Preoperative Intravenous Meloxicam for Moderate-to-Severe Pain in the Immediate Post-operative Period

A Phase IIIb Randomized Clinical Trial in 55 Patients Undergoing Primary Open or Laparoscopic Colorectal Surgery With Bowel Resection and/or Anastomosis

Jennifer D Silinsky[1], Jorge E Marcet[2], Vamshi Ruthwik Anupindi[3], Swapna U Karkare[3,*], Drishti R Shah[3], Randall J Mack[4], Stewart W McCallum[4], Wei Du[5], Alex Freyer[4], Libby K Black[4]

Pain Manag. **2021;11(1):9-21.**

[1]Department of Surgery, Tulane University, New Orleans, LA, 70112, USA; [2]Department of Surgery, Tampa General Hospital, Tampa, FL, 33606, USA; [3]IQVIA, Falls Church, VA, 22042, USA; [4]Baudax Bio Inc., Malvern, PA, 19355, USA; [5]Clinical Statistics Consulting, Blue Bell, PA, 19422, USA
*At the time this work was conducted

Objective

- To evaluate the safety and efficacy of perioperative administration of intravenous (IV) meloxicam, compared with placebo, in subjects undergoing colorectal surgery. The effect of meloxicam IV on postoperative recovery and healthcare resource utilization was also reported.[1]

Some uses of meloxicam injection described in this publication have not been approved or cleared by the FDA.

Funding for this study was provided by Baudax Bio, Inc., Malvern, Pennsylvania.

Vamshi Ruthwik Anupindi, Swapna U Karkare, and Drishti R Shah are employees of IQVIA and received funding for the study from Baudax Bio, formerly Recro Pharma; Swapna U Karkare was an employee of IQVIA at the time of the study; Stewart W McCallum, Randall J Mack, Alex Freyer, and Libby K Black are employees and stockholders of Baudax Bio, formerly Recro Pharma; Wei Du is a consultant (statistical analysis) for Baudax Bio, formerly Recro Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Please see full Prescribing Information, including Boxed Warning, at www.anjeso.com.

Methods

Study Design and Patients[1]

- Phase IIIb, multicenter, randomized, double-blind, placebo-controlled trial in 55 adult patients scheduled to undergo primary (no repeat procedures) open or laparoscopic colorectal surgery, with bowel resection and/or anastomosis
  - **Eligibility criteria:** patients included in the study were expected to require IV analgesia and remain in an inpatient setting for at least 48 to 72 hours

Dosing[1]

- Eligible patients were randomized 1:1 to receive ANJESO 30 mg (n=27) or placebo (n=28)
- Study treatments were administered as an IV bolus over ~15 seconds, with the first dose administered ~30 minutes before the start of surgery. Patients received study treatment every 24 hours from the first dose until discharge or until IV analgesia was no longer clinically appropriate (most patients received 2 or 3 doses)
- Surgeries were completed using an enhanced recovery after surgery (ERAS) protocol with strict analgesia requirements

Analgesia Protocol[1]

Preoperative	Perioperative	Postoperative
• **Study treatment, ~30 min preop** • Gabapentin 300 mg PO, ~30-90 min preop • Acetaminophen 650 mg PO or IV, ~30-90 min preop	• Maintained using IV opioids	• **Study treatment q24h*** • Acetaminophen 650 mg PO q8h until 24 h following last study treatment dose • PCA morphine 1 mg bolus, 6-min lockout; supplement with 1-2 mg IV morphine q1h PRN *OR* morphine IV bolus PRN - Dose should not exceed 12 mg/h • Convert to oral oxycodone 5 mg q4h PRN; supplement with 1-4 mg IV morphine up to every hour if needed

PCA, patient-controlled analgesia; PO, by mouth; PRN, as needed.

*Additional doses were administered every 24 ± 1 h from the first dose until discharge or until IV analgesia was no longer clinically appropriate.[1]

INDICATION

ANJESO is indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics.

Limitation of Use: Because of delayed onset of analgesia, ANJESO alone is not recommended for use when rapid onset of analgesia is required.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Risk

- Non-steroidal 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.
- ANJESO is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- 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 scroll down to see additional Important Safety Information.
Please see full Prescribing Information, including Boxed Warning, at www.anjeso.com.

Anjeso® (meloxicam) injection

Primary Endpoint

Safety and tolerability of ANJESO preoperative dosing

- The incidence of treatment-emergent adverse events (AEs) was lower in the ANJESO treatment group than in the placebo treatment group (85% vs 93%, respectively, reporting ≥1 treatment-emergent AE); see table below[1]
- AEs in this study were mostly mild or moderate in intensity (80% and 17%, respectively).[2] The most common AEs were nausea and vomiting[1]
- No patient was withdrawn from the study due to an AE [1]

Treatment-Emergent AEs Occurring in ≥2 Subjects in Either Study Group[1]

Adverse Event	ANJESO 30 mg (n=27), n (%)	Placebo (n=28), n (%)
Patients with ≥1 AE	23 (85%)	26 (93%)
Nausea	9 (33%)	14 (50%)
Vomiting	5 (19%)	5 (18%)
Hypokalemia	2 (7%)	7 (25%)
Hypophosphatemia	2 (7%)	6 (21%)
Hypertension	2 (7%)	3 (11%)
Pyrexia	2 (7%)	2 (7%)
Paranasal sinus hypersecretion	2 (7%)	0
Urinary retention	2 (7%)	0
Wound dehiscence*	2 (7%)	0
Wound infection	2 (7%)	0
Ileus	1 (4%)	5 (18%)
Anxiety	1 (4%)	3 (11%)
Insomnia	1 (4%)	3 (11%)
Oliguria	1 (4%)	3 (11%)
Constipation	1 (4%)	2 (7%)
Hypomagnesemia	1 (4%)	2 (7%)
Hypotension	1 (4%)	2 (7%)
Musculoskeletal pain	1 (4%)	2 (7%)
Gastroesophageal reflux disease	0	2 (7%)

*Neither incident of wound dehiscence was considered related to study treatment

- Physician-rated scores for interference with wound healing, clinical laboratory findings, and vital signs were similar between the ANJESO treatment group and the placebo treatment group[1]

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

ANJESO is contraindicated in patients with:

- Known hypersensitivity (eg, anaphylactic reactions and serious skin reactions) to meloxicam or any components of the drug product.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
- In the setting of coronary artery bypass graft (CABG) surgery.
- Moderate to severe renal insufficiency patients who are at risk for renal failure due to volume depletion

Please scroll down to see additional Important Safety Information.
Please see full Prescribing Information, including Boxed Warning, at www.anjeso.com.

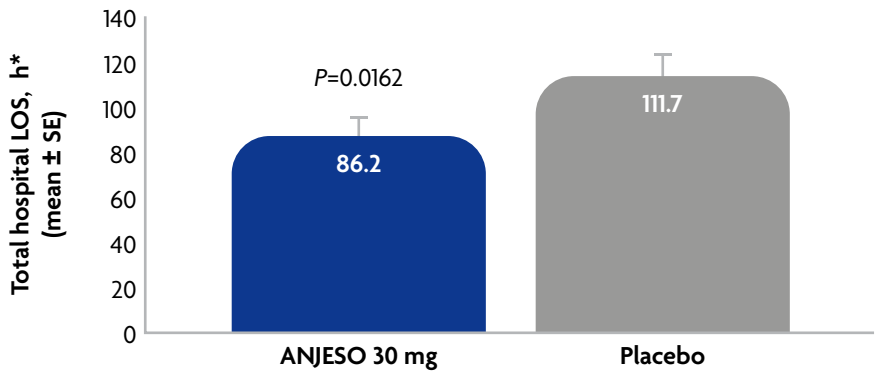
Anjeso® (meloxicam) injection

Secondary Endpoints

Healthcare Resource Utilization[1]

- ANJESO significantly reduced total length of stay (LOS) by 25.5 hours (1.1 days) compared with placebo

ANJESO Use Resulted in Significantly Shorter Length of Stay[1]

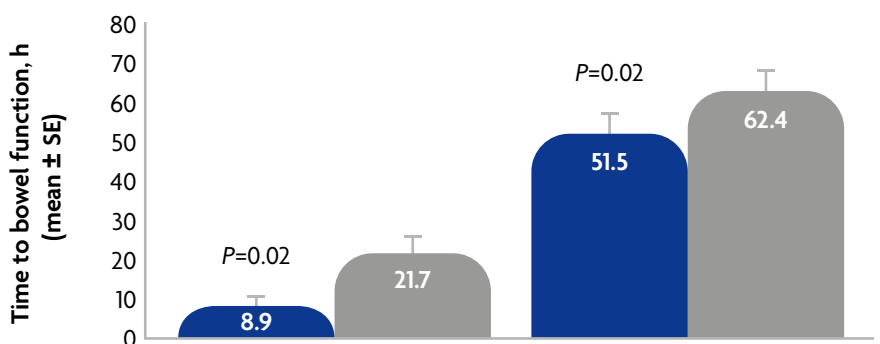


*Reported as number of hours from hospital admission to discharge.

Functional Outcomes[1]

- Treatment with ANJESO significantly reduced time to bowel function recovery compared with placebo
  - Mean time to first bowel sound with ANJESO was **59%** shorter than with placebo
  - Mean time to first bowel movement with ANJESO was **18%** shorter than with placebo

ANJESO Use Resulted in Significantly Shorter Time to Bowel Function Recovery[1]



Summary

- The incidence of treatment-emergent AEs was lower in the ANJESO treatment group than in the placebo treatment group[1]
- Preoperative use of ANJESO significantly reduced LOS by 1.1 days compared with placebo[1]
- Treatment with ANJESO significantly reduced time to bowel function recovery compared with placebo[1]

Limitations: This trial was not sufficiently powered to detect statistical differences on all study endpoints. Study was performed in the controlled settings of a clinical research study, which may not be able to be extrapolated to individual clinical use. Data monitoring board recommended stopping recruitment at interim analysis as primary endpoint was achieved.[1]

CLICK HERE TO ACCESS DIGITAL REPRINT

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Elevations of ALT or AST have been reported in patients with NSAIDs. In addition, rare, sometimes fatal, cases of severe hepatic injury including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue ANJESO immediately if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.

Hypertension: NSAIDs including ANJESO can lead to new onset of hypertension or worsening of preexisting hypertension, which may contribute to the increased incidence of cardiovascular (CV) events. Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Please scroll down to see additional Important Safety Information.
Please see full Prescribing Information, including Boxed Warning, at www.anjeso.com.

Anjeso® (meloxicam) injection

IMPORTANT SAFETY INFORMATION (cont'd)

Heart Failure and Edema: NSAID use increased the risk of myocardial infarction (MI), hospitalization for heart failure, and death. Avoid use of ANJESO in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. If ANJESO is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Post MI Patients: Avoid the use of ANJESO in patients with recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ANJESO is used in these patients, monitor for signs of cardiac ischemia.

Renal Toxicity: Long-term administration of NSAIDs has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury. ANJESO is not recommended in patients with moderate to severe renal insufficiency and is contraindicated in patients with moderate to severe renal insufficiency who are at risk for renal failure due to volume depletion. Correct volume status in dehydrated or hypovolemic patients prior to initiating ANJESO. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ANJESO in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. If ANJESO is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Anaphylactic Reactions: Meloxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma. Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity: ANJESO is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity).

Serious Skin Reactions: NSAIDs, including ANJESO, can cause serious skin reactions, including exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal and can occur without warning. Discontinue ANJESO at first appearance of skin rash or other signs of hypersensitivity.

Hematologic Toxicity: Anemia has occurred in NSAID-treated patients. Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. NSAIDs, including ANJESO, may increase the risk of bleeding events. Monitor patients for signs of bleeding.

DRUG INTERACTIONS

Drugs That Interfere With Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking ANJESO with drugs that interfere with hemostasis. Concomitant use of ANJESO and analgesic doses of aspirin is not generally recommended.

Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with ANJESO may diminish the antihypertensive effect of these drugs. Monitor blood pressure.

ACE Inhibitors and ARBs: Concomitant use with ANJESO 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 ensure diuretic efficacy including antihypertensive effects.

ADVERSE REACTIONS

The most common adverse reactions in controlled clinical trials occurring in ≥ 2% of patients treated with ANJESO and at a greater frequency than placebo include: constipation, gamma-glutamyl transferase increased, and anemia.

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation.

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of ANJESO in women who have trouble conceiving.

Please see additional Important Safety Information above and full Prescribing Information, including Boxed Warning, at www.anjeso.com.

References

1. Silinsky JD, Marcet JE, Anupindi VR, et al. Preoperative intravenous meloxicam for moderate-to-severe pain in the immediate post-operative period: a Phase IIIb randomized clinical trial in 55 patients undergoing primary open or laparoscopic colorectal surgery with bowel resection and/or anastomosis. *Pain Manag*. 2021;11(1):9-21. **2.** Data on file. CSR-17024. Baudax Bio.

Baudax BIO®

Anjeso® (meloxicam) injection