SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zynrelef (400 mg + 12 mg) / 14 mL prolonged-release wound solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.
Zynrelef prolonged-release solution is provided in the following doses:

- 60 mg/1.8 mg of bupivacaine/meloxicam.
- 200 mg/6 mg of bupivacaine/meloxicam.
- 400 mg/12 mg of bupivacaine/meloxicam.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release wound solution.
Clear, pale yellow to yellow, viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zynrelef is indicated for treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults (see section 5.1).

4.2 Posology and method of administration

Zynrelef should be administered in a setting where trained personnel and equipment are available to treat patients promptly who show evidence of neurological or cardiac toxicity.

Posology

The recommended dose depends upon the size of the surgical site and the volume required to coat the affected tissues within the surgical site that could result in pain generation. It should be ensured there is not an excess that could be expressed from the site during closure, especially for small confined surgical spaces (see section 4.4).

The volume to be withdrawn accounts for the hold-up in the Luer lock applicator. Examples of the volume to be withdrawn and dose available for administration are as follows:

- Bunionectomy – up to 2.3 mL (60 mg/1.8 mg)
- Open inguinal herniorrhaphy – up to 10.5 mL (300 mg/9 mg)

The maximum total dose of Zynrelef to be applied must not exceed 400 mg/12 mg (about 14 mL).

Use with other anaesthetics

When using Zynrelef with other local anaesthetics, overall local anaesthetic exposure must be considered through 72 hours. In total, the maximum administered dose of bupivacaine must not exceed 400 mg/day.

Special populations

Elderly patients (≥ 65 years of age)

Elderly patients should be given reduced doses commensurate with their age and physical condition. As elderly patients may have decreased renal function, this should be considered when performing dose selection.

Renal impairment

No dose adjustment of Zynrelef is necessary in patients with mild to moderate renal impairment (see section **5.2**). The use of Zynrelef in patients with non-dialysed severe renal impairment is contraindicated (see section 4.3) and use in patients with dialysed severe renal impairment is not recommended (see section 4.4).

Hepatic impairment

No dose adjustment of Zynrelef is necessary in patients with mild to moderate hepatic impairment. Patients should be monitored for signs of worsening liver function (see sections 4.4 and 5.2). The use of Zynrelef in patients with severe hepatic impairment is contraindicated (see section 4.3).

Paediatric population

The safety and efficacy of Zynrelef in children and adolescents under 18 years of age have not been established. No data are available.

Method of administration

Intralesional use.

Zynrelef is intended for application to the surgical site.

Zynrelef is intended for single-dose administration.

Zynrelef should only be prepared and administered with the sterile components provided in the procedure pack (vented vial spike, syringe, Luer

lock applicator). Full instructions for use are provided in the package leaflet for use by healthcare professionals.
Zynrelef should be applied into the surgical site following final irrigation and suction and prior to suturing. If multiple tissue layers are involved, the solution should be applied after final irrigation and suction of each layer before closing.
Zynrelef is not injected, it should be applied without a needle to the tissue layers below the skin incision. The solution should not be applied to the skin.
A sufficient amount of solution should be applied to coat the tissues.
When using monofilament sutures, 3 or more knots are recommended, as contact with Zynrelef may cause a single knot to loosen or untie.
For instructions on the preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Patients with a known hypersensitivity to any local amide-type anaesthetic or non-steroidal antiinflammatory drugs (NSAIDs). Meloxicam must not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema, or urticaria following the administration of acetyl salicylic acid or other NSAIDs.
- Third trimester of pregnancy (see section 4.6).
- Coronary artery bypass graft (CABG) surgery (see section 4.4).
- Severe heart failure (see section 4.4).
- Severely impaired liver function (see section 4.4).
- Non-dialysed severe renal failure (see section 4.4).

4.4 Special warnings and precautions for use

Efficacy and safety have not been established in major surgeries including abdominal, vascular and thoracic surgeries (see section 5.1). It is recommended not to use this medicine in major surgeries.
Local anaesthetic systemic toxicity (LAST)
As there is a potential risk of severe life-threatening adverse reactions associated with the administration of bupivacaine, any bupivacaine-containing product should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity.

Bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems if utilised for local anaesthetic procedures resulting in high blood concentrations of the active substance. This is especially the case after unintentional intravascular administration or injection into highly vascular areas. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse, and death have been reported in connection with high systemic concentrations of bupivacaine. The clinician responsible should take the necessary precautions to avoid local anaesthetic systemic toxicity (see section 4.2).
Patients who require special attention in order to reduce the risk of dangerous adverse reactions include the following:

- The elderly and patients in poor general condition should be given reduced doses commensurate with their physical status.
- Patients with partial or complete heart block – due to the fact that local anaesthetics may depress myocardial conduction.
- Patients with advanced liver disease or severe renal dysfunction.

The toxic effects of local anaesthetics are additive and their administration should be used with caution, including monitoring for neurologic and cardiovascular effects related to LAST.
Cardiovascular system
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Zynrelef. The use of Zynrelef in patients with a recent myocardial infarction should be avoided unless the benefits are expected to outweigh the risk of recurrent cardiovascular thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Zynrelef after careful consideration.
Gastrointestinal system
Gastrointestinal (GI) bleeding, ulceration, or perforation, which can be fatal, have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. As Zynrelef contains meloxicam, an NSAID, health care professionals should remain alert for signs and symptoms of GI ulceration and bleeding. If a serious GI adverse reaction is suspected, evaluation and treatment should be promptly initiated.
The risk of GI bleeding, ulceration, or perforation is higher with increasing NSAID doses in patients with a history of ulcer and in the elderly.
Combination therapy with protective medicinal products (e.g. misoprostol or proton pump inhibitors) should be considered for these patients and for patients requiring concomitant low-dose acetylsalicylic acid or other active substances likely to increase GI risk (see below and section 4.5).
Patients with a history of GI toxicity, particularly when elderly, should be advised to report any unusual abdominal symptoms (especially GI bleeding).
Caution is advised in patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as heparin,

anticoagulants such as warfarin, or other NSAIDs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1 g, as single intake, or ≥ 3 g, as total daily amount) (see section 4.5).

Serious skin reactions

Life-threatening cutaneous reactions (Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) have been reported with the use of meloxicam. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If the patient has developed SJS or TEN with the use of meloxicam, Zynrelef must not be administered in this patient at any time.

Monitoring of liver and renal function

Occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen, as well as other laboratory disturbances, have been reported with meloxicam. The majority of these instances involved transitory and slight abnormalities. Patients should be monitored for signs of worsening liver or renal function.

Renal toxicity and renal impairment

Renal toxicity has been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, nephrotic syndrome, lupus nephropathy, dehydration, hypovolemia, heart failure, severe liver dysfunction, those taking diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin-II antagonists, and the elderly.

Renal function should be monitored in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia after administration of Zynrelef.

The renal effects of meloxicam may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

No information is available from controlled clinical studies regarding the use of meloxicam in patients with advanced renal disease. Because some meloxicam metabolites are excreted by the kidney, the use of Zynrelef is not recommended in patients with dialysed severe renal impairment unless the benefits are expected to outweigh the risk of worsening renal function. Zynrelef is contraindicated in patients with non-dialysed severe renal impairment (see section 4.3).

Hepatic impairment

Since bupivacaine is metabolized by the liver, high doses should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anaesthetics normally, are at a greater risk of developing toxic plasma concentrations. The use of Zynrelef in patients with severe hepatic impairment is contraindicated (see section 4.3).

Hyperkalaemia

Increases in serum potassium concentration, including hyperkalaemia, have been reported for meloxicam in patients with diabetes or receiving

concomitant treatment known to increase potassium concentrations. Zynrelef should only be used in patients with hyperkalaemia if the benefits outweigh the risks.

Chondrolysis

There have been post-marketing reports of chondrolysis in patients receiving postoperative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion of Zynrelef should be avoided.

Wound healing impairment

Impaired wound healing has been observed in patients following bunionectomy (see section 4.8). For small, confined surgical spaces, avoid administration of excess volume (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine

Bupivacaine should be used with caution in patients receiving other local anaesthetics or active substances structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive (see section 4.4).

Meloxicam

ACE Inhibitors, Angiotensin-II Antagonists

NSAIDs may decrease the antihypertensive effect of ACE inhibitors, angiotensin-II antagonists, or beta-blockers (including propranolol).

In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or angiotensin-II antagonists may result in deterioration of renal function, including possible acute renal failure, which is usually reversible. Patients on ACE inhibitors, angiotensin-II antagonists, or beta-blockers should be monitored following treatment with Zynrelef to ensure that the desired blood pressure is obtained. Patients who are elderly, volume-depleted, or have impaired renal function, should be monitored for signs of worsening renal function (see section 4.4).

Diuretics

Patients on diuretics should be monitored following treatment with Zynrelef for signs of worsening renal function, in addition to assuring diuretic efficacy, including antihypertensive effects.

Lithium

NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended. If the use of Zynrelef with lithium appears necessary, patients should be monitored for signs of lithium toxicity following treatment with Zynrelef.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available human data on use of Zynrelef in pregnant women.

Bupivacaine

There is a limited amount of data from the use of bupivacaine in pregnant women. Animal studies have shown decreased pup survival and embryotoxic effects (see section 5.3).

Meloxicam

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to the following:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).
- Renal dysfunction, which may progress to renal failure with oligohydroamnios.

At the end of pregnancy, all prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- Possible prolongation of bleeding time, an anti-aggregating effect, which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

If Zynrelef is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Due to the meloxicam content, Zynrelef is contraindicated during the third trimester of pregnancy (see section 4.3). During the first and second trimester of pregnancy, meloxicam should not be given unless clearly necessary.

Breast-feeding

There are no available human data on the use of Zynrelef in breast-feeding women.

Bupivacaine enters human milk and NSAIDs are also known to pass into human milk. A decision must be made whether to start or discontinue breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of Zynrelef for the woman.

Fertility

Studies evaluating the effects of Zynrelef on male and female fertility have not been performed.

The use of meloxicam may impair fertility in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, Zynrelef should only be used if the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

Bupivacaine has minor influence on the ability to drive and use machines. Zynrelef may have a very mild effect on mental function and coordination even in the absence of overt central nervous system (CNS) toxicity, and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was dizziness (15.1%).

Tabulated list of adverse reactions

The following adverse reactions are based on experience from clinical trials and displayed by system organ class and frequency in Table 1 below. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency of the adverse reactions is expressed according to the following categories: very common (≥1/10); common (≥1/100 to <1/10).

Table 1: Adverse reactions reported for Zynrelef

System Organ Class	Very Common	Common
Nervous system disorders	Dizziness	Dysgeusia
Cardiac disorders		Bradycardia
Vascular disorders		Hypotension
Skin and subcutaneous tissue disorders		Skin odour abnormal
General disorders and administration site conditions		Cellulitis Impaired healing* Local site reaction Local site swelling Local site erythema Peripheral swelling

* Impaired wound healing, including wound dehiscence, has been observed in patients following bunionectomy (a model of surgery with a small, confined space available to instill the product).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Bupivacaine

Accidental intravascular injections of bupivacaine may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

Acute systemic toxicity

Systemic toxic reactions primarily involve the CNS and the cardiovascular system.

Central nervous system toxicity

CNS toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus, and visual disturbances. Dysarthria, muscular twitching, or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis, hyperkalaemia, and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic medicinal product from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of bupivacaine have been injected.

Cardiovascular system toxicity

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia, and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Treatment of acute toxicity

If signs of acute systemic toxicity appear, administration of Zynrelef should be immediately stopped.
At the first sign of toxicity, oxygen should be administered.
The first step in the management of convulsions, as well as under ventilation or apnoea, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that medicinal products used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of anaesthetics, with these anticonvulsant medicinal products. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine to enhance myocardial contractile force).
If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.
Endotracheal intubation, employing medicinal products, and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.
Meloxicam
There is limited experience with meloxicam overdose.
Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Anaphylactoid reactions may occur following an overdose.
Patients should be managed with symptomatic and supportive care following an overdose of Zynrelef.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anesthetics, Local anaesthesia drugs (amides),
ATC code: not yet assigned
Mechanism of action
Zynrelef is a fixed-dose, prolonged-release combination of bupivacaine and meloxicam. For approximately 72 hours after Zynrelef is applied into the

surgical site, it releases bupivacaine and meloxicam, which are then absorbed into the surrounding tissues. Meloxicam is believed to control the tissue inflammation thereby normalizing the pH and potentiating the effect of bupivacaine, resulting in an increase in analgesia.
Bupivacaine is a local anaesthetic of the amide type with both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia) with less pronounced motor block.
Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic, and antipyretic properties. Its precise mechanism of action remains unknown. Meloxicam inhibits the biosynthesis of prostaglandins, known inflammation mediators.
Pharmacodynamic effects
Bupivacaine
Bupivacaine 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.
Local anaesthetics may have similar effects on other excitable membranes, e.g. in the brain and myocardium. If excessive amounts of active substance reach the systemic circulation, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems.
Central nervous system toxicity (see section 4.9) usually precedes the cardiovascular effects as central nervous system toxicity occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism, and eventually cardiac arrest.
Clinical efficacy and safety
The efficacy of Zynrelef was evaluated in 2 multi-centre, double-blind, parallel-group, active- and placebo-controlled clinical trials.
Study 301 (Bunionectomy)
A total of 412 patients undergoing unilateral bunionectomy with osteotomy and fixation with a lidocaine Mayo block were randomized to 1 of the following 3 treatment groups in a 3:3:2 ratio (respectively): Zynrelef 60 mg/1.8 mg, bupivacaine hydrochloride 50 mg, or saline placebo. The mean patient age was 47 years (range 18 to 77 years) and patients were predominantly female (86%). Zynrelef was applied directly into the surgical site at the end of the procedure, after final irrigation and suction, but prior to closure. Bupivacaine hydrochloride and saline placebo were administered by injection and instillation, respectively. Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) out to 72 hours post-dose. Postoperatively, there was no scheduled pain medication regimen; however, patients were allowed rescue medicinal products as needed (10 mg oxycodone orally every 4 hours, 10 mg IV morphine every 2 hours, and/or 1,000 mg paracetamol orally every 6 hours).
Results for the primary endpoint and all 4 key secondary endpoints were positive. Zynrelef significantly reduced the mean AUC of the NRS-A pain intensity scores with activity through 72 hours post-surgery compared with both saline placebo (primary endpoint) and bupivacaine HCl (Figure 1). Zynrelef also significantly reduced opioid consumption and significantly

increased the proportion of subjects who required no postoperative opioid rescue medication (were “opioid-free”) (Table 2).

Figure 1: Mean pain intensity over 72 hours in Study 301 (bunionectomy)

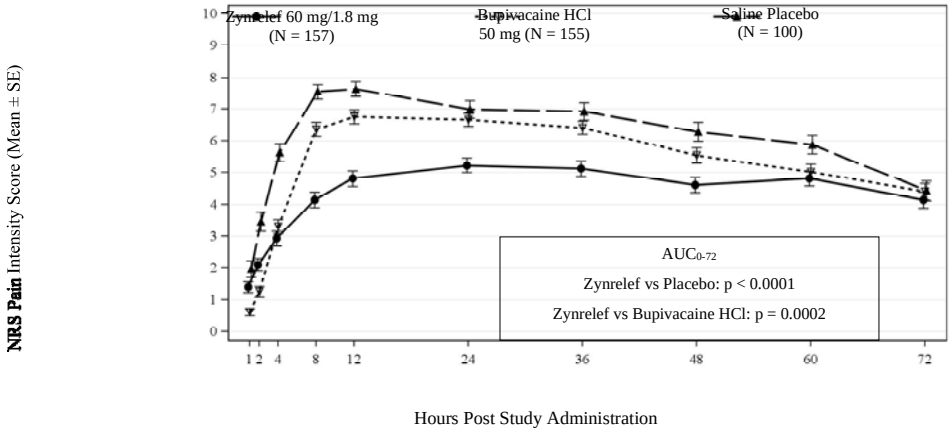

Table 2: Opioid-use over 72 hours in Study 301 (bunionectomy)

		Zynrelef 60 mg/1.8 mg (N = 157)	Bupivacaine Hydrochloride 50 mg (N = 155)	Saline Placebo (N = 100)
Total opioid consumption[a] 0-72 hours	Median	13	18	25
	p-value vs saline placebo	< 0.0001		
	p-value vs bupivacaine hydrochloride	0.0022		
Opioid-free 0-72 hours	n (%)	45 (29%)	17 (11%)	2 (2%)
	p-value vs saline placebo	< 0.0001		
	p-value vs bupivacaine hydrochloride	0.0001		

[a] In intravenous morphine milligram equivalents (IV MME).

Study 302 (Inguinal herniorrhaphy)

A total of 418 patients undergoing open inguinal herniorrhaphy with mesh under general anaesthesia were randomized to 1 of the following 3 treatment groups in a 2:2:1 ratio (respectively): Zynrelef 300 mg/9 mg, bupivacaine hydrochloride 75 mg, or saline placebo. The mean patient age was 49 years (range 18 to 83 years) and patients were predominantly male (94%). Zynrelef was applied directly into the surgical site at the end of the procedure, following irrigation and suction of each fascial layer but prior to closure. Bupivacaine hydrochloride and saline placebo were administered by injection and instillation, respectively. Pain intensity was rated by the patients on a 0 to 10 NRS out to 72 hours post-dose. Postoperatively, there was no scheduled pain medication regimen; however, patients were allowed rescue medicinal product as needed (10 mg oxycodone orally every 4 hours, 10 mg morphine IV every 2 hours, and/or 1,000 mg paracetamol orally every 6 hours). Results for the primary endpoint and all 4 key secondary endpoints were positive. Zynrelef significantly reduced the mean AUC of the NRS-A pain intensity scores with activity through 72 hours post-surgery compared with both saline placebo (primary endpoint) and bupivacaine HCl (Figure 2).

Zynrelef also significantly reduced opioid consumption and significantly increased the proportion of subjects who were “opioid-free” (Table 3).

Figure 2: Mean pain intensity (NRS) over 72 hours in Study 302 (herniorrhaphy)

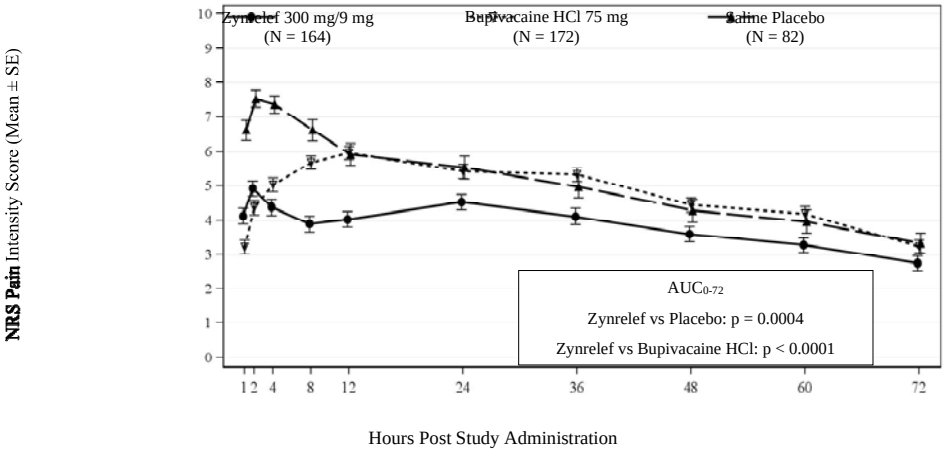

Table 3: Opioid-use over 72 hours in Study 302 (herniorrhaphy)

		Zynrelef 300 mg/9 mg (N = 164)	Bupivacaine Hydrochloride 75 mg (N = 172)	Saline Placebo (N = 82)
Total opioid consumption[a] 0-72 hours	Median	0	7	11
	p-value vs saline placebo	0.0001		
	p-value vs bupivacaine hydrochloride	0.0240		
Opioid-free 0-72 hours	n (%)	84 (51%)	69 (40%)	18 (22%)
	p-value vs saline placebo	< 0.0001		
	p-value vs bupivacaine hydrochloride	0.0486		

[a] In intravenous morphine milligram equivalents (IV MME).

Surgeries not evaluated with Zynrelef

Efficacy and safety have not been established in major surgeries including abdominal, vascular and thoracic surgeries (see section 4.4).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zynrelef in one or more subsets of the paediatric population in the treatment of acute post-operative pain (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Local application of Zynrelef into the surgical site results in detectable systemic plasma levels of bupivacaine through 72 hours and meloxicam through 120 hours. Systemic plasma levels of bupivacaine following application of Zynrelef are correlated with efficacy.

Absorption

Zynrelef is a prolonged-release formulation of bupivacaine and meloxicam using a polymer-based drug delivery system. Following single-dose application of Zynrelef, bupivacaine and meloxicam are released simultaneously from the polymer for approximately 3 days.

Pharmacokinetic parameters of bupivacaine and meloxicam from Zynrelef were evaluated following multiple surgical procedures.

Descriptive statistics of pharmacokinetic parameters of representative Zynrelef doses in each study are provided in Table 4.

Table 4: Summary of pharmacokinetic parameters for bupivacaine and meloxicam after administration of single doses of Zynrelef

Active Ingredient	Parameter	Bunionectomy: Zynrelef 60 mg/1.8 mg (N = 17)	Herniorrhaphy: Zynrelef 300 mg/9 mg (N = 16)
Bupivacaine	C_{max} (ng/mL)	53.6 (32.6)	271 (147)
	t_{max} (h)	3.00 (1.55-24.08)	18.22 (3.10-30.28)
	$AUC_{(0-t)}$ (h×ng/mL)	1,650 (1,130)	14,900 (8,470)
	$AUC_{(inf)}$ (h×ng/mL)	1,680 (1,190)	15,300 (8,780)
Meloxicam	C_{max} (ng/mL)	25.6 (13.8)	225 (96.3)
	t_{max} (h)	18.02 (8.13-60)	53.72 (24.2-96.02)
	$AUC_{(0-t)}$ (h×ng/mL)	1,600 (915)	18,600 (7,860)
	$AUC_{(inf)}$ (h×ng/mL)	1,660 (1,050)	15,500 (NC[a])

AUC = area under the curve; NC = not calculated.

Note: Arithmetic mean (standard deviation) except t_{max} where it is median (range). Doses of Zynrelef are shown as bupivacaine dose (mg)/meloxicam dose (mg).

[a] Terminal elimination phase was not captured in a sufficient number of patients; SD was not calculated.

Distribution

After bupivacaine and meloxicam have been released from Zynrelef and are absorbed systemically, bupivacaine and meloxicam distribution is expected to be the same as for any bupivacaine hydrochloride solution or meloxicam oral formulation.

Bupivacaine

Bupivacaine has a total plasma clearance of 0.58 L/min, a volume of distribution at steady state of 73 L and an intermediate hepatic extraction ratio of 0.38 after IV administration. It is mainly bound to alpha-l-acid glycoprotein with plasma binding of 96%.

Meloxicam

Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, on average 11 L. Inter-individual variation is in the order of 30-40%.

Biotransformation

Bupivacaine

Bupivacaine is extensively metabolised in the liver, predominantly by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to pipecoloxylidide (PPX), both mediated by cytochrome P450 (CYP) 3A4. The plasma concentrations of PPX and 4-hydroxy-bupivacaine after administration of bupivacaine are low as compared to the parent medicinal product. The metabolites have a pharmacological activity that is less than that of bupivacaine.

Meloxicam

Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive. The major metabolite, 5'-carboxymeloxicam (60% of dose), is formed by oxidation of an intermediate metabolite 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% of dose). *In vitro* studies suggest that CYP2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination

After bupivacaine and meloxicam have been released from Zynrelef and are absorbed systemically, their excretion is expected to be the same as for other bupivacaine hydrochloride solution formulations or meloxicam oral formulations.

Bupivacaine

About 1% of bupivacaine is excreted in the urine as unchanged drug in 24 hours and approximately 5% as PPX. The mean apparent terminal half-life ($t_{1/2}$) for bupivacaine from Zynrelef is approximately 14 to 15 hours.

Meloxicam

Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine. The mean apparent terminal half-life ($t_{1/2}$) for meloxicam from Zynrelef is approximately 22 to 25 hours. Total plasma clearance amounts on average 8 mL/min.

Special populations

After bupivacaine and meloxicam have been released from Zynrelef and are absorbed systemically, the effects of hepatic and renal impairment are expected to be the same as for other bupivacaine and meloxicam formulations.

Hepatic/renal impairment

Clearance of bupivacaine is almost entirely due to liver metabolism and is more sensitive to changes in intrinsic hepatic enzyme function than to liver perfusion.

Neither hepatic, nor mild nor moderate renal impairment, has a substantial effect on meloxicam pharmacokinetics. In severe renal failure, the increase in

the volume of distribution may result in higher free meloxicam concentrations (see sections 4.3 and 4.4).
Elderly
Following oral dosing of meloxicam, mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

5.3 Preclinical safety data

Non-clinical data on Zynrelef, bupivacaine, or meloxicam reveal no special hazard for humans based on conventional studies of general toxicity and toxicity to reproduction and development.
No evidence has been found of any mutagenic effect of meloxicam, either *in vitro* or *in vivo*. No carcinogenic risk for meloxicam has been found in the rat and mouse at doses far higher than those used clinically. Long-term studies in animals to evaluate the mutagenic and carcinogenic potential of Zynrelef and bupivacaine have not been conducted.
Bupivacaine crosses the placenta. In reproduction toxicity studies, decreased survival of the offspring of rats and embryolethality was noted in rabbits at bupivacaine doses, which were 1.9- or 2.1-fold the maximum recommended daily dose of Zynrelef in humans (based on body surface area using maximum daily exposure in a 60 kg person). A study in rhesus monkeys of bupivacaine suggested altered postnatal behaviour following exposure to bupivacaine at birth.
Oral reproductive studies of meloxicam in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher. Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits. These no observed effect levels exceeded the maximum daily exposure of meloxicam in Zynrelef by a factor of 7.4- and 295-fold (based on body surface area using maximum daily exposure in a 60 kg person). Foetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer
Triacetin
Dimethyl sulfoxide
Maleic acid

6.2 Incompatibilities

This medicinal product must not be mixed with water, sodium chloride solution, or other medicinal products as the product will become very viscous and difficult to administer.

Zynrelef should not come in contact with povidone-iodine solution.

6.3 Shelf life

3 years
Shelf-life after first opening: use immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.
This medicinal product should only be prepared immediately prior to use.

6.5 Nature and contents of container

400 mg bupivacaine/12 mg meloxicam
One 20 mL Type I glass vial, 1 vented vial spike, two 12 mL Luer lock syringes, and 2 Luer lock applicators.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Only clear solution without particles should be used.
The solution is for single-use. Any unused solution should be discarded.
The exterior of the Zynrelef vial is not sterile. Aseptic technique must be strictly observed throughout handling of the medicinal product to keep it free from microbial contamination. For operating room preparation it is recommended that a 2-person team prepares this product.
Zynrelef is a viscous solution that should only be prepared and administered with the components provided in the Zynrelef procedure pack.
Refer to the instructions for use intended for healthcare professionals presented in the package leaflet.

7 MARKETING AUTHORISATION HOLDER

Heron Therapeutics, B.V.
Herengracht 500
1017 CB Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53712/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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