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

REFERENCE GUIDE

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 Important Safety Information on back and full Prescribing Information, including Boxed Warning.

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MECHANISM OF ACTION REFERENCES

Manuscripts

- Ottoboni T, Quart B, Pawasauskas J, Dasta JF, Pollak RA, Viscusi ER. Mechanism of action of HTX-011: a novel, extended-release, dual-acting local anesthetic formulation for postoperative pain. *Reg Anesth Pain Med*. 2020;45(2):117-123. doi:10.1136/rapm-2019-100714.

Posters

- Minkowitz H, Luke C, Hardman D, Hu J. Overall safety of HTX-011 when used with scheduled non-opioid NSAID-containing multimodal analgesia (MMA). Poster presented at: American Society of Anesthesiologists Annual Meeting California 2021; October 9-12, 2021; San Diego, CA.
- Luke C, Saleh J, Hardman D, Ottoboni T. HTX-011: predictable release rates of bupivacaine and meloxicam for 72 hours. Poster presented at: American Society of Anesthesiologists Annual Meeting; October 2-5, 2020; virtual event. http://www.asaabstracts.com/strands/asaabstracts/abstract.htm?year=2020&index=18&absnum=7304. Accessed March 31, 2021.
- Viscusi E, Minkowitz H, Hu J. HTX-011: No evidence of local anesthetic systemic toxicity. Poster presented at: American Society of Anesthesiologists Annual Meeting; October 2-5, 2020; virtual event. http://www.asaabstracts.com/strands/asaabstracts/abstract.htm?year=2020&index=18&absnum=7391. Accessed March 31, 2021.

GENERAL SURGERY REFERENCES

Manuscripts

- Minkowitz H, Soto R, Fanikos J, et al. Opioid-free recovery after hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting: a randomized, open-label study. *Pain Ther*. 2021;10(2):1295-1308. doi:10.1007/s40122-021-00289-2.
- Singla N, Winkle P, Bertoch T, Hu J, Beaton A, Redan J. Opioid-free recovery after herniorrhaphy with HTX-011 as the foundation of a multimodal analgesic regimen. *Surgery*. 2020;168(5):915-920. doi:10.1016/j.surg.2020.06.036.
- Viscusi E, Minkowitz H, Winkle P, Ramamoorthy S, Hu J, Singla N. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in herniorrhaphy: results from the Phase 3 EPOCH 2 study. *Hernia*. 2019;23(6):1071-1080. doi:10.1007/s10029-019-02023-6.

Posters

- Fanikos J, Luke C, Shadduck P, Palazzo F, Hu J. Opioid-free recovery after inguinal hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting. Poster presented at: American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition; December 5-9, 2021; virtual event.
- Luke C, Palazzo F, Shadduck P, Fanikos J, Hu J. Opioid-free inguinal hernia repair with a non-opioid, multimodal analgesia (MMA) regimen including HTX-011 in a real-world setting. Poster presented at: ASRA 20th Annual Pain Medicine Meeting; November 18-20, 2021; virtual event.
- Evans-Shields J, Viscusi ER, Minkowitz H, Winkle P, Hu J, Singla N. Opioid-free postoperative recovery in patients undergoing herniorrhaphy with HTX-011 as the foundation of a scheduled, non-opioid multimodal analgesic regimen. Poster presented at: American Society of Health-System Pharmacists 2019 Midyear Clinical Meeting & Exhibition; December 9, 2019; Las Vegas, NV.
- Fanikos J, Minkowitz H, Reinhorn M, Quart B. HTX-011 as the foundation of a non-opioid, multimodal analgesic regimen reduces the need for opioids following herniorrhaphy in a real-world study. Poster presented at: American Society of Health-System Pharmacists 2019 Midyear Clinical Meeting & Exhibition; December 9, 2019; Las Vegas, NV.
- Singla N, Quart B, Evans-Shields J, Hu J, Redan J. Reduction in proportion of patients with severe pain following herniorrhaphy using HTX-011 as the foundation of a non-opioid multimodal analgesic regimen. Poster presented at: 38th Annual Congress of the European Society of Regional Anaesthesia & Pain Therapy; September 11-14, 2019; Bilbao, Spain.
- Singla N, Hu J, Redan J. Opioid-free hernia recovery with HTX-011, the first dual-acting local anesthetic, as foundation therapy. Poster presented at: 2019 Annual Congress of Enhanced Recovery and Perioperative Medicine; April 25-27, 2019; Washington, DC.

Please see Important Safety Information on front and back and full Prescribing Information, including Boxed Warning.

ORTHOPEDIC SURGERY REFERENCES

Manuscripts

- Pollak R, Cai D, Gan TJ. Opioid-free recovery from bunionectomy with HTX-011, a dual-acting local anesthetic combining bupivacaine and meloxicam, as the foundation of non-opioid multimodal analgesia. *J Am Podiatr Med Assoc*. 2021;111(3):Article_15. doi:10.7547/20-204.
- 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.
- Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee G-C. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: Phase III results from the randomized EPOCH 1 study. *Reg Anesth Pain Med*. 2019;44(7):700-706. doi:10.1136/rapm-2019-100531.

Posters

- Hacker S, Gerner P, Hu J, Rechter A. Total knee arthroplasty pain management with HTX-011 as the foundation of a multimodal analgesic regimen results in low incidence of severe pain. Poster presented at: American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting; August 31, 2021–September 3, 2021; San Diego, CA.
- Lee G-C, Cai D. Opioid-free postoperative pain management in patients undergoing bunionectomy with the extended-release analgesic HTX-011. Poster presented at: American Academy of Orthopaedic Surgeons Congress; March 24-28, 2020; virtual event. https://aaos.scientificposters.com/epsAbstractAAOS.cfm?id=4. Accessed March 31, 2021.
- 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.
- Hu J, Pollak R, Evans-Shields J, Lee G-C. Opioid-free postoperative recovery in patients undergoing bunionectomy with HTX-011, an extended-release local anesthetic. Poster presented at: American Society of Health-System Pharmacists 2019 Midyear Clinical Meeting & Exhibition; December 9, 2019; Las Vegas, NV.

PLASTIC SURGERY REFERENCES

Posters

- Yamamoto A, Ottoboni T, Quart B. Pharmacokinetics and safety of different bupivacaine formulations and administration techniques in augmentation mammoplasty. Poster presented at: American Society of Health-System Pharmacists Summer Meetings & Exhibition 2019; June 11, 2019; Boston, MA.
- Leiman D, Minkowitz HS, Patel SS, et al. HTX-011, a proprietary, unique, long-acting local anesthetic, reduces acute postoperative pain intensity and opioid consumption following abdominoplasty. Poster presented at: American College of Surgeons Clinical Congress; October 22-26, 2017; San Diego, CA.

SPECIFIC POPULATIONS REFERENCES

Manuscripts

- Yip T, Hu J, Hawn PS, Yamamoto A, Oderda G. HTX-011 effectively reduces postoperative pain intensity and opioid use in the elderly. *Pain Manag*. 2022;12(1):45-57. doi:10.2217/pmt-2021-0043.

Posters

- Grosh T, Hawn P, Hu J, Bekker A. Safety of HTX-011 in patients ≥65 years old as part of a postoperative multimodal analgesia regimen. Poster presented at: Annual Regional Anesthesiology and Acute Pain Management Medicine Meeting (ASRA); May 13-15, 2021; Lake Buena Vista FL, and virtual event.
- Hacker S, Hawn P, Hu J, Rechter A. Safety of HTX-011 in patients ≥65 years old as part of a postoperative multimodal analgesia regimen [encore presentation August 2021]. Poster originally presented at: Orthopedics Today; May 30–June 3, 2021; Wailea, HI.
- Yamamoto A, Wilker C, Griffith A, Brantley S, Saffer C. Concentrations of bupivacaine and meloxicam in breast milk after exposure to HTX-011. Poster presented at: American Society of Health-System Pharmacists Midyear 2020 Congress, December 6-10, 2020; virtual event.

You can access additional resources, including presentations and videos, by visiting formulary.zynrelef.com.

If you have any questions, please reach out to a Heron Therapeutics representative: 844-HERON11 (844-437-6611).

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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 ≥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.

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