Clinical Policy Title:	bupivacaine and meloxicam
Policy Number:	RxA.694
Drug(s) Applied:	Zynrelef™
Original Policy Date:	8/17/2021
Last Review Date:	9/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Zynrelef™ contains bupivacaine, an amide local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), and is indicated 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.

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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
bupivacaine and meloxicam (Zynrelef™)	Postoperative administration of analgesia	For bunionectomy*: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam. For open inguinal herniorrhaphy*: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam. For total knee arthroplasty*: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam.	Bunionectomy: Up to 2.3 mL (bupivacaine 60 mg/meloxicam 1.8 mg) as a single dose. Open inguinal herniorrhaphy: Up to 10.5 mL (bupivacaine 300 mg/meloxicam 9 mg) as a single dose. Total knee arthroplasty: Up to 14 mL (bupivacaine 400 mg/meloxicam 12 mg) as a single dose.

* Soft tissue or periarticular instillation to produce postsurgical analgesia in adults for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

Dosage Forms

Single-dose glass vials: 400 mg bupivacaine and 12 mg meloxicam, 300 mg bupivacaine and 9 mg meloxicam, 200 mg bupivacaine and 6 mg, meloxicam, 60 mg bupivacaine and 1.8 mg meloxicam.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Postoperative pain management (must meet all):

1. Member had any one of the following surgical procedures (a, b or c):
   a. Bunionectomy;
   b. Open inguinal herniorrhaphy;
   c. Total knee arthroplasty;
2. Prescribed by or in consultation with a pain management specialist;
3. Age ≥ 18 years;
4. Dose does not exceed one of the followings (a, b or c):
   a. Bunionectomy: 2.3 mL (bupivacaine 60 mg/meloxicam 1.8 mg) as a single dose.
   b. Open inguinal herniorrhaphy: 10.5 mL (bupivacaine 300 mg/meloxicam 9 mg) as a single dose.
   c. Total knee arthroplasty: 14 mL (bupivacaine 400 mg/meloxicam 12 mg) as a single dose.

Approval Duration
Commercial: One time authorization for 3 days
Medicaid: One time authorization for 3 days.

II. Continued Therapy Approval

A. Postoperative pain management:

1. Re-authorization is not permitted. Members must meet the initial approval criteria

Approval Duration: None

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
NSAID: Non-steroidal anti-inflammatory drugs
CABG: Coronary artery bypass graft surgery
DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

APPENDIX B: Therapeutic Alternatives
Not applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to any local anesthetic agent of the amide-type, NSAIDs, or any other component the product.
  - History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
  - Obstetrical paracervical block anesthesia.
  - Coronary artery bypass graft (CABG) surgery.

- Boxed Warning(s):
  - Cardiovascular thrombotic 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. Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

- GI bleeding, ulceration, and perforation: NSAIDs cause an increased risk of serious 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.

APPENDIX D: General Information

- 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 medications 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 function.
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.
- Methemoglobinemia: Cases of methemoglobinemia have been reported in association 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: Limit use of NSAIDs, including Zynrelef™, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the ductus arteriosus.
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia.

References

1. Zynrelef™. Lexicomp. [Internet database]. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: https://online.lexi.com/lco/action/search?q=zynrelef&t=name&va=zynrelef . Accessed August 18, 2021.
2. Zynrelef™ prescribing information. San Diego, CA: Heron Therapeutics Inc; May 2021. Available at: https://zynrelef.com/prescribing-information.pdf . Accessed August 18, 2021.
3. Zynrelef™. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Available at: http://www.micromedexsolutions.com. Accessed August 18, 2021.
4. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2021. Accessed with subscription at: http://www.clinicalkey.com . Accessed August 18, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	08/18/2021	09/14/2021