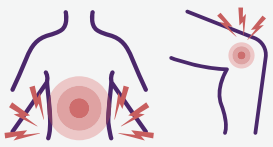
WHY LOCAL ANESTHETICS OFTEN STRUGGLE TO REDUCE PAIN BEYOND 24 HOURS

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

1



Surgical incisions result in an inflammatory response at the surgical site. This inflammation intensifies pain signals and increases the tissue's acidity.[1-3]

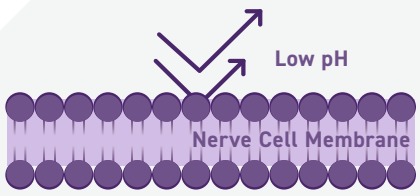
2

The first 72 hours after surgery are the most painful. Inflammation peaks around 24 hours postoperatively and remains relatively high through the first 72 hours.[4-6]

3

A surgeon will often inject a local anesthetic at the incision site to help block pain.[7]

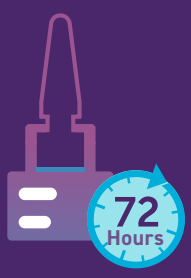
4



But tissue acidity decreases the ability of most local anesthetics to penetrate nerve cells and block pain signals, greatly limiting efficacy beyond 12-24 hours.[1-3]

5

With severe pain often lasting through 72 hours, healthcare providers rely on opioids to pick up where most local anesthetics leave off.[1,5,8]



A new way to manage pain after surgery

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.[9-13]

ZYNRELEF contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), and is approved for use in adults to reduce pain for up to 3 days after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures. ZYNRELEF is applied into the wound at the time of surgery.[14]

IMPORTANT SAFETY INFORMATION

ZYNRELEF CONTAINS AN NSAID (NON-STEROIDAL ANTI-INFLAMMATORY DRUG), A TYPE OF MEDICINE WHICH:

- Can increase the risk of a heart attack or stroke that can lead to death. This risk increases with higher doses and longer use of an NSAID.
- Cannot be used during heart bypass surgery.
- Can increase the risk of gastrointestinal bleeding, ulcers, and tears

ZYNRELEF SHOULD ALSO NOT BE USED:

- If you are allergic to any component of ZYNRELEF, similar local anesthetics, aspirin or other NSAIDs (such as ibuprofen or naproxen), or have had an asthma attack, hives, or other allergic reaction after taking any of these medicines.
- As a paracervical block, during childbirth.

The most common side effects of ZYNRELEF are constipation, vomiting, and headache.

The medicines in ZYNRELEF (a local anesthetic and an NSAID) may affect the nervous and cardiovascular system; may cause liver or kidney problems; may reduce the effects of some blood pressure medicines; should be avoided if you have severe heart failure; may cause adverse effects on cartilage; may cause a rare blood disorder, or life-threatening skin or allergic reactions; may harm your unborn baby if received at 20 weeks of pregnancy or later; and may cause low red blood cells (anemia).

Tell your healthcare provider about all your medical conditions and about all the medicines you take including prescription or over-the-counter medicines, vitamins, or herbal supplements to discuss if ZYNRELEF is right for you.

Talk to your healthcare provider for medical advice about side effects. Report side effects to Heron at 1-844-437-6611 or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The information provided here is not comprehensive. **Please see full Prescribing Information, including Boxed Warning.**

Learn more about ZYNRELEF by visiting **www.ZYNRELEF.com**

References: 1. Kim 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. **2.** Becker DE, Reed KL. Essentials of local anesthetic pharmacology. Anesth Prog. 2006;53(3):98-109. doi:10.2344/0003-3006(2006)53[98:EOLAP]2.0.CO;2. **3.** Hargreaves et al. Local anesthetic failure in endodontics: mechanisms and management. Endod Topics. 2002;1(1):26-39. doi:10.1034/j.1601-1546.2002.10103.x. **4.** Svensson et al. Assessment of pain experiences after elective surgery. J Pain Symptom Manage. 2000;20(3):193-201.doi:10.1016/S0885-3924(00)00174-3. **5.** Enoch S, Leaper DJ. Basic science of wound healing. Surgery (Oxford). 2008;26(2):31-37. doi:10.1016/j.mpsur.2007.11.005. **6.** Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004;140(6):441-451. doi:10.7326/0003-4819-140-8-200404200-00010. **7.** Golf M et al. A phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv Therapy. 2011;28(9):776-788. doi:10.1007/s12325-011-0052-y **8.** Ali et al. Doubtful effect of continuous intraarticular analgesia after total knee arthroplasty: a randomized, double-blind study of 200 patients. Acta Orthop. 2015;86(3):373-377. doi:10.3109/17453674.2014.991629 **9.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **10.** Viscusi et al. 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. **11.** Viscusi et al. 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. **12.** Lachiewicz et al. 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. **13.** Ottoboni et al. 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. **14.** ZYNRELEF [Summary of Product Characteristics]. Heron Therapeutics. Available at: www.ZYNRELEF.com

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