

MANAGING PAIN FOLLOWING YOUR SURGERY

**With a Non-Opioid
Medicine as the
Foundation**

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

ZYNRELEF is a medicine applied during surgery that is designed to reduce pain for up to 72 hours as you recover.

ZYNRELEF is approved for use in adults to reduce pain for up to 3 days after foot and ankle surgeries, small-to-medium open abdominal surgeries, and total joint replacement surgeries of the lower extremity. ZYNRELEF is applied into the wound at the time of surgery.

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.

See additional Important Safety Information throughout.



TREATING PAIN AFTER SURGERY

It is normal to feel pain after surgery. As you heal, your nurses and doctors will use a specific **multimodal analgesic (MMA) treatment plan to keep you out of pain as much as possible.**

So, what are MMA treatment plans?¹

- MMA treatment plans may start with local anesthetics during surgery and use multiple ways to treat pain after surgery. These can include physical therapy, heat or ice, and over-the-counter drugs like Advil® or Tylenol®.*
- MMA treatment plans may also include opioid pain medications, but the goal is to use lower doses²
- Many MMA treatments are used to lower opioid use after surgery

Why do doctors want to reduce the use of opioids?

- Tylenol and Advil can have side effects like nausea and loss of appetite, but the side effects from opioids can be more severe. Side effects from opioids can include constipation, itchy skin, nausea, vomiting, difficulty breathing, increased sleepiness, and increased sensitivity to pain.³
- Opioids can also be addictive. More and more healthcare systems are starting to use non-opioid-based MMA treatment plans to reduce opioid prescriptions after surgery.⁴

*Trademarks are owned by their respective companies.

A NON-OPIOID MEDICINE FOR PAIN RELIEF AFTER SURGERY

How does ZYNRELEF extended-release solution work to treat pain after surgery?

- ZYNRELEF is applied by your doctor at the end of surgery and can reduce your pain for up to 72 hours⁵
- ZYNRELEF is a dual-acting local anesthetic (DALA) that combines 2 non-opioid drugs⁵⁻⁸
- Bupivacaine and meloxicam are the active ingredients in ZYNRELEF. They are contained in a special technology called Biochronomer®, which releases the active ingredients over time so they can last for up to 72 hours.⁵
- Studies show ZYNRELEF reduces or gets rid of the need for opioids in many patients after surgery⁵

Following surgery, it is important that you follow the non-opioid-based MMA treatment plan your doctor prescribes.

IMPORTANT SAFETY INFORMATION (CONT)

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).

IMPORTANT SAFETY INFORMATION (CONT)

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 read the Patient Brief Summary of Full Prescribing Information about ZYNRELEF on the following page.**

ZYNRELEF® (BUPIVACAINE AND MELOXICAM) EXTENDED-RELEASE SOLUTION, FOR SOFT TISSUE OR PERIARTICULAR INSTILLATION USE

CONSUMER BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

What is ZYNRELEF, and what is it used for?

ZYNRELEF is a prescription medicine that contains 2 medicines - bupivacaine, a local anesthetic, and meloxicam, an NSAID (non-steroidal anti-inflammatory drug), that act together to reduce pain for up to 3 days after foot and ankle surgeries, small-to-medium open abdominal surgeries, and total joint replacement surgeries of the lower extremity. ZYNRELEF is applied into the wound at the end of surgery.

IMPORTANT SAFETY INFORMATION

All NSAIDs, including meloxicam, which is contained in ZYNRELEF:

- 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 components 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.

What Warnings should I know about ZYNRELEF?

The medicines in ZYNRELEF may:

- Affect your nervous system and your heart. You are at an increased risk if you have severe liver disease due to high blood levels of bupivacaine.
- Cause liver or kidney problems including liver or kidney failure.
- Reduce the effects of some blood pressure medicines.
- Cause life-threatening allergic reactions and serious skin reactions. Seek immediate medical attention if you experience difficulty breathing, swelling of the face or throat, or any type of rash or fever.
- Cause a rare blood condition that impairs oxygen delivery (methemoglobinemia). Seek immediate medical attention if you experience pale, gray, or blue-colored skin (cyanosis), headache, rapid heart rate, shortness of breath, lightheadedness, or fatigue.
- Cause adverse effects on cartilage.
- Harm your unborn baby if received at 20 weeks of pregnancy or later. Your healthcare provider will restrict use of ZYNRELEF between about 20 to 30 weeks of pregnancy and avoid use after about 30 weeks pregnancy. Your healthcare provider may avoid use of ZYNRELEF if you are breastfeeding your baby.
- Increase the risk of gastrointestinal problems if you take an NSAID or salicylate (such as diflunisal or salsalate) after surgery following treatment with ZYNRELEF.
- Cause low levels of red blood cells (anemia). Your healthcare provider may check for signs or symptoms of anemia.

Serious side effects including seizures and insufficient breathing may occur from getting too much ZYNRELEF and may require special treatment. The healthcare provider treating you is trained to deal with these situations.

What should I tell my healthcare provider before receiving ZYNRELEF?

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins, or herbal supplements, as well as your medical conditions, including the following:

- Heart problems, previous stroke, or heart attack.
- Bleeding from your stomach or gastrointestinal tract, a stomach ulcer, or inflammation of the stomach (gastritis).
- A serious skin reaction after taking medicines containing aspirin or other NSAIDs.
- Kidney or liver problems.
- If you are taking any medicines to treat high blood pressure, heart or kidney disease (such as ACE inhibitors, angiotension receptor blockers, beta-blockers, and thiazide or loop diuretics).
- If you are taking warfarin, aspirin, or antidepressants.

If you are not sure whether any of the above applies to you, talk to your healthcare provider before you are given ZYNRELEF.

What are the possible side effects of ZYNRELEF?

The most common side effects of ZYNRELEF are constipation, vomiting, and headache. Bupivacaine-containing products can cause temporary loss of sensation near the surgical site.

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.

More Information

ZYNRELEF is available by prescription only. This information is not comprehensive. Visit www.zynrelef.com to obtain the full Prescribing Information, including Boxed Warning.



Manufactured and marketed by: Heron Therapeutics, Inc., 4242 Campus Point Court, Suite 200, San Diego, CA, 92121, USA.

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YOUR HEALTHCARE PROVIDERS HAVE A PLAN TO MANAGE YOUR PAIN AFTER SURGERY.

The information in this pamphlet does not take the place of talking with your healthcare provider.

References: **1.** Polomano RC, Fillman M, Giordano NA, Vallerand AH, Wiltse Nicely KL, Jungquist CR. Multimodal analgesia for acute postoperative and trauma-related pain. *Am J Nurs.* 2017;117(3)(suppl 1):S12-S26. doi:10.1097/01.NAJ.0000513527.71934.73. **2.** Crews JC. Multimodal pain management strategies for office-based and ambulatory procedures. *JAMA.* 2002;288(5):629-632. doi:10.1001/jama.288.5.629. **3.** National Center for Injury Prevention and Control, Centers for Disease Control and Prevention. Prescription opioids. <https://www.cdc.gov/drugoverdose/opioids/prescribed.html>. Updated August 29, 2017. Accessed April 15, 2021. **4.** Graff V, Grosh T. Multimodal analgesia and alternatives to opioids for postoperative analgesia. *Anesth Patient Saf Found Newsl.* 2018;33(2):46-47. <https://www.apsf.org/wp-content/uploads/newsletters/2018/3302/APS3302.pdf>. Accessed April 15, 2021. **5.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **6.** 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. **7.** 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. **8.** 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.



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