



Heron Therapeutics Announces Publication Showing ZYNRELEF® as the Foundation of a Perioperative Non-Opioid Multimodal Analgesic Regimen Reduced Severe Pain and Opioid Use in Patients Undergoing Total Knee Arthroplasty

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SAN DIEGO, June 14, 2022 /PRNewswire/ -- Heron Therapeutics, Inc. (Nasdaq: HRTX), a commercial-stage biotechnology company focused on improving the lives of patients by developing and commercializing therapeutic innovations that improve medical care, today announced the online publication of a new study evaluating the efficacy and safety of ZYNRELEF (bupivacaine and meloxicam) extended-release solution as the foundation of a perioperative non-opioid multimodal analgesic (MMA) regimen in patients undergoing total knee arthroplasty (TKA). ZYNRELEF is approved by the U.S. Food and Drug Administration (FDA) for use 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.

The study was published in the *Journal of Knee Surgery*, a peer-reviewed journal. All patients in the study received ZYNRELEF with an MMA regimen consisting of a nonsteroidal anti-inflammatory drug (NSAID), acetaminophen and a gabapentinoid. The study showed that more than 80% of patients did not experience severe pain at any individual time point through 72 hours after TKA surgery. Forty-seven percent of patients took ≤ 20 morphine milligram equivalents (≤ 4 oxycodone 10mg tablets) over the 72-hour postoperative period, 12% of patients remaining opioid-free through 72 hours. Additionally, 39% percent of patients were discharged without an opioid prescription and did not call back to the study site to request additional pain medication between discharge at 72 hours and the Day 11 follow-up visit. Patient satisfaction with pain management was very good with 88% of patients reported "good" or "excellent" pain control 24 hours following surgery, with all patients maintaining that same level of pain control at 72 hours. Approximately 61% of patients were ready for discharge by 12 hours after surgery and up to 69% by 24 hours.

The use of ZYNRELEF 400mg/12mg in patients undergoing TKA with bupivacaine spinal anesthesia and scheduled MMA did not identify safety concerns, and there was no evidence of NSAID-related toxicity, suggesting that the MMA regimen did not impact the safety profile of ZYNRELEF.

"Total knee arthroplasty procedures have typically been associated with significant postoperative pain and high opioid requirements. The results presented in this study are promising for ZYNRELEF's ability to reduce severe pain and opioid consumption," said Gwo-Chin Lee, M.D., Orthopedic Surgeon at Hospital for Special Surgery. "While controlled clinical trials are needed, I am encouraged by the results in this group of patients showing ZYNRELEF's effectiveness when paired with a scheduled non-opioid multimodal pain regimen."

"Postoperative pain is one of the main concerns we hear in the clinical setting, and as many orthopedic procedures continue to transition to the outpatient setting, it is becoming increasingly more important to manage pain effectively so patients can be ready for discharge the same day," said Alan Rechter, M.D., Orthopaedic Surgeon at Orthopaedic Associates LLP. "These data reinforce ZYNRELEF's ability to provide long-lasting pain control in the critical postoperative period, and it is exciting to see its potential to bring positive change to the overall patient experience as the foundation of a multimodal analgesic regimen."

In this single-arm study, patients undergoing unilateral TKA under spinal anesthesia received ZYNRELEF 400mg/12 mg instilled without a needle into the surgical space in conjunction with a non-opioid MMA regimen consisting of preoperative oral acetaminophen, celecoxib and pregabalin, and postoperative oral acetaminophen and celecoxib for 72 hours followed by oral acetaminophen and ibuprofen for 4 days. Patients were required to stay in the treatment facility to collect pain scores through the 72-hour time point following surgery. Rescue medications, including oral immediate-release oxycodone, IV morphine, and/or IV hydromorphone, were permitted on request.

ZYNRELEF is the first and only therapy for postoperative pain management to be rigorously tested in Phase 3 studies and demonstrate superiority to bupivacaine solution. ZYNRELEF demonstrated superior, sustained postoperative pain relief for up to 72 hours and decreased the need for opioids, with more patients opioid-free compared to bupivacaine solution.

The *Journal of Knee Surgery* article can be found [here](#).

Important Safety Information for Patients

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 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.

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 have 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).

Please see full Prescribing Information, including Boxed Warning.

About ZYNRELEF® for Postoperative Pain

ZYNRELEF is the first and only dual-acting local anesthetic that delivers a fixed-dose combination of the local anesthetic bupivacaine and a low dose of nonsteroidal anti-inflammatory drug meloxicam. ZYNRELEF is the first and only extended-release local anesthetic to demonstrate in Phase 3 studies significantly reduced pain and significantly increased proportion of patients requiring no opioids through the first 72 hours following surgery compared to bupivacaine solution, the current standard-of-care local anesthetic for postoperative pain control. ZYNRELEF was initially approved by the FDA in May 2021 for use in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty. In December 2021, the FDA approved an expansion of ZYNRELEF's indication. ZYNRELEF is now indicated in the U.S. 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. Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures. In September 2020, the European Commission granted a marketing authorization for ZYNRELEF for the treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults. As of January 1, 2021, ZYNRELEF is approved in 31 European countries including the countries of the European Union and European Economic Area and the United Kingdom. In March 2022, Health Canada issued a Notice of Compliance for ZYNRELEF for instillation into the surgical wound for postoperative analgesia after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty surgical procedures.

Please see full prescribing information, including Boxed Warning, at www.ZYNRELEF.com.

About Heron Therapeutics, Inc.

Heron Therapeutics, Inc. is a commercial-stage biotechnology company focused on improving the lives of patients by developing and commercializing therapeutic innovations that improve medical care. Our advanced science, patented technologies, and innovative approach to drug discovery and development have allowed us to create and commercialize a portfolio of products that aim to advance the standard-of-care for acute care and oncology patients. For more information, visit www.heronrx.com.

Forward-looking Statements

This news release contains "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. Heron cautions readers that forward-looking statements are based on management's expectations and assumptions as of the date of this news release and are subject to certain risks and uncertainties that could cause actual results to differ materially, including, but not limited to, the potential market opportunity for ZYNRELEF in the U.S.; the extent of the impact of the ongoing Coronavirus Disease 2019 pandemic on our business; and other risks and uncertainties identified in the Company's filings with the U.S. Securities and Exchange Commission. Forward-looking statements reflect our analysis only on their stated date, and Heron takes no obligation to update or revise these statements except as may be required by law.

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