NEW DRUG APPROVAL

Brand Name	Zynrelef™
Generic Name	bupivacaine and meloxicam
Drug Manufacturer	Heron Therapeutics, Inc.

New Drug Approval

FDA Approval Date: May 12, 2021
Review Designation: Priority
Type of Review: Type 4 - New Combination, New Drug Application (NDA): 211988
Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

The goal of postoperative pain control is to reduce the negative consequences associated with acute postsurgical pain and help the patient make a smooth transition back to normal function. Traditionally, opioid analgesic therapy has served as the mainstay of treatment for acute postoperative pain. However, the recent rise in morbidity and mortality associated with opioid misuse has led to increasing demands for more investigative effort into developing pain treatment strategies that place more emphasis on using a multimodal approach. These efforts have proved to be challenging, as the subjective nature of pain perception further complicates the ability to achieve satisfactory pain control. Furthermore, specific patient comorbidities and social factors may predispose patients to have increased pain perception.

Approximately 75 percent of patients who undergo surgery experience acute postoperative pain, which is often medium-high in severity. Less than half of patients undergoing surgery report adequate postoperative pain relief. This percentage presents a significant problem as inadequate postoperative pain control may lead to adverse physiologic effects among patients in the immediate postoperative period and places them at increased risk of developing chronic pain associated with the procedure. Severe persistent postoperative pain affects 2 to 10 percent of adults.

Among the issues that make pain control difficult is a lack of pain level surveillance protocols or intervention guidelines that would help provide more efficient means of adjusting therapy for providing better pain relief.

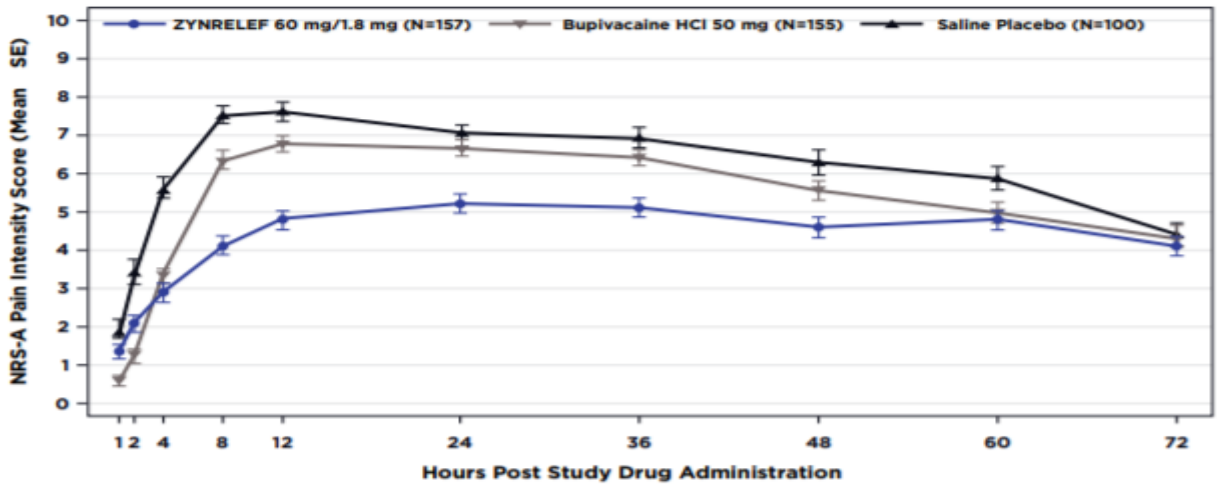
Efficacy

Study 1:

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical trial (NCT03295721), 412 patients undergoing unilateral simple bunionectomy 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, bupivacaine HCl 50 mg, or saline placebo. The mean patient age was 47 years (range 18 to 77) and patients were predominantly female (86%).

Patients treated with Zynrelef™ demonstrated a significant reduction in pain intensity compared to those treated with either bupivacaine HCl or saline placebo for up to 72 hours . A significant proportion of patients treated with Zynrelef™ did not receive opioid analgesia (29%) over 72 hour.

Mean Pain Intensity with Activity Over 72 Hours for STUDY 1 (Bunionectomy)

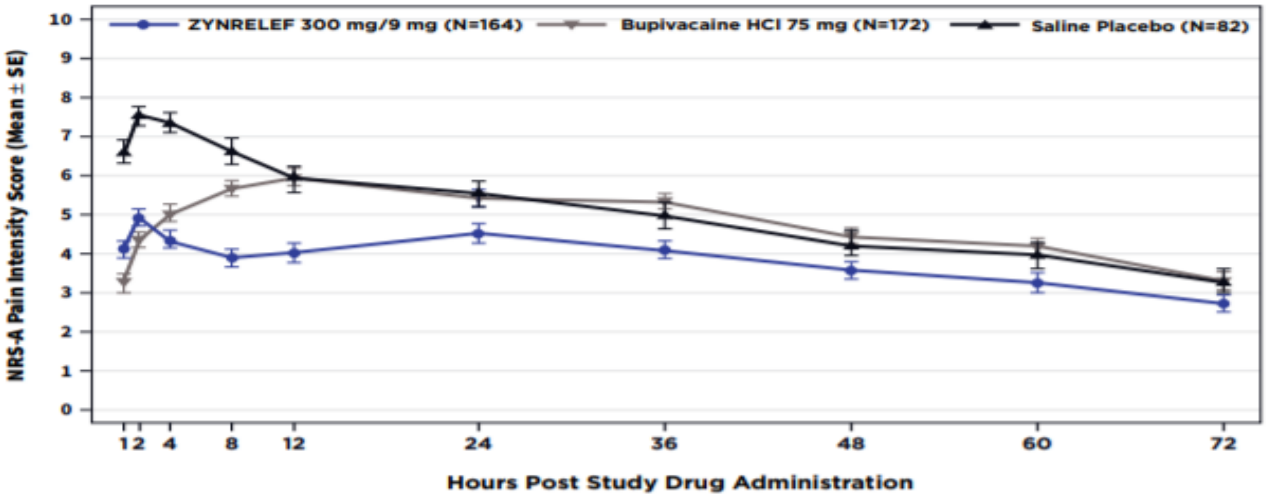


Study 2:

In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical trial (NCT03237481), 418 patients undergoing unilateral 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, bupivacaine HCl 75 mg, or saline placebo.

Patients treated with Zynrelef™ demonstrated a statistically significant reduction in pain intensity compared to those treated with either bupivacaine HCl or saline placebo for up to 72 hours. A significant proportion of patients treated with Zynrelef™ did not receive opioid analgesia (51%) over 72 hours compared to those treated with either bupivacaine HCl (40%) or saline placebo (22%). A significant reduction in total opioid consumption over 72 hours was also observed for patients treated Reference ID: 4794625 34 with Zynrelef™ (median consumption 0 mg) compared to those treated with either bupivacaine HCl (7.3 mg) or saline placebo (11.3 mg).

Mean Pain Intensity with Activity Over 72 Hours for STUDY 2 (Herniorrhaphy)



Study 3:

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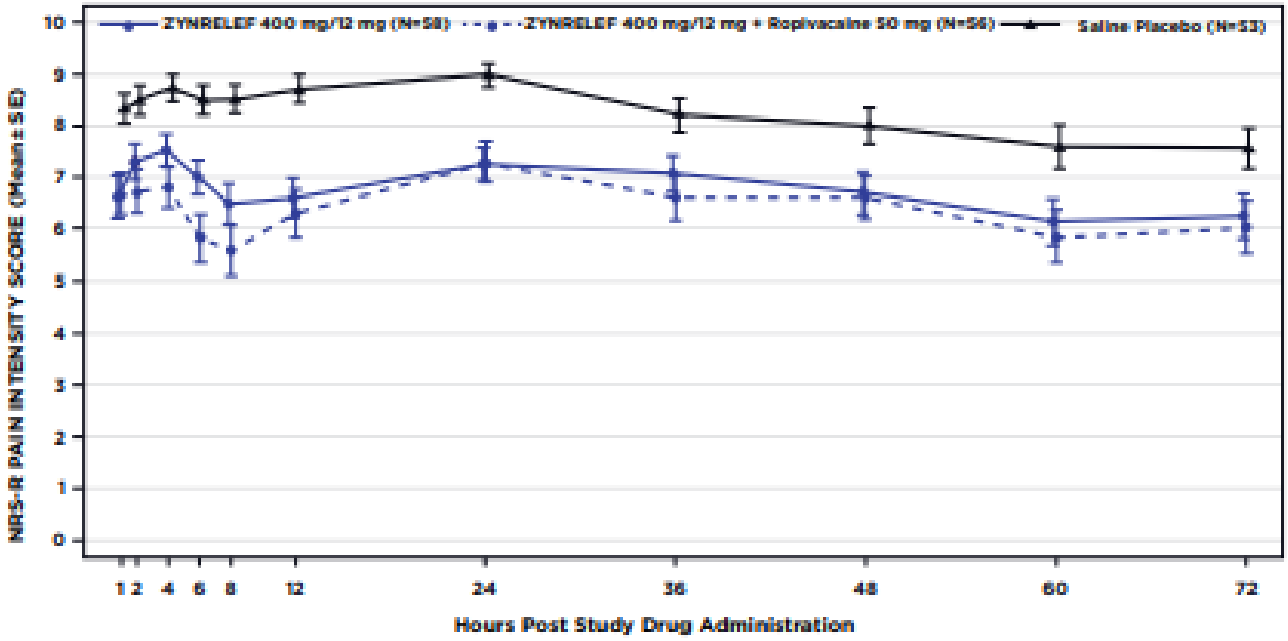
In this multicenter, double-blind, parallel-group, active- and placebo-controlled clinical study (NCT03015532), 222 patients undergoing primary unilateral total knee arthroplasty under general anesthesia were randomized to one of the following treatment groups in a 1:1:1:1 ratio: Zynrelef™ 400 mg/12 mg, Zynrelef™ 400 mg/12 mg plus ropivacaine 50 mg (injected into the posterior capsule), bupivacaine HCl 125 mg, or saline placebo. The mean age was 62 years (range 33 to 85) and 51% of patients were female.

Mean Pain Intensity at Rest Over 72 Hours for STUDY 3 (Total Knee Arthroplasty)



Safety

ADVERSE EVENTS

Most common adverse reactions (incidence ≥10% are constipation, vomiting, and headache.

WARNINGS & 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 medications 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 function.
- **Anaphylactic Reactions:** Seek emergency help if an anaphylactic reaction occurs.

- **Methemoglobinemia**: Cases of methemoglobinemia have been reported in association with local anaesthetic 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:** Limit use of NSAIDs, including Zynrelef™, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the ductus arteriosus.
- **Hematologic Toxicity**: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia.

CONTRAINDICATIONS

Zynrelef™ is contraindicated for:

- Patients with a known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to any local anesthetic agent of the amide-type, NSAIDs, or to any of the other components of Zynrelef™.
- Patients with a 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.
- Patients undergoing obstetrical paracervical block anesthesia.
- Patients undergoing coronary artery bypass graft (CABG) surgery.

Clinical Pharmacology

MECHANISMS OF ACTION

Zynrelef™ is a fixed-dose combination of bupivacaine and meloxicam.

Bupivacaine

Local anesthetics 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. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Meloxicam

The mechanism of action of meloxicam, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Meloxicam is a potent inhibitor of prostaglandin synthesis in vitro. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Dose & Administration

ADULTS

- Bunionectomy, up to bupivacaine 60 mg/meloxicam 1.8 mg (up to 2.3 mL).
- Open inguinal herniorrhaphy, up to bupivacaine 300 mg/meloxicam 9 mg (up to 10.5 mL).
- Total knee arthroplasty, up to bupivacaine 400 mg/meloxicam 12 mg (up to 14 mL).

PEDIATRICS

Safety and effectiveness of Zynrelef™ in pediatric patients has not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

The use of Zynrelef™ in patients with severe renal impairment is not recommended.

HEPATIC IMPAIRMENT

No dose adjustment of Zynrelef™ is necessary in patients with mild to moderate hepatic impairment. Zynrelef™ should only be used in patients with severe hepatic impairment if the benefits are expected to outweigh the risks, monitor patients for signs of worsening liver function.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Zynrelef™ (bupivacaine and meloxicam) extended-release solution is available in four dosage strengths as single-dose glass vials:

- 400 mg bupivacaine and 12 mg meloxicam.
- 300 mg bupivacaine and 9 mg meloxicam.
- 200 mg bupivacaine and 6 mg meloxicam.
- 60 mg bupivacaine and 1.8 mg meloxicam.