Bupivacaine and meloxicam (HTX-011) for post-operative pain

<table>
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<th>NIHRIO ID</th>
<th>11640</th>
<th>NICE ID</th>
<th>10228</th>
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<tr>
<td>Developer/Company</td>
<td>Heron Therapeutics Inc.</td>
<td>UKPS ID</td>
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**Summary**

Bupivacaine and meloxicam (HTX-011) in a fixed-dose combination is in development for the management of post-operative pain. Post-operative pain is a typical example of acute pain. Acute pain typically lasts for less than 3-6 months (unlike chronic pain which carries on for longer than 12 weeks), and is provoked by identifiable stimuli and disappears as soon as the tissue injury or damage that had caused it is healed. All surgical procedures are associated with a certain level of post-operative pain. Opioids are often used to manage post-operative pain but carry the risk of harmful side effects, abuse and addiction.

In HTX-011, the inclusion of low-dose meloxicam reduces local inflammation and reverses the acidic environment caused by surgery, allowing enhanced penetration of bupivacaine (a local anaesthetic) into the nerves and thereby increasing its effect. HTX-011 is in development for application into the surgical site and early studies have shown its potential to reduce severe post-operative pain and the need for opioid analgesics for up to 72 hours. If licensed, HTX-011 may offer an additional treatment option for the management of post-operative pain with a potential to reduce the need for opioids.
PROPOSED INDICATION

Post-operative pain.\textsuperscript{1-3}

TECHNOLOGY

DESCRIPTION

HTX-011, which utilizes Heron's proprietary Biochronomer\textsuperscript{®} drug delivery technology, is an investigational, long-acting, extended-release formulation of the local anaesthetic bupivacaine in a fixed-dose combination with the nonsteroidal anti-inflammatory drug (NSAID) meloxicam for the management of post-operative pain.\textsuperscript{4}

Bupivacaine is a long acting local anaesthetic of the amide type with both anaesthetic and analgesic effects. Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. The sodium channels of the nerve membrane are considered a receptor for local anaesthetic molecules.\textsuperscript{5}

Meloxicam is a NSAID of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.\textsuperscript{6}

Inclusion of low-dose meloxicam in HTX-011 reduces local inflammation and reverses the acidic environment caused by surgery, allowing enhanced penetration of bupivacaine into the nerves and thereby potentiating its effect.\textsuperscript{3}

HTX-011 is currently in clinical development for management of post-operative pain. In phase III clinical trials (NCT03295721; EPOCH 1, NCT03237481; EPOCH 2, NCT03974932, and NCT03907176), the analgesic efficacy and safety of HTX-011 has been assessed in subjects undergoing bunonecctomy, total knee arthroplasty, and unilateral open inguinal herniorrhaphy. Details of the dosing regimen and administration schedule assessed in each study are detailed in the clinical trial table section of this briefing.\textsuperscript{1,2,7,8}

INNOVATION AND/OR ADVANTAGES

HTX-011 is a long-acting, extended-release formulation of bupivacaine with meloxicam. By delivering sustained levels of both a potent anaesthetic and a local anti-inflammatory agent directly to the site of tissue injury, HTX-011 was designed to deliver pain relief while reducing the need for systemically administered pain medications such as opioids, which carry the risk of harmful side effects, abuse and addiction.\textsuperscript{4}

HTX-011 is ideally suited for needle-free administration. Compared to injection, simply coating the affected tissue without using a needle: is easier to administer and less invasive, avoids up to 120 needles sticks and reduces the risk of inadvertent intravascular puncture and accidental needle sticks.\textsuperscript{9}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

HTX-011 does not currently have Marketing Authorization in the EU for any indication.

HTX-011 is currently in phase II clinical trials for the treatment of women undergoing a planned C-section and in paediatric subjects undergoing inguinal herniorrhaphy.\textsuperscript{10}
HTX-011 was granted Fast Track designation from the U.S. Food and Drug Administration (FDA) in the fourth quarter of 2017 and Breakthrough Therapy designation in the second quarter of 2018. Heron has resubmitted a New Drug Application (NDA) to the FDA for HTX-011 in 2019.11

**PATIENT GROUP**

**DISEASE BACKGROUND**

Acute pain is one of the most common symptoms for which physicians are consulted. The purpose of acute pain is to inform the organism about tissue insult (caused by injury, disease, surgical procedure, or childbirth) in order to prevent further damage. Acute pain is an unpleasant sensory and emotional experience which can lead to behavioural changes. It usually lasts for several hours to days, rarely more than a month.12

Post-operative pain is a typical example of acute pain.12 All surgical procedures are associated with a certain level of post-operative pain. Fear of pain is deeply rooted among patients who are about to have surgery.13 Satisfactory perioperative pain management is crucial to assuring a good patient experience, optimising post-operative outcomes, and enhancing functional recovery after surgery.14 Controlling acute pain after surgery is important not only in the immediate post-operative phase but also to prevent chronic postsurgical pain, which can develop in as many as 10% of patients. Pain is a highly personal and subjective experience, which is increasingly recognised to be influenced by life events, mood, fear, anxiety, and anticipation, among other influences.15

**CLINICAL NEED AND BURDEN OF DISEASE**

According to Core Standards for Pain Management Service in the UK, two-thirds of hospital patients experience pain during their admission. Pain is often poorly relieved, with up to 20% of all inpatients suffering moderate to severe pain at any given time.

Even within the surgical population, where the noxious stimulus (the surgery) is well defined and systems are in place to manage acute pain, almost 60% of patients experience severe pain in the post-operative period, with a marked negative impact on health-related quality of life.16

The number of surgical procedures performed in England 2017-18 was 11,897,542. If 60% of patients experience severe pain in the postoperative period, this would equate to approximately 7,138,525 of persons who were operated on in 2017-18.17

**PATIENT TREATMENT PATHWAY**

**TREATMENT PATHWAY**

The involvement of patients in pain control is important because pain is such a personal experience. Following the operation, patients should have their pain level assessed using a 0-10 scale. The pain score should be recorded which will help the doctors and nurses know whether pain treatments are working.18

Both drug and non-drug treatments can be successful in helping to control pain. In most cases drugs are given to control pain for a few days after surgery. However, non-drug treatments can be just as important in helping to control pain.18
Drug treatment to control pain
Pain should be treated early rather than allowing it to become worse. The type of drugs should be selected according to the extent of surgery and the amount of pain the patient has. There are many different types of pain killers and the doctors and nurses will choose the best ones to control the pain after talking to the patient about it.18

Non-drug treatment to control pain
Non-drug treatments include some complementary therapies that can be effective for mild to moderate pain and boost the pain-relief effects of drugs. They include:18

- simple relaxation techniques such as abdominal breathing, visualization exercises, and listening to relaxing music
- supporting the wound when coughing, deep breathing and moving after surgery
- massage, which works on the muscles to release excess tension and can help with relaxation

CURRENT TREATMENT OPTIONS

Painkillers are medicines which relieve pain. There are several types which may be used, depending on how severe is the pain. Some examples are:19

- Paracetamol – good for mild to moderate pain and works well with other painkillers e.g. NSAIDs such as ibuprofen and weak opiates, such as codeine.
- Anti-inflammatory painkillers – examples of these are ibuprofen and diclofenac. These work by reducing inflammation and can be used with other painkillers such as paracetamol and codeine.
- Weak opioids – codeine, tramadol for mild to moderate pain.
- Strong opioids – morphine, oxycodone for moderate to severe pain.
- Local anaesthetics – these work by making the area feel numb so that you don’t feel any pain.

A combination of the above painkillers may work better than taking one on its own.19

PLACE OF TECHNOLOGY

If licensed, HTX-001 will offer an additional treatment option for the management of post-operative pain with a potential to reduce the need for opioids.

CLINICAL TRIAL INFORMATION

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT03907176, HTX-011-304; adults aged ≥18 years; HTX-011 vs Ibuprofen and acetaminophen; phase III</th>
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<td>Sponsor</td>
<td>Heron Therapeutics Inc.</td>
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<td>Status</td>
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<td>Source of Information</td>
<td>Trial registry</td>
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<tr>
<td>Location</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled, open-label</td>
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<tr>
<td>Participants</td>
<td>n= 90; aged ≥18 years old; scheduled and medically fit to undergo an elective unilateral open inguinal herniorrhaphy with mesh under deep</td>
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</table>
sedation or general anaesthesia; no neuraxial technique (e.g., no spinal or epidural).

**Schedule**

Patients allocated for both cohort 1 and 2 will receive the HTX-011 at a dose of 300 mg through luer-lock applicator for instillation, ibuprofen at a dose of 600 mg and acetaminophen at a dose of 1 g.

**Follow-up**

Screening through 15 days

**Primary Outcomes**

Proportion of subjects receiving no opioid rescue [Time frame: screening through day 15]

**Secondary Outcomes**

- Total post-operative opioid consumption [Time frame: screening through day 15]
- Mean total TSQM-9 score [Time frame: screening through day 15]

**Key Results**

- Adverse effects (AEs)
  - Estimated primary completion date was in July 2019.

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**Trial**

NCT03974932, HTX-011-306; adults aged ≥18 years; HTX-011, Ibuprofen, celecoxib, ibuprofen and acetaminophen; phase III

**Sponsor**

Heron Therapeutics Inc.

**Status**

Ongoing

**Source of Information**

Trial registry

**Location**

United States

**Design**

Single group assignment, open-label

**Participants**

n= 30; aged ≥18 years old; scheduled to undergo primary unilateral total knee replacement arthroplasty under spinal anaesthesia and has not previously undergone total knee arthroplasty in either knee.

**Schedule**

Patients will receive the HTX-011 at a dose of 400 mg through luer-lock applicator for instillation, ibuprofen at a dose of 600 mg days 4-7, acetaminophen at a dose of 1 g days 1-7 and celecoxib at a dose of 200 mg days 1-3.

**Follow-up**

12 hours through 29 days

**Primary Outcomes**

Mean area under the curve (AUC) of the visual analogue scale (VAS). [Time frame: 12 through 48 hours]

**Secondary Outcomes**

- Mean AUC of VAS scores. [Time Frame: 72 hours]
- Mean AUC of the NRS of pain intensity at rest (NRS-R). [Time frame: 72 hours]
- Proportion of subjects with an NRS-R score ≥7. [Time frame: 10 time points through 72 hours, and day 11 and day 29]
- Mean total post-operative opioid consumption (in IV morphine milligram equivalents [MME]). [Time frame: 72 hours]
- Proportion of subjects who are opioid-free. [Time frame: through 72 hours, and through Day 11]
- Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through 72 hours who remain opioid-free. [Time frame: 72 hours through day 11]
- Median time to first opioid rescue medication. [Time frame: 72 hours]
- Proportion of subjects who do not receive an opioid prescription at discharge. [Time frame: 72 hours]
- Proportion of subjects who do not receive an opioid prescription between discharge and the Day 11 visit. [Time frame: 72 hours through day 11]
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on Patient Global Assessment (PGA). [Time frame: 24 hours, 48 hours, 72 hours, day 11]
- Median time to first ambulation post-surgery. [Time frame: 72 hours]
- Proportion of subjects unable to participate in each rehabilitation session because of pain. [Time frame: 72 hours]
- Proportion of subjects who first achieve an MPADSS score ≥9. [Time frame: 10 time points through 72 hours]
- Proportion of subjects who are discharged home vs to a skilled nursing facility. [Time frame: 72 hours]
- Mean overall benefit of analgesia score (OBAS). [Time frame: 24 hours, 48 hours, 72 hours, day 11]
- Mean total TSQM-9 score [Time frame: 72 hours through day 11]

### Key Results

**Adverse effects (AEs)**

- **Expected reporting date**

  Estimated primary completion date in September 2019.

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**Trial**

EPOCH 1, [NCT03295721](https://clinicaltrials.gov/ct2/show/NCT03295721), HTX-011-301; adults aged ≥18 years; HTX-011 vs placebo or bupivacaine HCl; phase III

**Sponsor**

Heron Therapeutics Inc.

**Status**

Completed

**Source of Information**

Trial registry¹

**Location**

United States

**Design**

Randomised, placebo and active controlled, triple blind

**Participants**

n= 412; aged ≥18 years old; scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anaesthesia.

**Schedule**

Patients were randomised in three different groups. Patients assigned to the experimental group received HTX-011 at a dose of 60 mg through luer-lock applicator for instillation. Subjects assigned to the placebo group received saline placebo through luer-lock applicator for instillation and subjects assigned to the active comparator group received bupivacaine injection without epinephrine at a dose of 50 mg.

**Follow-up**

72 hours

**Primary Outcomes**

Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) for HTX-011 compared with saline placebo. [Time frame: 72 hours]

**Secondary Outcomes**

Time frame 72 hours:

- Mean AUC of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
- Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with saline placebo.
- Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl.
Key Results

- Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with bupivacaine HCl.

Adverse effects (AEs)

- 

Expected reporting date

Study completion date was in March 2018.

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### Trial

- **EPOCH 2, NCT03237481**, HTX-011-302; adults aged ≥18 years; HTX-011 vs placebo or bupivacaine HCl; phase III

### Sponsor

Heron Therapeutics Inc.

### Status

Completed

### Source of Information

Trial registry

### Location

United States and Belgium

### Design

Randomised, placebo and active controlled, triple blind

### Participants

n= 418; aged ≥18 years; scheduled to undergo a unilateral open inguinal herniorrhaphy with mesh under general anaesthesia.

### Schedule

Patients were randomised in three different groups. Patients assigned to experimental group received HTX-011 at a dose of 300 mg through luer-lock applicator for instillation. Subjects assigned to the placebo group have saline placebo through luer-lock applicator for instillation and subjects assigned to the active comparator group received bupivacaine HCl without epinephrine at a dose of 75 mg injection.

### Follow-up

72 hours

### Primary Outcomes

Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) for HTX-011 compared with saline placebo. [Time frame: 72 hours]

### Secondary Outcomes

- Mean AUC of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
- Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with saline placebo.
- Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl.
- Mean total post-operative opioid consumption (in morphine equivalents) for HTX-011 compared with bupivacaine HCl.

### Key Results

- 

### Adverse effects (AEs)

- 

### Expected reporting date

Study completion date was in January 2018.

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ESTIMATED COST

The cost of HXT-011 is not known yet.
RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- Chou R. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. 2016.20

ADDITIONAL INFORMATION

Heron Therapeutics Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES


NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.