

MMA PROTOCOL TOTAL KNEE ARTHROPLASTY

Using ZYNRELEF as the Foundation of a Multimodal Analgesic Regimen

As the first and only extended-release dual-acting local anesthetic (DALA), ZYNRELEF reduces postoperative pain for up to 72 hours.^{1,2} When used as the foundation of a multimodal analgesic regimen, ZYNRELEF can reduce or eliminate the need for opioids in many patients following surgery.^{3,4}

MMA Protocol

AS USED IN THE EPOCH TKA SINGLE-ARM^a FOLLOW-ON STUDY^{3,4}

Medication	Preoperative Medication	Intraoperative Medication	Postoperative Medication			
			Within 8 Hours of 1st Dose	Days 1-3 ^b	Days 4-7 ^c	After Day 7 (as needed)
IV tranexamic acid (TXA)	1 g 1st dose ^d		1 g 2nd dose			
PO pregabalin	300 mg single dose ^e					
PO celecoxib	200 mg single dose ^e			200 mg BID		
PO acetaminophen	1 g single dose ^e			1 g q8h	1 g q6h	2nd-line therapy 1 g q6h
ZYNRELEF		Up to 14 mL (400 mg/12 mg) single instillation ^f				
IV fentanyl		≤4 ug/kg single dose				
PO ibuprofen					600 mg q6h	1st-line therapy 600 mg q6h
PO aspirin				325 mg BID		

^aSingle-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. ^bDay 1 is day of surgery when patient is able to tolerate oral intake. ^cMMA regimen: OTC oral analgesics taken every 6 hours at alternating intervals so that an analgesic is taken every 3 hours (starting with ibuprofen followed in 3 hours by acetaminophen). ^dFirst dose within 4 hours prior to surgery for antifibrinolysis. ^eAdminister immediately before being taken to the operating room. ^fFollowing final irrigation and suctioning and prior to suturing.

POSTOPERATIVE MEDICATION

IMPORTANT: 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. For all postoperative medications, do not exceed the maximum daily dose specified on each medication label.

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.**

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



IMPORTANT SAFETY INFORMATION (CONT)

Contraindications

ZYNRELEF is contraindicated in patients with 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 $\geq 10\%$) in controlled clinical trials with ZYNRELEF are constipation, vomiting, and headache.

Report side effects to Heron at 1-844-437-6611 or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including Boxed Warning.

References: **1.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Lachiewicz PF, Lee G-C, Pollak R, Leiman D, Hu J, Sah A. HTX-011 reduced pain and opioid use after primary total knee arthroplasty: results of a randomized Phase 2b trial. *J Arthroplasty*. 2020;35(10):2843-2851. doi:10.1016/j.arth.2020.05.044. **3.** Data on file. Study HTX-011-306. San Diego, CA: Heron Therapeutics Inc; 2020. **4.** Hacker S. Postoperative pain management of total knee arthroplasty using HTX-011 with multimodal analgesia: results from a Phase 3b open-label study. Poster presented at: Orthopedics Today Hawaii 2020; January 12-16, 2020; Koloa, HI.

For more information, visit ZYNRELEF.com/TKA