versus the individual effects of its 2 active ingredients. The first 2 bars show reduction in pain intensity relative to placebo for extended-release meloxicam and extended-release bupivacaine (both formulated using the Biochronomer technology). The third bar shows data for ZYNRELEF, which combines the 2 components in a fixed ratio. ZYNRELEF resulted in a mean difference from placebo that was greater than the sum of the 2 active ingredients at each of these time intervals: 0 to 24 hours, 0 to 48 hours, and 0 to 72 hours. Pain scores were analyzed with adjustment for the analgesic duration of opioid rescue medications.[1,32,33]

Figure 12. Bunionectomy: ZYNRELEF demonstrated greater reduction of pain intensity vs placebo than either ER bupivacaine or ER meloxicam alone, or the sum of the 2 components[32,33]



[a]Investigational products not approved by FDA; used to evaluate the activity of each component of ZYNRELEF.

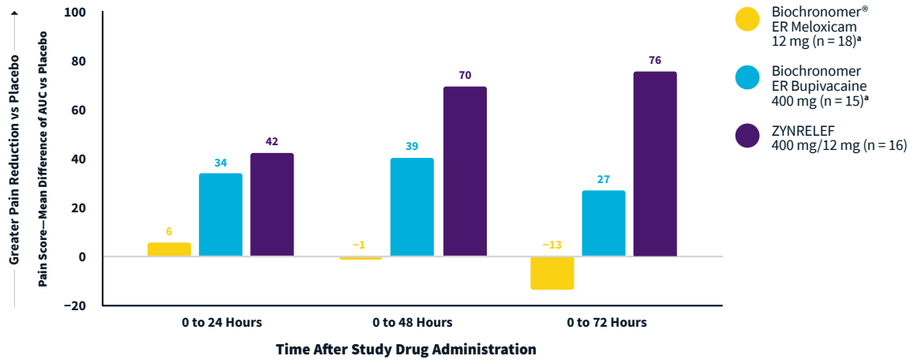
IMPORTANT SAFETY INFORMATION

Drug Interactions (cont)

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.

Figure 13. Herniorrhaphy: ZYNRELEF demonstrated greater reduction of pain intensity vs placebo than either ER bupivacaine or ER meloxicam alone, or the sum of the 2 components[1,33]



[a]Investigational products not approved by FDA; used to evaluate the activity of each component of ZYNRELEF.

IMPORTANT SAFETY INFORMATION

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.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

ZYNRELEF Bupivacaine Plasma Levels and Efficacy Through 72 Hours in Phase 2 Bunionectomy Study[32]

Instillation of ZYNRELEF into the surgical site results in systemic plasma levels of bupivacaine and meloxicam for up to the duration as described in Table 2 (see page 24). Both ZYNRELEF's efficacy profile and the bupivacaine exposure profile were observed through 72 hours. In contrast, when bupivacaine without meloxicam is administered in the same 72-hour release formulation, the efficacy is limited to 8 to 12 hours even though the bupivacaine exposure profile continues through 72 hours.

Figure 14. ZYNRELEF PK/PD[32]

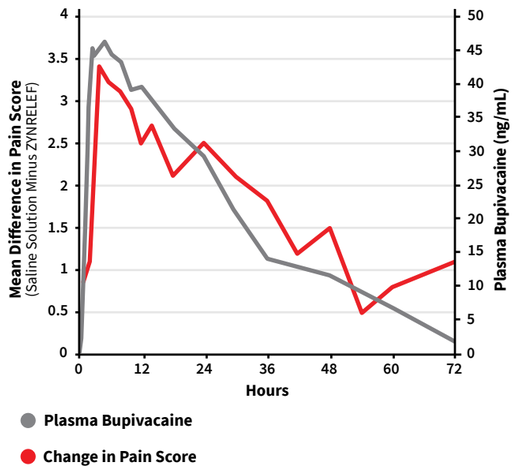
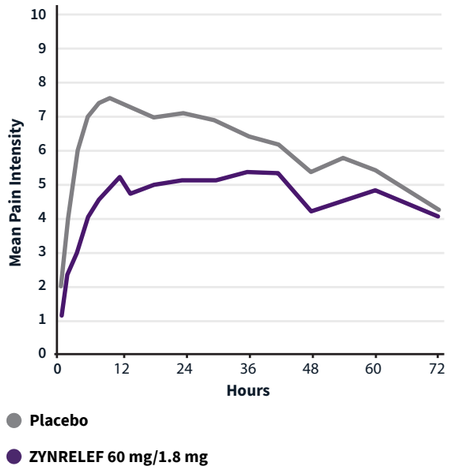


Figure 15. Mean Pain Intensity Versus Time[32]



Absorption[1]

ZYNRELEF is an extended-release formulation of bupivacaine and meloxicam using a polymer-based drug delivery system. Following single-dose application of ZYNRELEF, bupivacaine and meloxicam are released simultaneously from the polymer via controlled diffusion over approximately 3 days.

The rate of systemic absorption of bupivacaine or meloxicam from ZYNRELEF is dependent upon the total dose of drug administered.

Pharmacokinetic parameters of bupivacaine and meloxicam after single-dose administration by instillation of ZYNRELEF were evaluated following multiple surgical procedures.

Descriptive statistics of pharmacokinetic parameters of representative ZYNRELEF doses are provided in Table 2.

Table 2. Summary of pharmacokinetic parameters for bupivacaine and meloxicam after single-dose administration of ZYNRELEF by instillation [1]

Active Ingredient	Parameter	Bunionectomy: 60 mg/1.8 mg ZYNRELEF (n = 17)	Herniorrhaphy: 300 mg/9 mg ZYNRELEF (n = 16)	Total Knee Arthroplasty: 400 mg/12 mg ZYNRELEF (n = 53)[a]
Bupivacaine	C_{max} (ng/mL)	54 (33)	271 (147)	695 (411)
	T_{max} (h)	3.0 (1.6-24)	18 (3-30)	20.87 (4-59)
	$AUC_{(0\text{-}t)}$[a] (h×ng/mL)	1,681 (1,154)	15,174 (8,470)	35,890 (28,400)
	$AUC_{(inf)}$ (h×ng/mL)	1718 (1211)	15524 (8921)	38173 (29400)[b]
	$t_{½}$ (h)	15 (8)	16 (9)	17 (7)[b]
	C_{72h} (ng/mL)	5.0 (5.3)	96 (75)	227 (283)
	C_{96h} (ng/mL)	1.7 (2.9)[e]	37 (43)	NS
	C_{144h} (ng/mL)	NS	NS	5.3 (21)[c]
Meloxicam	C_{max} (ng/mL)	26 (14)[e]	225 (96)	275 (134)
	T_{max} (h)	18 (8, 60)[e]	54 (24, 96)	36 (12, 72)
	$AUC_{(0\text{-}t)}$ (h × ng/mL)	1621 (927)[e]	18721 (7923)	19525 (12259)
	$AUC_{(inf)}$ (h × ng/mL)	2079 (1631)[e]	NR	25673 (17666)[d]
	$t_{½}$ (h)	33 (36)[e]	NR	42 (37)[d]
	C_{72h} (ng/mL)	13 (9)[e]	197 (95)	202 (120)
	C_{96h} (ng/mL)	7.7 (5.8)[f]	146 (86)	NS
	C_{144h} (ng/mL)	NS	NS	28 (37)[g]

Note: Arithmetic mean (standard deviation) except T_{max} where it is median (min, max). Doses of ZYNRELEF are shown as bupivacaine dose (mg)/meloxicam dose (mg).
[a]$AUC_{(0\text{-}t)}$: 0 to 120 h post-dose for bunionectomy and herniorrhaphy; 0 to 144 h post-dose for total knee arthroplasty.
[b]N=50; [c]N=32; [d]N=35; [e]N=16; [f]N=15; [g]N=28
NS: not sampled.
NR: not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Distribution[1]

After bupivacaine and meloxicam have been released from ZYNRELEF and are absorbed systemically, their distribution is expected to be the same as for other bupivacaine HCl solution formulations or meloxicam oral formulation.

BUPIVACAINE[1]

Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma proteins.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2-0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid-soluble, nonionized drugs, such as bupivacaine, readily enter the fetal blood from the maternal circulation.

MELOXICAM[1]

Meloxicam is approximately 99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range of oral meloxicam. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to approximately 99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam. Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5x higher than in plasma due to the lower albumin content in synovial fluid as compared to plasma. The significance of this penetration is unknown.

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.**

Elimination

METABOLISM[1]

Bupivacaine: Amide-type local anesthetics such as bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxylidine is the major metabolite of bupivacaine. The elimination of the drug from tissue distribution depends largely upon the ability of plasma protein binding sites in the circulation to carry it to the liver, where it is metabolized.

Meloxicam: Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5′-carboxy meloxicam (60% of dose), from P450 mediated metabolism formed by oxidation of an intermediate metabolite 5′-hydroxymethyl meloxicam, which is also excreted to a lesser extent (9% of dose). In vitro studies indicate that CYP2C9 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients' peroxidase activity is probably responsible for the other 2 metabolites, which account for 16% and 4% of the administered dose, respectively. The 4 metabolites are not known to have any in vivo pharmacological activity.

EXCRETION[1]

After bupivacaine and meloxicam have been released from ZYNRELEF and are absorbed systemically, their excretion is expected to be the same as for other bupivacaine HCl solution formulations or meloxicam oral formulations.

Bupivacaine: The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage. The mean apparent terminal half-life ($t_{1/2}$) for bupivacaine from ZYNRELEF is approximately 14 to 15 hours.

Meloxicam: Meloxicam excretion is predominately in the form of metabolites and occurs to equal extents in the urine and feces. Following oral meloxicam, only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5-mg oral meloxicam doses: 0.5%, 6%, and 13% of the dose were found in urine in the form of meloxicam, and the 5′-hydroxymethyl and 5′-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single intravenous (IV) dose of meloxicam decreased the area under the curve (AUC) of meloxicam by 50%. The mean apparent terminal half-life ($t_{1/2}$) for meloxicam from ZYNRELEF is approximately 22 to 25 hours.

Pharmacodynamics

CONTRIBUTION OF MELOXICAM AND BUPIVACAINE TO ACTIVITY OF ZYNRELEF

The contribution of each active ingredient in ZYNRELEF to its activity was demonstrated in nonclinical pharmacodynamic studies and confirmed in Phase 2 double-blind, randomized, active- and placebo-controlled clinical studies in subjects undergoing herniorrhaphy or bunionectomy, utilizing ZYNRELEF and formulations of meloxicam alone or bupivacaine alone in the ZYNRELEF vehicle. In both studies, meloxicam alone demonstrated negligible local analgesia and bupivacaine alone demonstrated superior analgesia compared with placebo through 24 hours postsurgery, despite exposure to bupivacaine for approximately 72 hours. Compared with bupivacaine alone in both studies, ZYNRELEF (at the same bupivacaine doses) demonstrated synergistic activity of the combination with greater and longer analgesia through 24, 48, and 72 hours.

EFFECT ON CARDIAC REPOLARIZATION[1]

The effect of ZYNRELEF on cardiac repolarization as assessed by the QTc interval was evaluated in patients undergoing surgical procedures. ZYNRELEF, at single doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval.

BUPIVACAINE[1]

Systemic absorption of local anesthetics, including bupivacaine, produces effects on the cardiovascular and central nervous system (CNS), which can be serious at toxic blood concentrations. At blood concentrations achieved with normal therapeutic doses, manifestations of CNS stimulation and depression or changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. Clinical reports and animal research suggest that cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine.

IMPORTANT SAFETY INFORMATION

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.

ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution

EFFICACY

Based on similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity

- between bunionectomy and other foot and ankle surgical procedures
- between open inguinal herniorrhaphy and other small-to-medium open abdominal surgical procedures
- between total knee arthroplasty and other lower extremity total joint arthroplasty surgical procedures

the pharmacokinetic profile and effectiveness of ZYNRELEF are not expected to be clinically significantly different when ZYNRELEF is administered at the same dose.[1]

CLINICAL TRIAL DATA

Heron conducted rigorous clinical trials of ZYNRELEF across multiple surgical models, beginning with the Phase 2a studies, which in addition to establishing safety and efficacy in a smaller population were designed to measure the synergistic analgesic effect of ZYNRELEF compared with extended-release bupivacaine and extended-release meloxicam given alone, and the sum of the 2 individual components.[32,33]

The Phase 3 trials (EPOCH 1 Bunionectomy and EPOCH 2 Herniorrhaphy) and EPOCH TKA were designed to meet regulatory requirements testing ZYNRELEF against standard-of-care bupivacaine HCl solution and placebo, and did not include an underlying multimodal analgesic (MMA) regimen. Patients received rescue medication only upon request for pain control during the 72-hour postoperative observation period and after discharge.[1-4]

To further improve pain control and reduce opioid utilization in a real-world setting, Heron Therapeutics, Inc, also undertook follow-on studies in bunionectomy, herniorrhaphy, and total knee arthroplasty to assess the impact of using ZYNRELEF in conjunction with a scheduled non-opioid MMA regimen.[36-38]

Heron also initiated The HOPE Project, which studied the impact of ZYNRELEF when used as the foundation of a non-opioid MMA regimen in a real-world setting. The purpose of The HOPE Project was to develop simplified, easy-to-implement postoperative pain management protocols that use ZYNRELEF in conjunction with non-opioid over-the-counter (OTC) oral analgesics to reduce or even eliminate the need for postoperative opioids.[39]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Table 3. Summary of studies of ZYNRELEF in bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty[1-4,32,33,36,39,40]

	Bunionectomy With Osteotomy (foot and ankle)	Open Inguinal Herniorrhaphy With Mesh (small-to-medium open abdominal)	Total Knee Arthroplasty (lower extremity total joint arthroplasty)
Phase 2a Studies Demonstrating Synergy	**Phase 2a** (Synergy vs bupivacaine and ER meloxicam alone) Study 208	**Phase 2a** (Synergy vs bupivacaine and ER meloxicam alone) Study 202	
RCT Studies Included in PI •Did not include non-opioid MMA regimen •Included 72-hour in-hospital postoperative monitoring	EPOCH 1 Phase 3 (vs placebo and bupivacaine) Study 301	EPOCH 2 Phase 3 (vs placebo and bupivacaine) Study 302	EPOCH TKA Phase 2b (vs placebo and bupivacaine) Study 209
Follow-On Studies •Open label, single arm, uncontrolled •Included non-opioid MMA regimen •Included 72-hour in-hospital postoperative monitoring	**EPOCH 1 Single-Arm Follow-On** Study 218	**EPOCH 2 Single-Arm Follow-On** Study 215	**EPOCH TKA Single-Arm Follow-On** Study 306
Real-World Setting •Open label •Included non-opioid MMA regimen •Discharged per site practice (2.41 hours after surgery on average)		HOPE **HOPE Hernia 1** Study 304	

EPOCH 1 Bunionectomy[1,2]

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical trial, 412 patients across 13 sites undergoing unilateral bunionectomy with osteotomy and internal fixation with a lidocaine Mayo block were randomized to 1 of the following 3 treatment groups in a 3:3:2 ratio (respectively): ZYNRELEF 60 mg/1.8 mg instillation, bupivacaine HCl solution 50 mg injection, or saline placebo instillation.

Table 4. ZYNRELEF met primary and key secondary endpoints in EPOCH 1 Bunionectomy[1,2]

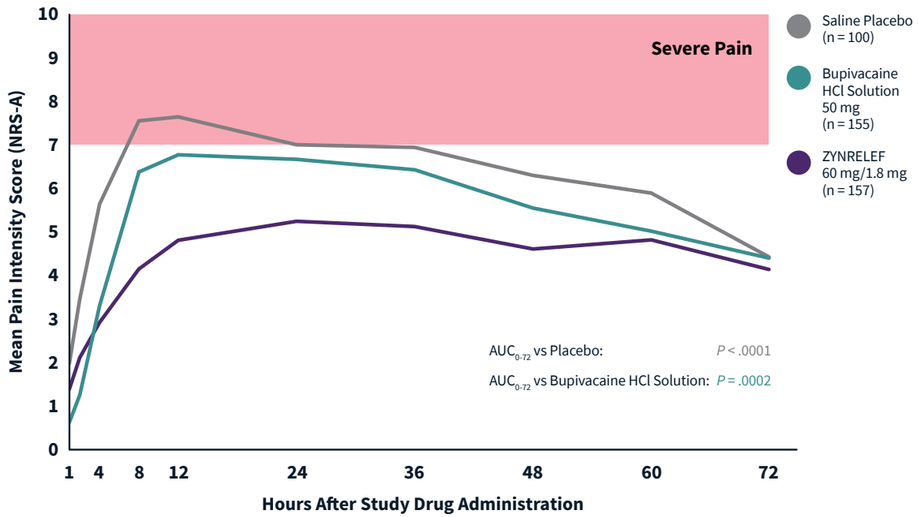
Hierarchical hypothesis testing ($P \leq .05$)[a]	Endpoint		*P* Value
	Primary	Pain Intensity (AUC_{0-72}) vs Placebo	$P < .0001$
↓	1st Key Secondary	Pain Intensity (AUC_{0-72}) vs Bupivacaine HCl Solution	$P = .0002$
↓	2nd Key Secondary	Opioid Use (0-72 hours) vs Placebo	$P < .0001$
↓	3rd Key Secondary	Opioid-Free (0-72 hours) vs Bupivacaine HCl Solution	$P = .0001$
↓	4th Key Secondary	Opioid Use (0-72 hours) vs Bupivacaine HCl Solution	$P = .0022$

[a]This study applied a strict testing hierarchy to control the study at the .05 level. This means the primary endpoint had to reach significance ($P \leq .05$) before the first key secondary endpoint was tested, continuing through each additional endpoint.

EPOCH 1 Bunionectomy (cont)

Patients rated pain intensity on the 0-to-10 Numeric Rating Scale (NRS) of pain. Pain scores were analyzed with adjustment for the analgesic duration of rescue medications. **ZYNRELEF demonstrated a significant reduction in pain intensity compared to both bupivacaine HCl solution and saline placebo through 72 hours.**[1,2]

Figure 16. EPOCH 1 Bunionectomy: pain intensity score (NRS-A) through 72 hours[1,2]



- ZYNRELEF patients had less pain in the 0- to 8-hour and 0- to 12-hour periods than bupivacaine HCl solution patients (AUC_{0-8}: $P = .0477$,[a] AUC_{0-12}: $P < .0001$[b]), **when bupivacaine HCl solution is still effective**[2]
- ZYNRELEF patients had lower pain intensity than bupivacaine HCl solution patients through 72 hours, **even excluding the first 24 hours from analysis, indicating that the first 24 hours did not drive the statistical significance through 72 hours** (AUC_{24-72}: $P = .0072$)[2,a]

[a]Analysis not prespecified; nominal *P* value not controlled for multiplicity.
[b]Nominal *P* value not controlled for multiplicity.

IMPORTANT SAFETY INFORMATION

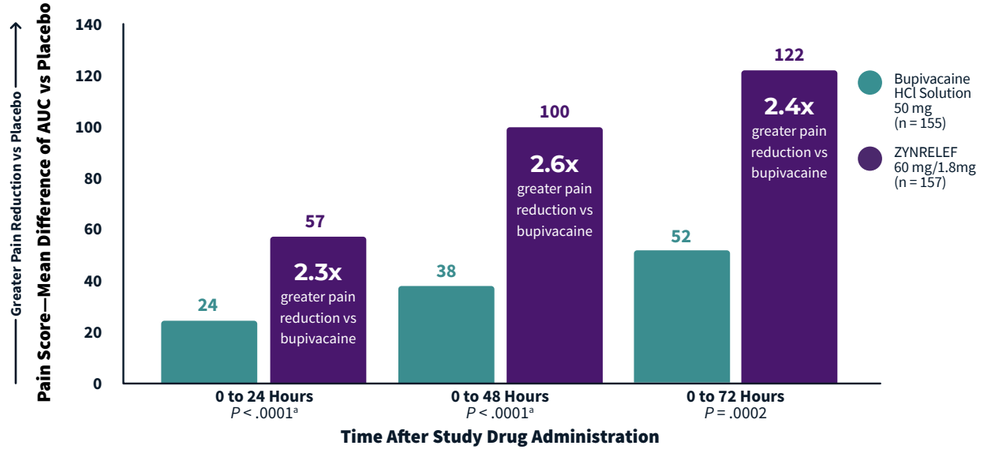
Warnings and Precautions (cont)

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

Methemoglobinemia: Cases have been reported with local anesthetic use.

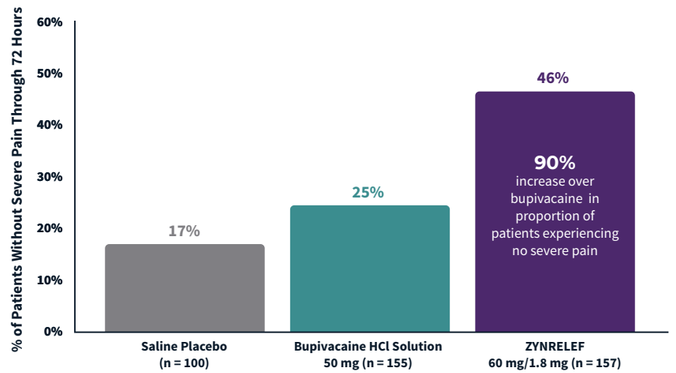
ZYNRELEF demonstrated a superior reduction in pain intensity versus placebo compared to that of bupivacaine HCl solution versus placebo through 72 hours (Figure 17).[1,2,41]

Figure 17. EPOCH 1 Bunionectomy pain reduction: least squares mean difference of pain intensity score (NRS) AUC vs placebo[1,2,41]



There was a reduction in the proportion of patients **without severe pain** at any timepoint for ZYNRELEF (46%) compared to bupivacaine HCl solution (25%; $P < .0001$[a]) and saline placebo (17%; $P < .0001$[a]).[2]

Figure 18. EPOCH 1 Bunionectomy: percentage without severe pain through 72 hours[2]



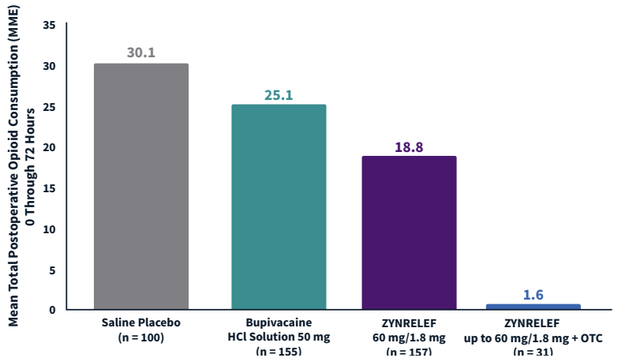
Severe Pain: pain intensity score of ≥7 on a Numeric Rating Scale of 0 to 10.

[a]Nominal *P* value not controlled for multiplicity.

EPOCH 1 Bunionectomy (cont)

A significant reduction in total opioid consumption over 72 hours was also observed for ZYNRELEF (median consumption, 12.5 mg) compared to both bupivacaine HCl (17.5 mg; *P* = .0022) and placebo (25.0 mg; *P* < .0001).[1,2]

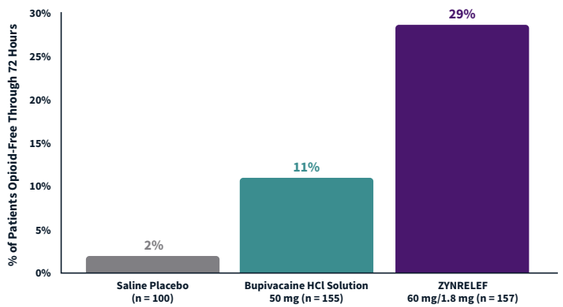
Figure 19. EPOCH 1 Bunionectomy: total postoperative opioid consumption through 72 hours[2]



Reduction in opioid consumption:
25% vs bupivacaine
37% vs placebo[2]

ZYNRELEF demonstrated an increase in the proportion of patients who were opioid-free (29%) compared to both bupivacaine HCl solution (11%; *P* = .0001) and placebo (2%; *P* < .0001[a]).[1,2]

Figure 20. EPOCH 1 Bunionectomy: percentage of patients requiring no opioids through 72 hours[1,2]



Of ZYNRELEF patients who were opioid-free at 72 hours[2]:

91% remained opioid-free through day 10	82% remained opioid-free through day 28

The proportion of patients who were both without severe pain and opioid-free through 72 hours was higher for ZYNRELEF than for both bupivacaine HCl solution and placebo (*P* < .0001 for both comparisons).[41,b]

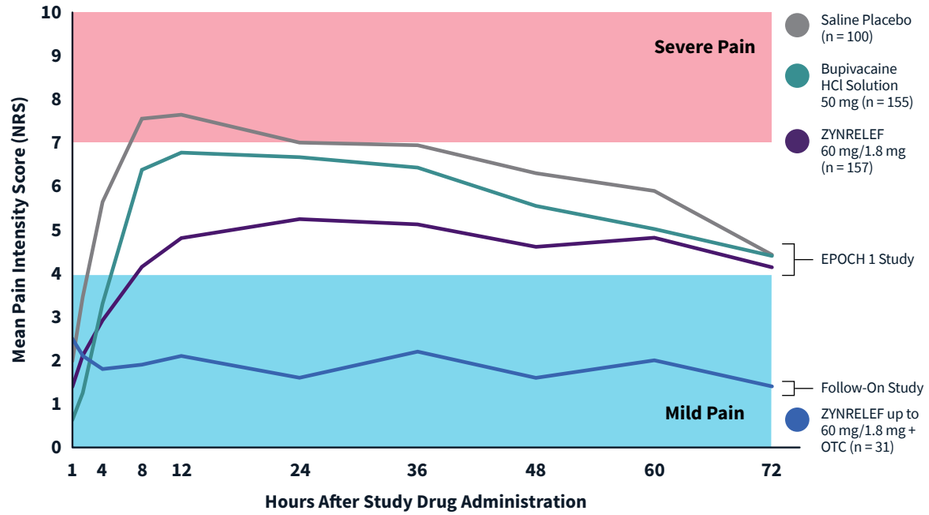
[a]Nominal *P* value not controlled for multiplicity.
[b]Analysis not prespecified; nominal *P* value not controlled for multiplicity.

EPOCH 1 Single-Arm[a] Follow-On[37]

In this open-label, single-arm, multicenter, follow-on study, 31 patients undergoing unilateral bunionectomy with osteotomy and internal fixation received ZYNRELEF as the foundation of a scheduled regimen of generic non-opioid over-the-counter (OTC) oral analgesics (acetaminophen and ibuprofen). This follow-on study was conducted using entry and exclusion criteria and patient demographics similar to those of EPOCH 1 at clinical sites where EPOCH 1 was conducted. The ZYNRELEF dose was up to 60 mg. A non-opioid multimodal oral analgesic regimen was added to understand its impact on pain and the necessity of opioid prescriptions at discharge. **The study was conducted without an active comparator arm (bupivacaine HCl solution with a non-opioid multimodal analgesic regimen) as superiority to standard-of-care bupivacaine HCl solution had already been established in EPOCH 1.** Patients rated pain intensity on the 0-to-10 Numeric Rating Scale (NRS) of pain. Pain scores were analyzed with adjustment for the analgesic duration of rescue medications. ZYNRELEF as the foundation of a non-opioid oral OTC analgesic regimen kept pain in the mild range through 72 hours.

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

Figure 21. Cross-study comparison (EPOCH 1/EPOCH 1 Single-Arm Follow-On): pain intensity score (NRS) through 72 hours[1,2,37]



[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

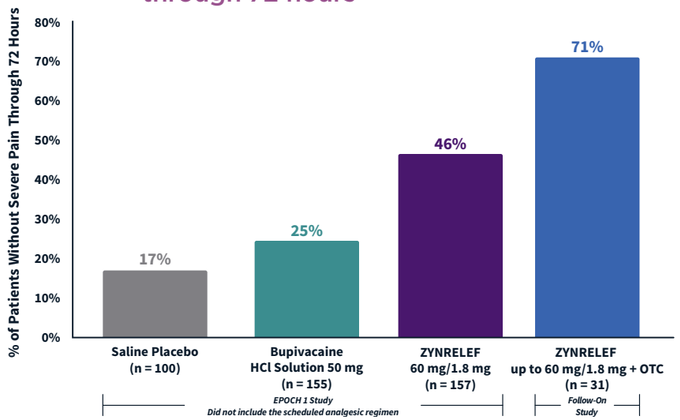
Serious Skin Reactions: NSAIDs, including meloxicam, can cause serious skin adverse reactions. If symptoms present, evaluate clinically.

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

EPOCH 1 Single-Arm[a] Follow-On (cont)

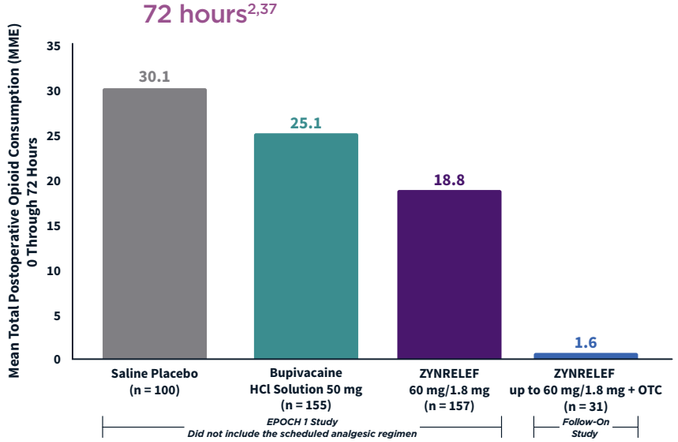
Seventy-one percent of patients receiving ZYNRELEF with the non-opioid over-the-counter (OTC) analgesic regimen experienced no severe pain through 72 hours after surgery, which correlates with the large portion of patients who required no opioid analgesics postoperatively.[37]

Figure 22. Cross-study comparison (EPOCH 1/EPOCH 1 Single-Arm Follow-On): percentage of patients without severe pain through 72 hours[2,37]



ZYNRELEF with a scheduled regimen of non-opioid OTC oral analgesics resulted in reduction of postoperative opioid consumption through 72 hours in EPOCH 1 Single-Arm Follow-On.[37]

Figure 23. Cross-study comparison (EPOCH 1/EPOCH 1 Single-Arm Follow-On): total postoperative opioid consumption through 72 hours[2,37]

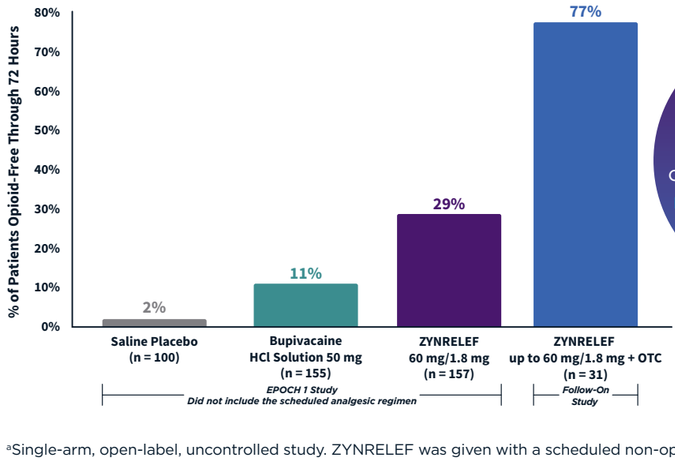


[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Seventy-seven percent of patients required no opioids through 72 hours and remained opioid-free through 28 days when treated with ZYNRELEF and a scheduled non-opioid oral analgesic regimen.[37]

Figure 24. Cross-study comparison (EPOCH 1/EPOCH 1 Single-Arm[a] Follow-On): percentage opioid-free through 72 hours[1,2,37]



100% of patients receiving ZYNRELEF plus OTC who were opioid-free at 72 hours **remained opioid-free through 28 days**[37]

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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.

EPOCH 2 Herniorrhaphy[1,3]

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical trial, 418 patients across 17 sites undergoing open inguinal herniorrhaphy with mesh under general anesthesia were randomized to 1 of the following 3 treatment groups in a 2:2:1 ratio (respectively): ZYNRELEF 300 mg/9 mg instillation, bupivacaine HCl solution 75 mg injection, or saline placebo instillation.

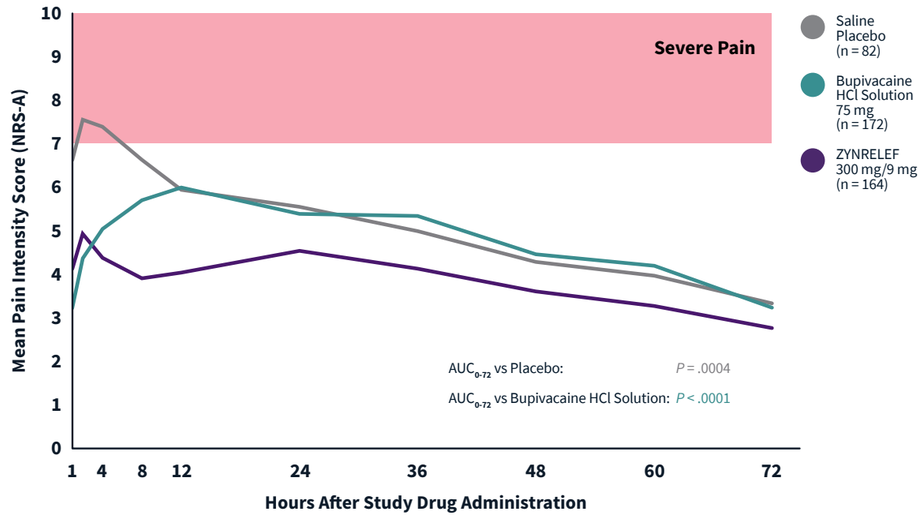
Table 5. ZYNRELEF met all primary and key secondary endpoints in EPOCH 2 Herniorrhaphy[1,3]

Hierarchical hypothesis testing ($P \leq .05$)[a]	Endpoint		*P* Value
↓	Primary	Pain Intensity (AUC_{0-72}) vs Placebo	$P = .0004$
↓	1st Key Secondary	Pain Intensity (AUC_{0-72}) vs Bupivacaine HCl Solution	$P < .0001$
↓	2nd Key Secondary	Opioid Use (0-72 hours) vs Placebo	$P = .0001$
↓	3rd Key Secondary	Opioid-Free (0-72 hours) vs Bupivacaine HCl Solution	$P = .0486$
↓	4th Key Secondary	Opioid Use (0-72 hours) vs Bupivacaine HCl Solution	$P = .0240$

[a]This study applied a strict testing hierarchy to control the study at the .05 level. This means the primary endpoint had to reach significance ($P \leq .05$) before the first key secondary endpoint was tested, continuing through each additional endpoint.

Patients rated pain intensity on the 0-to-10 Numeric Rating Scale (NRS) of pain. Pain scores were analyzed with adjustment for the analgesic duration of rescue medications. **ZYNRELEF demonstrated a significant reduction in pain intensity compared to both bupivacaine HCl solution and placebo through 72 hours.[1,3]**

Figure 25. EPOCH 2 Herniorrhaphy: pain intensity score (NRS-A) through 72 hours[1,3]



- ZYNRELEF patients had less pain in the 0- to 8-hour and 0- to 12-hour periods than bupivacaine HCl solution patients (AUC_{0-8}: $P = .0426$,[a] AUC_{0-12}: $P = .0001$[b]), **when bupivacaine HCl solution is most effective**[3]
- ZYNRELEF patients had lower pain intensity than bupivacaine HCl solution patients through 72 hours, **even excluding the first 24 hours from analysis, indicating that the first 24 hours did not drive the statistical significance through 72 hours** (AUC_{24-72}: $P = .0007$)[3,a]

[a]Analysis not prespecified; nominal *P* value not controlled for multiplicity.
[b]Nominal *P* value not controlled for multiplicity.

IMPORTANT SAFETY INFORMATION

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.

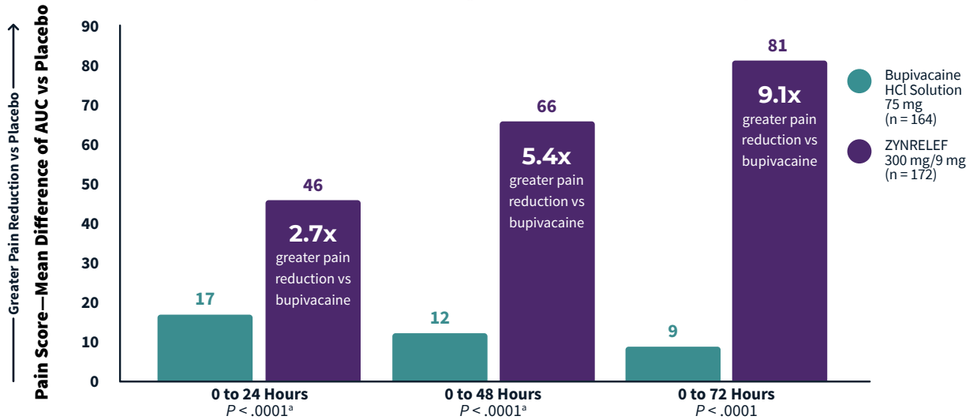
Severe Renal Impairment: Not recommended.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

EPOCH 2 Herniorrhaphy (cont)

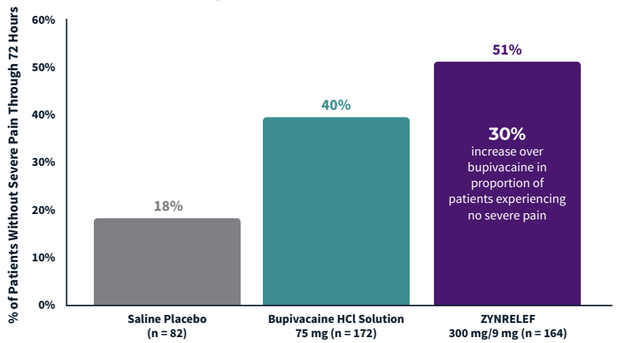
ZYNRELEF demonstrated a superior reduction in pain intensity versus placebo compared to that of bupivacaine HCl solution versus placebo through 72 hours (Figure 26).[1,3,42]

Figure 26. EPOCH 2 Herniorrhaphy pain reduction: least squares mean difference of pain intensity score (NRS) AUC vs placebo[1,3,42]



There was a reduction in the proportion of patients **without severe pain** at any timepoint for ZYNRELEF (51%) compared to bupivacaine HCl solution (40%; *P* = .0372[a]) and saline placebo (18%; *P* < .0001[a]).[3]

Figure 27. EPOCH 2 Herniorrhaphy: percentage without severe pain through 72 hours[3]

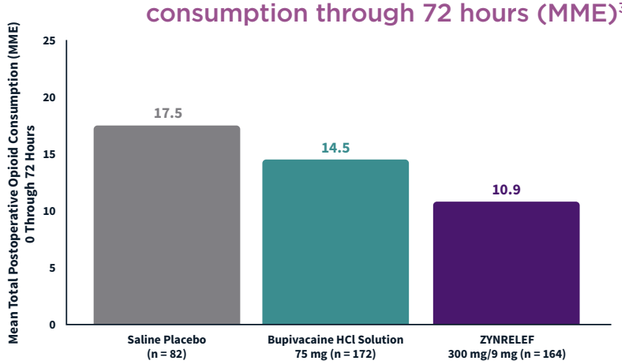


Severe pain: pain intensity score of ≥7 on a Numeric Rating Scale of 0 to 10.

[a]Nominal *P* value not controlled for multiplicity.

A significant reduction in total opioid consumption over 72 hours was also observed for ZYNRELEF (median consumption 0.0 mg) compared to both bupivacaine HCl solution (7.3 mg; *P* = .0240) and placebo (11.3 mg; *P* = .0001).[1,3]

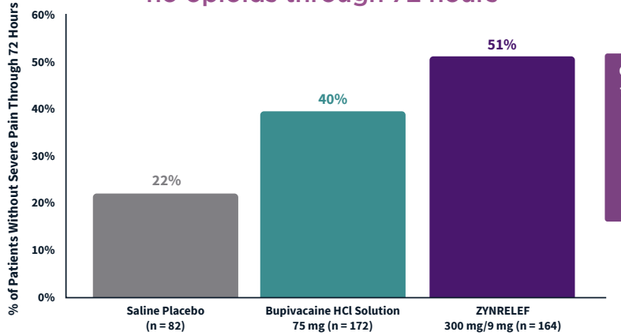
Figure 28. EPOCH 2 Herniorrhaphy: total postoperative opioid consumption through 72 hours (MME)[3]



Reduction in opioid consumption:
25% vs bupivacaine
38% vs placebo[3]

ZYNRELEF demonstrated an increase in the proportion of patients who were opioid-free (51%) compared to both bupivacaine HCl solution (40%; *P* = .0486) and placebo (22%; *P* < .0001[a]).[1,3]

Figure 29. EPOCH 2 Herniorrhaphy: percentage of patients requiring no opioids through 72 hours[1,3]



Of ZYNRELEF patients who were opioid-free at 72 hours[3]:

95% remained opioid-free **through day 10**

85% remained opioid-free **through day 28**

The proportion of patients who were both without severe pain and opioid-free through 72 hours was higher for ZYNRELEF than for both bupivacaine HCl solution (*P* = .0111[b]) and placebo (*P* < .0001[b]).[41]

[a]Nominal *P* value not controlled for multiplicity.
[b]Analysis not prespecified; nominal *P* value not controlled for multiplicity.

IMPORTANT SAFETY INFORMATION

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.

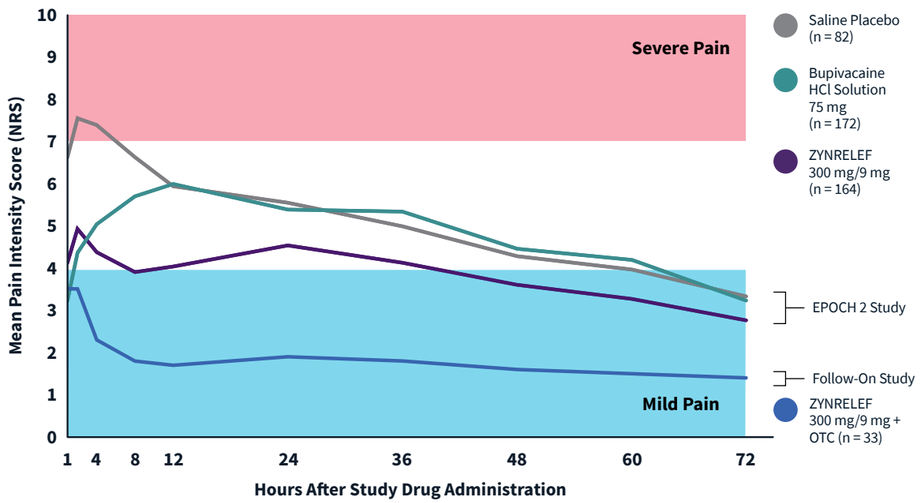
EPOCH 2 Single-Arm[a] Follow-On[36]

In this open-label, single-arm, multicenter, follow-on study, 63 patients undergoing open inguinal herniorrhaphy with mesh received ZYNRELEF as the foundation of a scheduled non-opioid multimodal oral analgesic regimen: Cohort 1 (n = 33) received generic non-opioid over-the-counter (OTC) oral analgesics (acetaminophen and ibuprofen), while Cohort 2 (n = 30) received the same non-opioid OTC oral analgesics as well as a dose of IV ketorolac intraoperatively. The addition of IV ketorolac provided no additional benefit beyond oral acetaminophen and ibuprofen; therefore, data from Cohort 1 alone was used for all following analyses.

This follow-on study was conducted using entry and exclusion criteria and patient demographics similar to those of EPOCH 2 at clinical sites where EPOCH 2 was conducted. The ZYNRELEF dose was the same. A non-opioid multimodal oral analgesic regimen was added to understand its impact on pain and the necessity of opioid prescriptions at discharge. **This study was conducted without an active comparator arm (bupivacaine HCl solution with a non-opioid multimodal analgesic regimen) as superiority to standard-of-care bupivacaine HCl solution had already been established in EPOCH 2.** Patients rated pain intensity on the 0-to-10 Numeric Rating Scale (NRS) of pain. Pain scores were analyzed with adjustment for the analgesic duration of rescue medications. ZYNRELEF as the foundation of a non-opioid oral OTC analgesic regimen kept pain in the mild range through 72 hours.

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

Figure 30. Cross-study comparison (EPOCH 2/EPOCH 2 Single-Arm Follow-On): pain intensity score (NRS) through 72 hours[1,3,36]



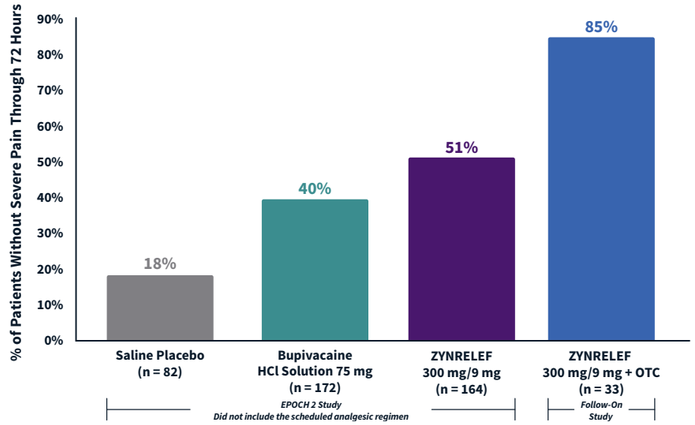
[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

Note: EPOCH 2 Single-Arm Follow-On study results reflect reported pain intensity at rest; EPOCH 2 results reflect reported pain intensity with activity (after sitting up from a resting position).[43,44]

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Eighty-five percent of patients receiving ZYNRELEF with the non-opioid over-the-counter (OTC) analgesic regimen experienced no severe pain through 72 hours after surgery, which correlates with the large portion of patients who required no opioid analgesics postoperatively.[43]

Figure 31. Cross-study comparison (EPOCH 2/EPOCH 2 Single-Arm[a] Follow-On): percentage of patients without severe pain through 72 hours[3,36]



[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

Severe Pain: pain intensity score of ≥7 on a Numeric Rating Scale of 0 to 10.

IMPORTANT SAFETY INFORMATION

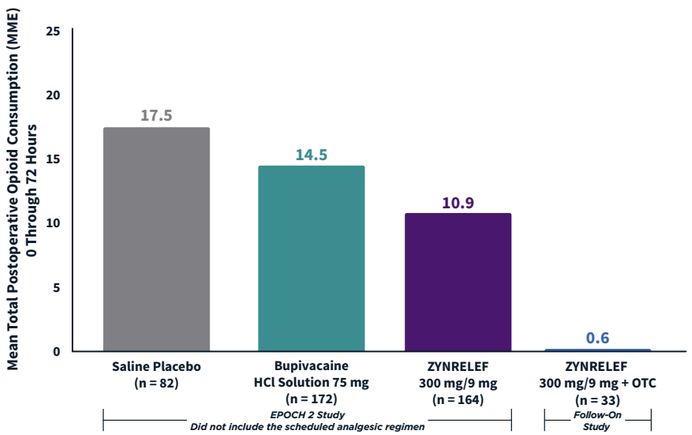
WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

- **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.**

EPOCH 2 Single-Arm[a] Follow-On (cont)

ZYNRELEF with a scheduled regimen of non-opioid OTC oral analgesics resulted in reduction of postoperative opioid consumption through 72 hours in EPOCH 2 Single-Arm Follow-On.[36]

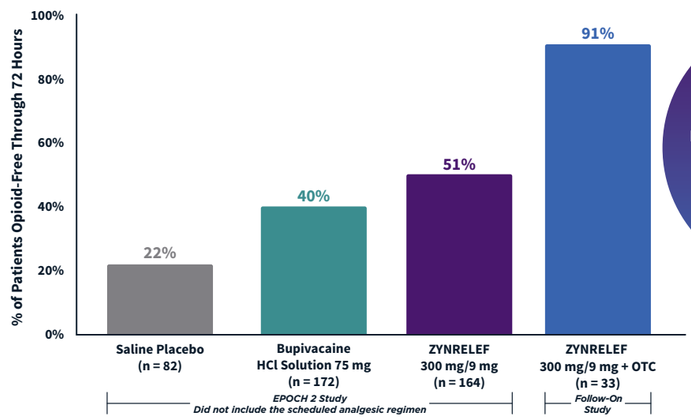
Figure 32. Cross-study comparison (EPOCH 2/EPOCH 2 Single-Arm Follow-On): total postoperative opioid consumption through 72 hours[3,36]



[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

Ninety-one percent of herniorrhaphy patients in the follow-on study required no opioids through 72 hours when treated with ZYNRELEF as the foundation of a scheduled non-opioid multimodal oral analgesic regimen. Eighty-five percent of all Cohort 1 patients treated with ZYNRELEF and a scheduled non-opioid, multimodal oral analgesic regimen remained opioid-free through day 28.[36]

Figure 33. Cross-study comparison (EPOCH 2/EPOCH 2 Single-Arm[a] Follow-On): percentage opioid-free through 72 hours[1,3,36]



85% of patients receiving ZYNRELEF plus OTC remained opioid-free **through 28 days**[36]

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

IMPORTANT SAFETY INFORMATION

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.

ZYNRELEF
(bupivacaine and meloxicam)
extended-release solution

HOPE Helping Opioid Prescription Elimination

Real-World Setting: The HOPE Project[39]

The HOPE Project collected data on opioid elimination protocols in a real-world setting. The purpose of The HOPE Project was to develop simplified, easy-to-implement postoperative pain management protocols that use ZYNRELEF in conjunction with non-opioid OTC pain medicines to reduce or even eliminate the need for postoperative opioids. A simple algorithm was used to identify who does or does not require an opioid prescription postoperatively, which was then validated through The HOPE Project.[45]

The initial part of The HOPE Project, HOPE Hernia 1, was an open-label, multicenter study without a control group in which 93 patients underwent open inguinal herniorrhaphy with mesh under general anesthesia or deep sedation. HOPE Hernia 1 was conducted using entry and exclusion criteria and patient demographics similar to those of EPOCH 2. Patients received ZYNRELEF (300 mg bupivacaine/9 mg meloxicam) and were randomized to 1 of 2 parallel cohorts, each receiving different scheduled, non-opioid multimodal oral regimens of analgesics: Cohort 1 (n = 46) received alternating postoperative oral acetaminophen and oral ibuprofen, while Cohort 2 (n = 47) received concurrent postoperative oral acetaminophen and oral ibuprofen. Both cohorts received preoperative oral acetaminophen and oral ibuprofen.

This study was conducted without active comparator arms as superiority to bupivacaine HCl solution had already been established in EPOCH 2. Unlike the Phase 3 studies, in which patients were kept in the hospital for observation for 72 hours after surgery, in HOPE Hernia 1 patients were discharged as per site practice (2.41 hours after surgery on average), with instructions to follow their assigned non-opioid MMA regimen at home during the first 5 days after surgery.[40]

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

Table 6. Primary and secondary endpoints of HOPE Hernia 1[39]

Endpoint	
Primary	No Opioid Prescription Through Day 15
Secondary	No Opioid Prescription at Discharge
	No Opioid Prescription: Discharge Through Day 15
	Pain Intensity at Discharge
	Opioid Use: Discharge Through Day 15
	Satisfaction (TSQM-9 Scores) With Postoperative OTC Regimen

IMPORTANT SAFETY INFORMATION

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.

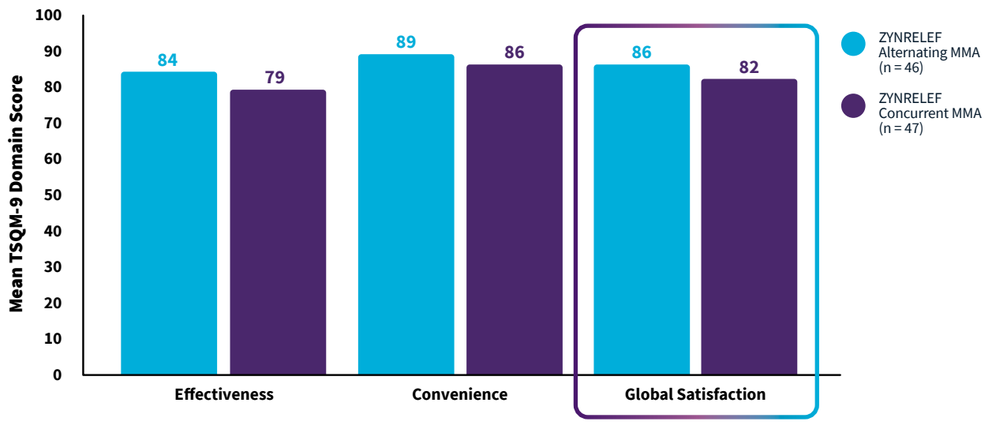
See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

ZYNRELEF when used as the foundation of an MMA regimen resulted in similar findings in both cohorts, with high proportions of patients requiring no opioid prescription after open inguinal herniorrhaphy. Of the 93 patients, 95% did not require opioids to manage their postoperative pain through discharge, and 95% remained opioid-free from surgery through day 15. **Ninety-one percent of patients received no opioid discharge prescription; among these patients, none called the site for postoperative pain through day 15.** Five of the 8 patients who did receive an opioid discharge prescription did not take an opioid after discharge, meaning that 97% of patients consumed no opioids from discharge through day 15.[39]

Figure 34. HOPE Hernia 1: opioid-free patients[39,46]

Ninety-three percent of patients were satisfied with their medication. Both MMA regimens were well tolerated, with no evidence of NSAID-related toxicity.[40]

Figure 35. HOPE Hernia 1: patient satisfaction[39,46,b]



Note: Study protocol specified that opioids would only be prescribed at discharge for patients who rated their pain at discharge ≥6 (NRS) or received opioid rescue medication prior to discharge.

[a]Through day 15, 1 patient who received a discharge opioid prescription called the site for postoperative pain.

[b]Satisfaction with postdischarge, non-opioid, multimodal analgesic regimen for treatment of herniorrhaphy-related pain was assessed at day 15 using the Nine-item Treatment Satisfaction Questionnaire for Medication (TSQM-9).[47]

EPOCH TKA[1,4]

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical study, 222 patients undergoing primary unilateral total knee arthroplasty (TKA) under general anesthesia were randomized to 1 of the following treatment groups in a 1:1:1:1 ratio: ZYNRELEF 400 mg/12 mg instillation, ZYNRELEF 400 mg/12 mg instillation and low-dose ropivacaine 50 mg (injected into the posterior capsule), bupivacaine HCl solution 125 mg injection, or saline placebo instillation. Bupivacaine HCl solution was included for assay sensitivity. The mean age was 62 years (range 33 to 85); 51% of patients were female, and 49% were male. ZYNRELEF met all primary and key secondary endpoints, which were the AUC of the NRS pain intensity scores (cumulative pain scores) versus placebo collected over the first 48 hours and the first 72 hours, respectively.[a] A strict testing hierarchy was applied to control the study at the .05 level.[b]

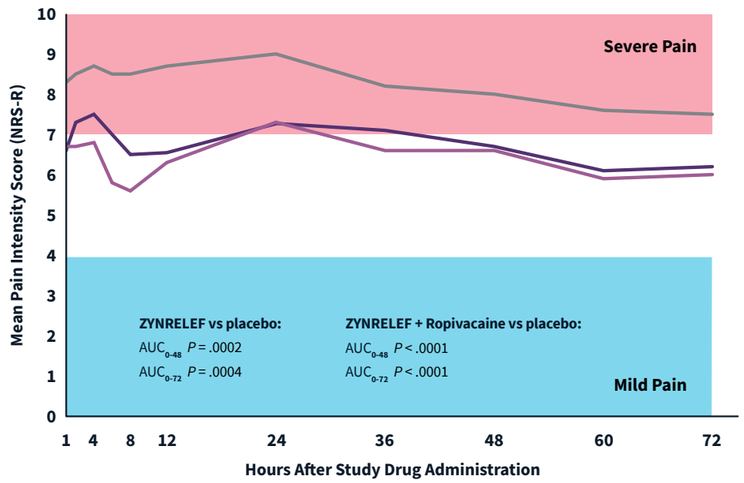
The study protocol did not include a scheduled postoperative multimodal analgesic regimen. Upon request, patients requiring postoperative rescue medication could receive oral immediate-release oxycodone or IV morphine. Non-opioid analgesics were not permitted during the 72-hour postoperative observation period.[c] Investigators followed their standard practice regarding the use of drains, tourniquets, and implant type (cruciate retaining or posterior stabilizing).

Table 7. ZYNRELEF met all primary and key secondary endpoints in the EPOCH TKA study[1,4]

Hierarchical hypothesis testing ($P \leq .05$)[a]

	Endpoint	*P* Value
Primary	Pain Intensity (AUC_{0-48}) ZYNRELEF 400 mg + Ropivacaine vs Placebo	$P < .0001$
	Pain Intensity (AUC_{0-48}) ZYNRELEF 400 mg vs Placebo	$P = .0002$
Key Secondary	Pain Intensity (AUC_{0-72}) ZYNRELEF 400 mg + Ropivacaine vs Placebo	$P < .0001$
	Pain Intensity (AUC_{0-72}) ZYNRELEF 400 mg vs Placebo	$P = .0004$

Figure 36. EPOCH TKA: pain Intensity score (NRS-R) through 72 hours, adjusting for opioid rescue medication use[1]



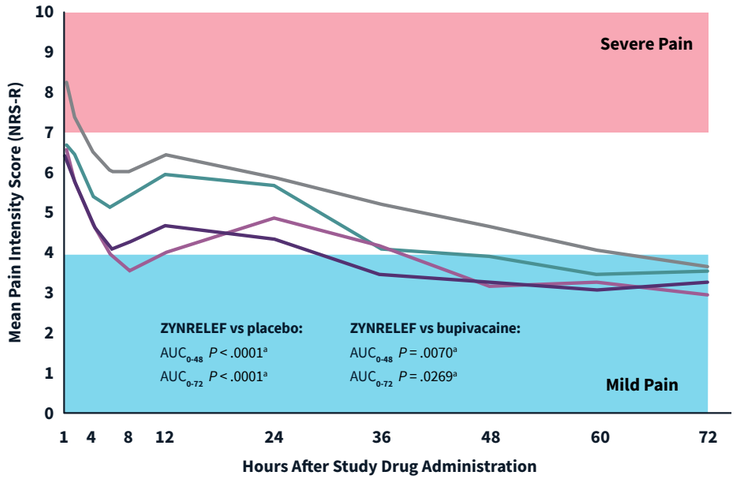
[a]Pain scores reported adjusting for opioid rescue medication use.

[b]The primary endpoint had to reach significance ($P \leq .05$) before the first key secondary endpoint was tested, continuing through each additional endpoint.

[c]Preoperatively, all patients were administered tranexamic acid, oral pregabalin, and IV acetaminophen.

ZYNRELEF demonstrated a significant reduction in pain intensity compared with saline placebo for the 72-hour postoperative period ($P = .0004$). Additionally, ZYNRELEF with low-dose ropivacaine demonstrated reduction in pain intensity compared with bupivacaine HCl solution in a secondary analysis ($P = .0456$[a]) and saline placebo in a sensitivity analysis ($P = .0002$[a]) using actual reported pain scores[b] over the same time period. Patients treated with ZYNRELEF required fewer opioids than those treated with bupivacaine HCl solution or saline placebo, as measured in morphine milligram equivalents (MME).[4]

Figure 37. EPOCH TKA: pain intensity score (NRS-R) through 72 hours compared to bupivacaine HCl solution, without adjustment for opioid rescue medication use[4]



[a]Nominal *P* value not controlled for multiplicity. This analysis is appropriate since ZYNRELEF patients consumed fewer opioids and is clinically meaningful because it demonstrates that ZYNRELEF patients experienced less pain even while consuming fewer opioids. Analysis represents data from Cohort 2.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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

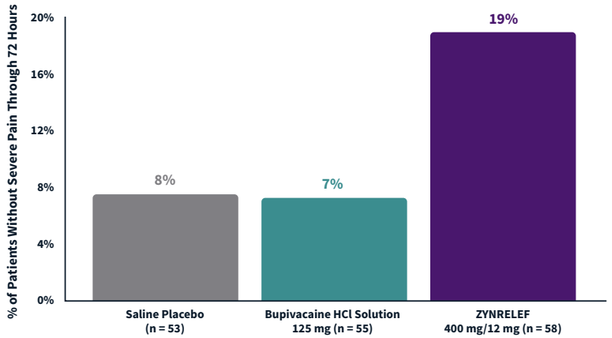
Hypertension: Patients taking some antihypertensive medication may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

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.

EPOCH TKA (cont)

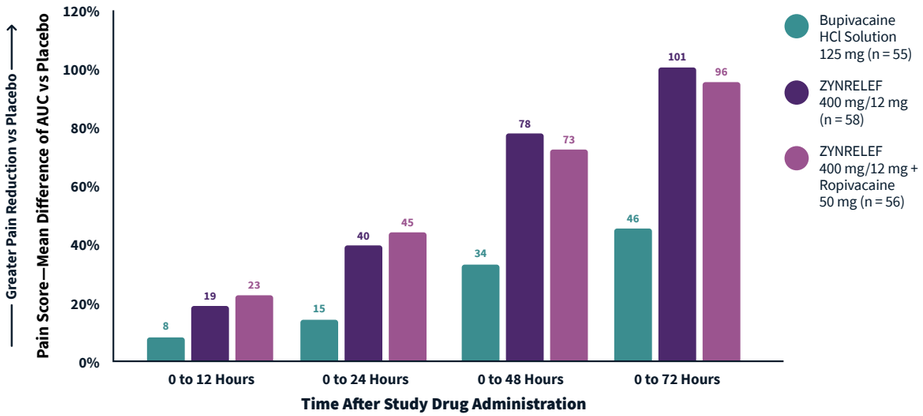
There was an increase in the proportion of patients without severe pain through all timepoints for ZYNRELEF (19%) compared to bupivacaine HCl solution (7%) and saline placebo (8%).[4]

Figure 38. EPOCH TKA: percentage without severe pain through 72 hours[4]



A prespecified secondary analysis (using pain scores as reported without adjustment for opioid rescue medication use) indicates that the statistical significance of the primary efficacy outcome was not driven by the adjustment for opioid rescue medication use. Therefore, while patients in the control groups benefited from the pain-reducing effects of increased opioid use, **patients who received ZYNRELEF experienced less pain than those in the placebo and bupivacaine HCl solution control groups through 48 and 72 hours, despite taking fewer opioids.[4]**

Figure 39. EPOCH TKA pain reduction: least squares mean difference of pain intensity scores[a] (NRS) AUC vs placebo at all timepoints[4]



[a]As reported without adjustment for opioid rescue medication use.

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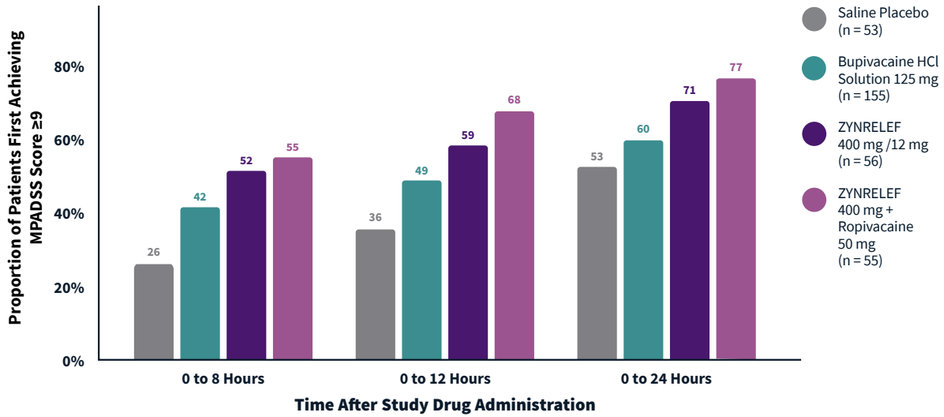
Additionally, ZYNRELEF, with or without low-dose ropivacaine, also increased the proportion of patients ready for discharge compared with saline placebo at 8 hours (52% and 55% vs 26%) and at 12 hours (59% and 68% vs 36%).[4] Discharge readiness was assessed using the Modified Postanesthetic Discharge Scoring System (MPADSS) criteria, with a score ≥9 indicating that a patient was ready for discharge. MPADSS considers numerous clinical variables such as vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding.[48] A greater proportion of patients in both ZYNRELEF groups first achieved an MPADSS score ≥9 by 8 hours and by 12 hours, compared with both bupivacaine HCl solution and placebo. An increase in patients considered ready for discharge along with an improvement in postoperative pain control and lower total opioid consumption may allow for greater application of TKA in the outpatient setting and reduced length of stay.[4]

Figure 40. Over 50% of patients treated with ZYNRELEF were "discharge ready" by 8 hours following surgery[4]



IMPORTANT SAFETY INFORMATION

Warnings and Precautions (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.

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

Methemoglobinemia: Cases have been reported with local anesthetic use.

EPOCH TKA Single-Arm[a] Follow-On Study[38,49]

In this open-label, single-arm, multicenter, follow-on study, 51 patients undergoing primary unilateral TKA under bupivacaine spinal anesthesia (≤20 mg) received ZYNRELEF in conjunction with a scheduled postoperative non-opioid oral analgesic regimen to better reflect real-world conditions. The EPOCH TKA Single-Arm Follow-On study was conducted using similar entry and exclusion criteria as the EPOCH TKA study, with similar patient demographics. The dose and administration method for ZYNRELEF were the same as in the EPOCH TKA study.

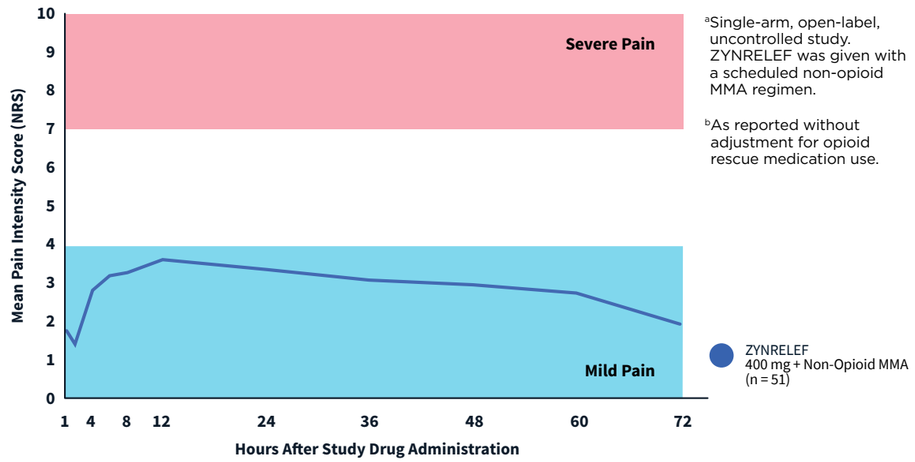
Preoperatively, patients were administered oral acetaminophen 1 g, oral celecoxib 200 mg, and oral pregabalin 300 mg. Intraoperatively, intravenous fentanyl (≤4 µg/kg) was permitted. No other opioids, analgesics, or anti-inflammatory agents (except ZYNRELEF) were permitted intraoperatively, unless needed to treat an adverse event, for pretreatment prior to needle placement, or to decrease venous irritation. Postoperatively, patients were administered oral acetaminophen 1 g every 8 hours and celecoxib 200 mg every 12 hours through 72 hours. Post discharge (beyond 72 hours), patients received oral ibuprofen 600 mg and then 3 hours later oral acetaminophen 1 g, alternating every 6 hours for 72 hours, then as needed through day 7. The MMA regimen and primary endpoint were selected based on a published Phase 4 study of a long-acting liposomal bupivacaine with a scheduled, non-opioid MMA regimen in TKA.[28]

ZYNRELEF as the foundation of a scheduled non-opioid MMA regimen kept pain in the mild range through 72 hours, using pain scores as reported without adjustment for use of opioid rescue medication.

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

Figure 41. EPOCH TKA Single-Arm Follow-On: mean reported pain intensity scores[b] (NRS) through 72 hours[38]

A secondary analysis of the EPOCH TKA Single-Arm Follow-On study shows how patients reported their pain when treated with ZYNRELEF and an MMA regimen similar to those commonly used in practice. Without adjustment for use of opioid rescue medication, **mean reported pain scores remained in the mild range through 72 hours.[38]**

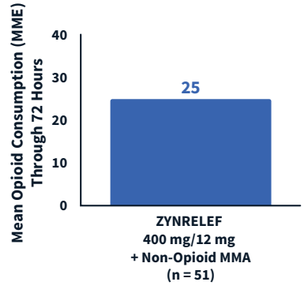


[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

[b]As reported without adjustment for opioid rescue medication use.

The mean consumption of opioids in the EPOCH TKA Single-Arm Follow-On study was 1 to 2 pills of oxycodone 10 mg per day through 72 hours (25 MME).[49] Thirty-seven percent of patients receiving ZYNRELEF with the non-opioid multimodal analgesic regimen experienced no severe pain through 72 hours after surgery, which correlates with the large portion of patients who required no opioid analgesics postoperatively.[37] **Thirty-nine percent of TKA patients treated with ZYNRELEF and a scheduled non-opioid MMA regimen received no opioid discharge prescription and had no callbacks through day 11 of recovery about surgically related postdischarge pain.[47]**

Figure 42. EPOCH TKA Single-Arm[a] Follow-On: postoperative opioid consumption[38,49]



[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

When treated with ZYNRELEF and a scheduled non-opioid MMA regimen, most patients rated their pain control as "good" or "excellent" in the first 3 days of recovery: 88% of patients on day 1, 90% of patients on day 2, and 100% of patients on day 3. Patients were asked to evaluate their pain control over the preceding 24 hours using a 4-point patient global assessment (PGA) scale: 0 = "poor"; 1 = "fair"; 2 = "good"; 3 = "excellent".[49,50]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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.

ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution

CLINICAL SAFETY

Overview

The safety of ZYNRELEF has now been evaluated in over 1,500 patients in clinical trials.[5] At the time of the New Drug Application (NDA) submission, approximately 1,000 patients undergoing various surgical procedures had taken part in randomized, double-blind, bupivacaine- and placebo-controlled studies designed to investigate ZYNRELEF.[1] Patients treated with ZYNRELEF whose data was included in the NDA ranged in age from 18 to 85 years (median age 47 years), with 61.8% female, 78.9% White, 16.0% African-American, and 5.1% all other races.

Among 504 patients who received ZYNRELEF in single doses of 60 mg/1.8 mg to 400 mg/12 mg via instillation into the surgical site, the most common adverse reactions (incidence ≥10% and higher than with saline placebo) following ZYNRELEF administration were constipation, vomiting, and headache.[1]

ZYNRELEF was well tolerated when used concomitantly with aspirin, ropivacaine, and acetaminophen.[36,37,39] In cohorts receiving ketorolac, celecoxib, or ibuprofen in addition to ZYNRELEF, no increase in NSAID-related toxicity was seen.[36-38,51]

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

Common Adverse Reactions[2-5,35-37,39,41-43,52-54]

ZYNRELEF had a similar safety profile to that of placebo and bupivacaine HCl solution. ZYNRELEF was generally well tolerated with no premature discontinuations due to drug-related adverse events, no deaths, comparable or fewer opioid-related adverse events, and no evidence of drug-related local anesthetic systemic toxicity (LAST), compared to bupivacaine HCl solution. The adverse reactions of ZYNRELEF with or without low-dose ropivacaine were similar.

Table 8. Adverse reactions with ZYNRELEF in EPOCH 1 Bunionectomy occurring with ≥5% incidence and higher than with saline placebo[1,2,41]

	Saline Placebo (n = 101)	Bupivacaine HCl Solution 50 mg (n = 154)	ZYNRELEF 60 mg/1.8 mg (n = 157)
Dizziness	18%	23%	22%
Incision Site Edema	13%	14%	17%
Headache	10%	13%	14%
Incision Site Erythema	8%	12%	13%
Bradycardia	6%	8%	8%
Impaired Healing	1%	4%	6%
Muscle Twitching	5%	5%	6%

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Local inflammatory adverse events occurring in ≥2% of patients treated with ZYNRELEF with a higher incidence than with saline placebo included incision site cellulitis (4% incidence with ZYNRELEF, compared to 1% with both bupivacaine HCl solution and saline placebo); wound dehiscence (4% with ZYNRELEF, compared to 1% with bupivacaine HCl solution and 2% with saline placebo); and incision site infection (3% with ZYNRELEF, compared to 1% with bupivacaine HCl solution and 0% with saline placebo).

In EPOCH 1 Bunionectomy, bone healing was assessed by X-ray on days 28 and 42. There was no difference in bone healing between treatment groups. A total of 4 subjects had delayed bone healing: 1 in the ZYNRELEF group, 1 in the saline placebo group, and 2 in the bupivacaine HCl group.

Table 9. EPOCH 1 Bunionectomy: lower overall incidence of opioid-related adverse events (ORAEs) with ZYNRELEF[2,41]

	Saline Placebo (n = 101)	Bupivacaine HCl Solution 50 mg (n = 154)	ZYNRELEF 60 mg/1.8 mg (n = 157)
Any ORAE	**53%**	**51%**	**44%**
Nausea	44%	45%	38%
Vomiting	19%	21%	15%
Constipation	7%	12%	6%
Pruritus	6%	1%	5%
Pruritus Generalized	4%	5%	3%
Somnolence	0	1%	1%

ORAEs were defined as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention. These adverse events were considered ORAEs regardless of whether a patient received opioids.

Table 10. Treatment-emergent adverse events in EPOCH 1 Single-Arm[a] Follow-On study in bunionectomy[37,54]

	ZYNRELEF up to 60 mg/1.8 mg + OTC Analgesic Regimen (n = 31)
Any AE	**65%**
AE Possibly Related to Study Drug	0
Opioid-Related AE	29%
Local Inflammatory AE	3%
Potential LAST-Related AE	3%
AE Leading to Study Withdrawal	0
Severe AE	0
Serious AE	0
Fatal AE	0

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

Table 11. Adverse reactions with ZYNRELEF in EPOCH 2 Herniorrhaphy occurring with ≥5% incidence and higher than with saline placebo[1,3,42]

	Saline Placebo (n = 82)	Bupivacaine HCl Solution 75 mg (n = 173)	ZYNRELEF 300 mg/9 mg (n = 163)
Headache	12%	14%	13%
Bradycardia	7%	9%	9%
Dysgeusia	4%	12%	9%
Skin Odor Abnormal[a]	1%	1%	8%

[a]All incidences of skin odor abnormal were recorded at a single site and by a single observer and are potentially related to the smell of dimethyl sulfoxide (DMSO) in ZYNRELEF.[42,55]

Table 12. EPOCH 2 Herniorrhaphy: lower overall incidence of opioid-related adverse events (ORAEs) with ZYNRELEF[3,42]

	Saline Placebo (n = 82)	Bupivacaine HCl Solution 75 mg (n = 173)	ZYNRELEF 300 mg/9 mg (n = 163)
Any ORAE	**44%**	**42%**	**33%**
Nausea	34%	21%	18%
Constipation	18%	24%	17%
Vomiting	5%	7%	4%
Pruritus Generalized	1%	1%	1%
Urinary Retention	1%	2%	1%
Pruritus	0	2%	0

ORAEs were defined as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention. These adverse events were considered ORAEs regardless of whether a patient received opioids.

Table 13. Treatment-emergent adverse events in EPOCH 2 Single-Arm[a] Follow-On study in herniorrhaphy[36,43]

	ZYNRELEF 300 mg/9 mg + OTC Analgesic Regimen (n = 33)	ZYNRELEF 300 mg/9 mg + OTC Analgesic Regimen + Ketorolac (n = 30)
Any AE	**36%**	**40%**
Severe AE	0	3%
Opioid-Related AE	6%	17%
Potential LAST-Related AE	3%	10%
Serious AE	0	0
AE Leading to Study Withdrawal	0	0

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

Table 14. Treatment-emergent adverse events in HOPE Hernia 1[39]

	Cohort 1: ZYNRELEF 300 mg/9 mg + Alternating MMA Regimen[a] (n = 46)	Cohort 2: ZYNRELEF 300 mg/9 mg + Concurrent MMA Regimen[b] (n = 47)
Any TEAE	**28%**	**38%**
Nausea	11%	15%
Constipation	2%	9%
Vomiting	7%	4%
Severe AE	0	0
Serious AE	0	0
AE Leading to Study Withdrawal	0	0

[a]Alternating: OTC regimen of ibuprofen 600 mg q6h alternated 3 hours later with acetaminophen 1 g q6h.
[b]Concurrent: OTC regimen of ibuprofen 600 mg and acetaminophen 1 g, taken together q6h.

Table 15. Adverse reactions with ZYNRELEF in EPOCH TKA occurring with ≥5% incidence and higher than with saline placebo[1,4,35]

	Saline Placebo (n = 53)	Bupivacaine HCl Solution 125 mg (n = 55)	ZYNRELEF 400 mg/12 mg (n = 58)
Nausea	47%	55%	50%
Constipation	23%	33%	24%
Vomiting	19%	27%	26%
Hypertension	15%	13%	19%
Pyrexia	4%	15%	14%
Leukocytosis	0	2%	7%
Pruritus	2%	5%	7%
Headache	0	7%	7%
Anemia	2%	0	5%
Hyperhidrosis	4%	0	5%
Hypotension	4%	2%	5%

Table 16. Treatment-emergent adverse events in EPOCH TKA Single-Arm[a] Follow-On study with an incidence ≥5%[49]

	ZYNRELEF 400 mg/12 mg + Non-Opioid MMA Regimen (n = 51)
Any TEAE	**82%**
Nausea	57%
Vomiting	27%
Constipation	20%
Dizziness	12%
Anemia Postoperative	6%
Bradycardia	6%
Urinary Retention	6%

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

Maximum Dose (400 mg/12 mg)[1]

The maximum recommended human dose (MRHD) of ZYNRELEF is 400 mg and 12 mg of bupivacaine and meloxicam, respectively.

IMPORTANT SAFETY INFORMATION

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.

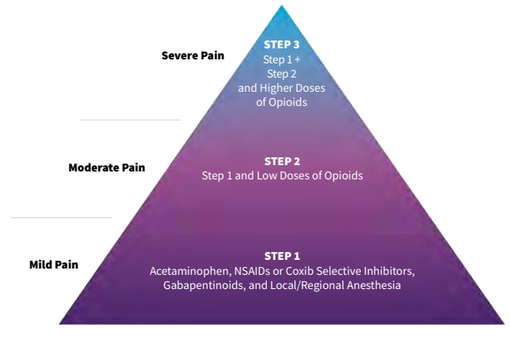
See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

CONCLUSIONS

Changing the Paradigm of Postoperative Pain Management With ZYNRELEF

A 72-hour dual-acting local anesthetic (DALA) could impact the way we treat postoperative pain. Many experts agree that the World Health Organization (WHO) analgesic ladder is outdated and needs to reflect advances in the understanding of the pathophysiology of pain as well as new innovative therapeutic options.[56-59]

Figure 43. The current World Health Organization (WHO) analgesic ladder[56]

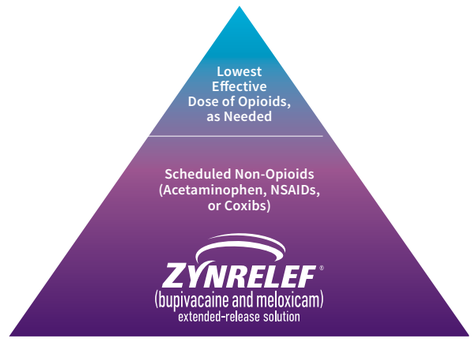


Adapted from Crews JC. *JAMA.* 2002;288(5):629-632.

Modified WHO Analgesic Ladder

Figure 44, below, demonstrates how the ladder can be updated with ZYNRELEF supplemented with scheduled non-opioids, such as acetaminophen or NSAIDs.

Figure 44. ZYNRELEF could be the new foundation of a multimodal analgesic regimen[36-39]



New Proposed Model for Treating Pain

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

Summary

The first 72 hours after surgery are the most painful.[6] Uncontrolled pain can impede patient recovery.[60] Inflammation peaks around 24 hours postoperatively and remains relatively high through the first 72 hours.[9] This inflammation can limit the efficacy of local anesthetics.[29,30]

Generic local anesthetics are not designed to provide pain relief beyond 8 to 12 hours.[10,13] Other longer-acting local anesthetics, including liposomal bupivacaine and formulations delivered via wound infiltration catheters or pumps, exhibit limited and inconsistent efficacy beyond 12 to 24 hours in part because the inflammatory process inhibits their ability to efficiently penetrate the nerve cell membrane and block pain signals from reaching the brain.[11-14,29,30] While clinicians typically rely on opioids for the period beyond local anesthetics' window of effectiveness, opioids are not an ideal solution, as they cannot prevent transmission of pain signals from the site of injury.[15,17] Further, opioids can cause serious adverse reactions, including respiratory depression.[18] Therefore, a 72-hour local anesthetic could impact the way we treat postoperative pain.[36-39]

ZYNRELEF is the first and only extended-release dual-acting local anesthetic (DALA), with a novel mechanism of action that delivers postoperative pain relief for up to 72 hours via a single needle-free application.[1-4,23] It is also the only local anesthetic to demonstrate superiority to standard-of-care bupivacaine HCl solution in Phase 3 trials.[1-3] ZYNRELEF utilizes Heron's known proprietary Biochronomer® drug delivery technology to deliver an extended-release formulation of the local anesthetic bupivacaine in a fixed-dose combination with the nonsteroidal anti-inflammatory drug meloxicam for the management of postoperative pain.[1,23] The presence of meloxicam is thought to normalize pH at the surgical site, resulting in fewer hydrogen ions and potentiating the effect of bupivacaine.[23] ZYNRELEF has demonstrated an increase in analgesia through 72 hours compared with the same extended-release formulation of either bupivacaine or meloxicam alone, or the sum of the 2 individual components.[1,32-34]

By delivering sustained levels of both a potent local anesthetic and a low dose of a non-steroidal anti-inflammatory agent directly to the site of tissue injury, ZYNRELEF has been shown to manage pain better than standard-of-care bupivacaine HCl solution through 72 hours, including fewer patients with severe pain, and to significantly reduce or even eliminate opioid utilization following surgery.[1-3] In clinical trials, 77% of bunionectomy patients and 91% of herniorrhaphy patients remained opioid-free through 72 hours when treated with ZYNRELEF and a scheduled non-opioid oral analgesic regimen.[37,44]

In The HOPE Project, designed to reflect real-world use of ZYNRELEF and a scheduled non-opioid oral OTC analgesic regimen, 95% of herniorrhaphy patients remained opioid-free through day 15. Of the 91% of patients discharged without an opioid prescription, there were no callbacks to the site for postoperative pain through the 15-day study period.[39]

ZYNRELEF had a similar safety profile to that of placebo and bupivacaine HCl solution. ZYNRELEF was generally well tolerated with no premature discontinuations due to drug-related adverse events, no deaths, comparable or fewer opioid-related adverse events, no evidence of drug-related local anesthetic systemic toxicity (LAST), and no evidence of delayed bone healing. The adverse reactions of ZYNRELEF with or without low-dose ropivacaine were similar.[5,35-37,39,41-43,51-54]

For additional information and materials, please visit formulary.ZYNRELEF.com.

See Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

ABBREVIATIONS

AE	adverse event
AUC	area under the curve
CNS	central nervous system
C_{max}	maximum plasma concentration
DALA	dual-acting local anesthetic
ER	extended-release
HCl	hydrochloric acid
IV	intravenous
LAST	local anesthetic systemic toxicity
MME	morphine milligram equivalents
MPADSS	Modified Postanesthetic Discharge Scoring System
MRHD	maximum recommended human dose
NC	not calculated
NRS	Numeric Rating Scale
NRS-A	Numeric Rating Scale with activity
NRS-R	Numeric Rating Scale at rest
NSAID	nonsteroidal anti-inflammatory drug
ORAE	opioid-related adverse event
OTC	over-the-counter
PK/PD	pharmacokinetic/pharmacodynamic
q6h	every 6 hours
RCT	randomized controlled trial
SD	standard deviation
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TKA	total knee arthroplasty
T_{max}	time of occurrence of maximum concentration
TSQM-9	Nine-item Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution

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.

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

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PP-HTX011-0368 | 01/22