ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zynrelef (60 mg + 1.8 mg) / 2.3 mL prolonged-release wound solution

Zynrelef (200 mg + 6 mg) / 7 mL prolonged-release wound solution

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The volume to be withdrawn accounts for the hold-up in the Luer lock applicator. Examples of the volume to be withdrawn and dose available for administration are as follows :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. Wipe off excess Zynrelef from the skin prior to or during closure of the wound.

When tying knots with monofilament sutures, contact with Zynrelef may cause knots to loosen or untie due to the viscosity of Zynrelef. Minimise administration of Zynrelef near the incision line and wipe off excess Zynrelef from the skin prior to suturing. Three (3) or more knots ending in a multi-throw knot (e.g. a Surgeon's knot) are recommended with monofilament sutures. Consider braided or barbed sutures, especially for closure of deeper layers.

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 outweight 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.

From the 20th week of pregnancy onward, meloxicam in Zynrelef may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment and is usually reversible. In addition, there have been reports of ductus arteriosus constriction following treatment with meloxicam in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Zynrelef should not be given unless clearly necessary. 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 as possible. Antenatal monitoring for oligohydramenios and ductus arteriosus constriction should be considered for several days after exposure to Zynrelef from gestational week 20 onward.

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

- Cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension).
- Renal dysfunction (see above).

The mother and neonate, at the end of pregnancy, to:

- 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.

Consequently, due to the meloxicam component, Zynrelef is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding

Bupivacaine and meloxicam are excreted in human milk in small amounts. Based on a clinical study,

the total estimated average infant dose of bupivacaine and meloxicam from breast milk would be approximately 0.3% and 1.0% of the weight-adjusted maternal dose, respectively.

However, as the effects of Zynrelef exposure on the breastfed newborns/infants are unknown, 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)

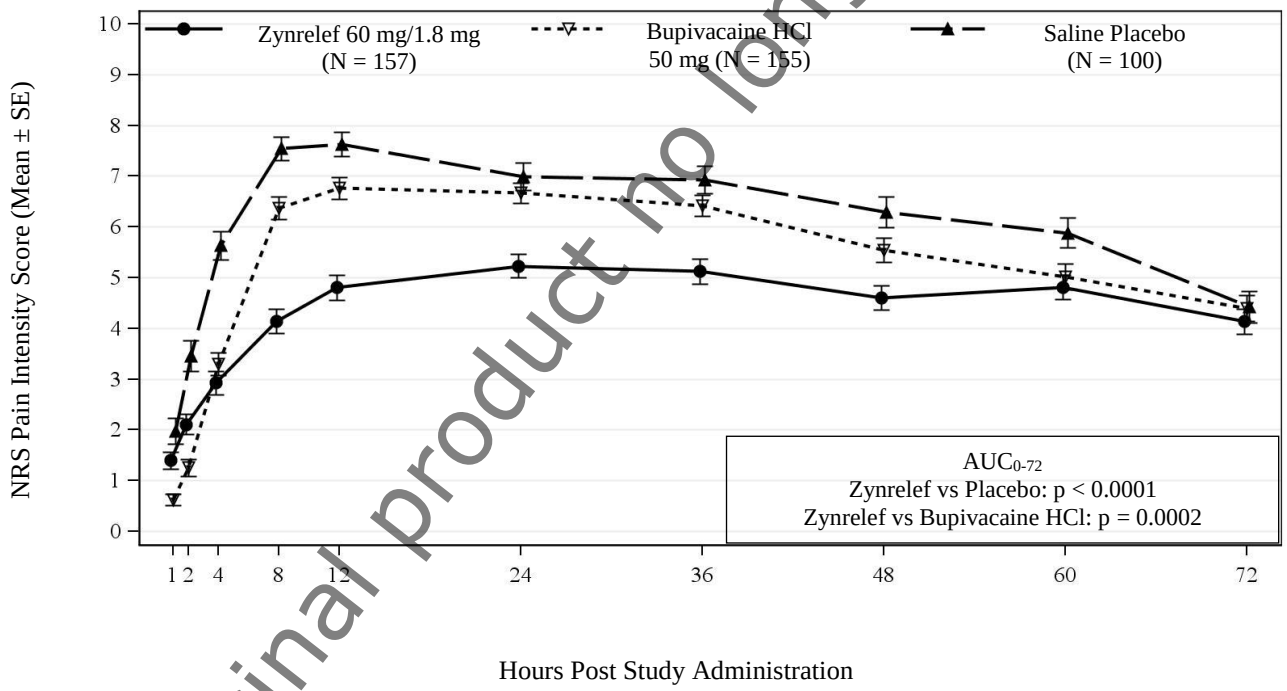


Table 2: Opioid-use over 72 hours in Study 301 (bunionectomy)

		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		

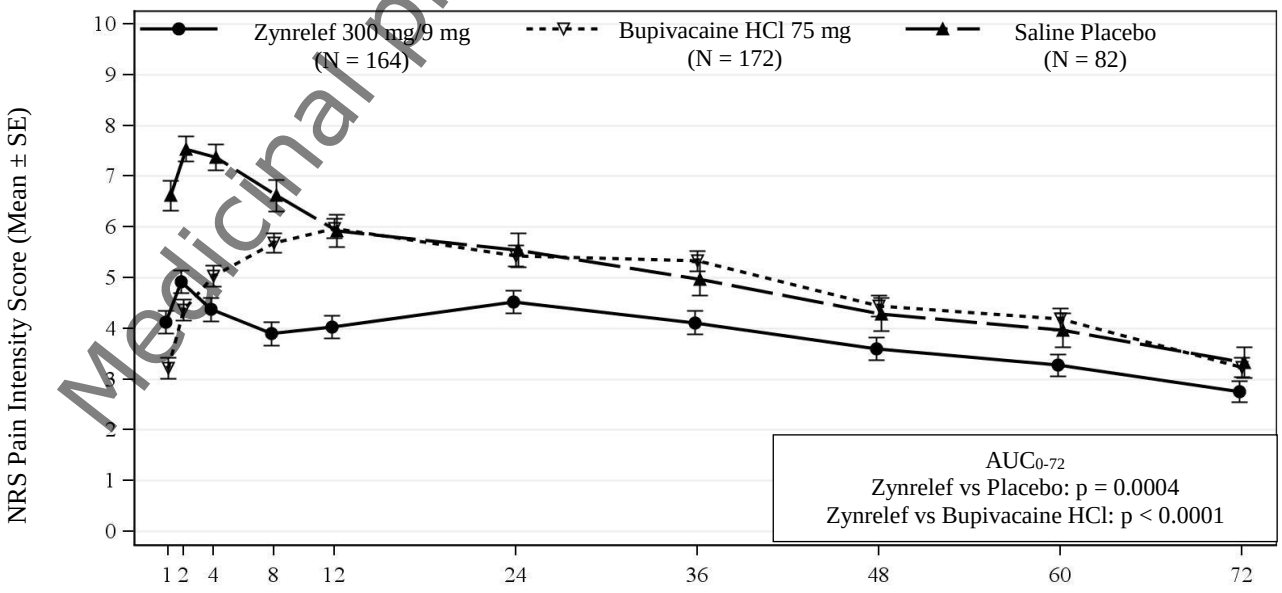
[a] In intravenous morphine milligram equivalents (IV MME).

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)



Hours Post Study Administration

Table 3: Opioid-use over 72 hours in 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

60 mg/1.8 mg of bupivacaine/meloxicam: 2 years
200 mg/6 mg of bupivacaine/meloxicam: 3 years
400 mg/12 mg of bupivacaine/meloxicam: 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

<u>60 mg bupivacaine/1.8 mg meloxicam</u>

One 10 mL Type I glass vial, 1 vented vial spike, one 3 mL Luer lock syringe, and 1 Luer lock applicator.

<u>200 mg bupivacaine/6 mg meloxicam</u>

One 10 mL Type I glass vial, 1 vented vial spike, one 12 mL Luer lock syringe, and 1 Luer lock applicator.

<u>400 mg bupivacaine/12 mg meloxicam</u>

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 and other handling

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)

EU/1/20/1478/001
EU/1/20/1478/002
EU/1/20/1478/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 September 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Millmount Healthcare Limited
Block-7, City North Business Campus
Stamullen K32 YD60
Co. Meath
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zynrelef (60 mg + 1.8 mg) / 2.3 mL prolonged-release wound solution
bupivacaine/meloxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Each vial delivers a dose of 60 mg/1.8 mg of bupivacaine/meloxicam.

3. LIST OF EXCIPIENTS

Also contains: DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer, triacetin, dimethyl sulfoxide, maleic acid.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release wound solution

1 x 10 mL vial, 1 vented vial spike, 1 Luer lock syringe, and 1 Luer lock applicator.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intralesional use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.
Prepare immediately prior to use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1478/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zynrelef (60 mg + 1.8 mg) / 2.3 mL prolonged-release wound solution
bupivacaine/meloxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Each vial delivers a dose of 60 mg/1.8 mg of bupivacaine/meloxicam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release wound solution
1 x 10 mL vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intralesional use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light.
Prepare immediately prior to use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Heron Therapeutics, B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1478/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zynrelef (60 mg + 1.8 mg) / 2.3 mL prolonged-release wound solution
bupivacaine/meloxicam
Intralesional use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 mg/1.8 mg/dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zynrelef (200 mg + 6 mg) / 7 mL prolonged-release wound solution
bupivacaine/meloxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Each vial delivers a dose of 200 mg/6 mg of bupivacaine/meloxicam.

3. LIST OF EXCIPIENTS

Also contains: DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer, triacetin, dimethyl sulfoxide, maleic acid.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release wound solution

1 x 10 mL vial, 1 vented vial spike, 1 Luer lock syringe, and 1 Luer lock applicator.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intralesional use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.
Prepare immediately prior to use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1478/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zynrelef (200 mg + 6 mg) / 7 mL prolonged-release wound solution
bupivacaine/meloxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Each vial delivers a dose of 200 mg/6 mg of bupivacaine/meloxicam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release wound solution
1 x 10 mL vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intralesional use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light.
Prepare immediately prior to use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Heron Therapeutics, B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1478/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zynrelef (200 mg + 6 mg) / 7 mL prolonged-release wound solution
bupivacaine/meloxicam
Intralesional use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/6 mg/dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Each vial delivers a dose of 400 mg/12 mg of bupivacaine/meloxicam.

3. LIST OF EXCIPIENTS

Also contains: DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer, triacetin, dimethyl sulfoxide, maleic acid.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release wound solution

1 x 20 mL vial, 1 vented vial spike, 2 Luer lock syringes, and 2 Luer lock applicators.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intralesional use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.
Prepare immediately prior to use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1478/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Each vial delivers a dose of 400 mg/12 mg of bupivacaine/meloxicam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release wound solution
1 x 20 mL vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intralesional use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light.
Prepare immediately prior to use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Heron Therapeutics, B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1478/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zynrelef (400 mg + 12 mg) / 14 mL prolonged-release wound solution
bupivacaine/meloxicam
Intralesional use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg/12 mg/dose

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zynrelef (60 mg + 1.8 mg) / 2.3 mL prolonged-release wound solution

Zynrelef (200 mg + 6 mg) / 7 mL prolonged-release wound solution

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

bupivacaine/meloxicam

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zynrelef is and what it is used for

Zynrelef contains the medicines bupivacaine and meloxicam.
- Bupivacaine belongs to a group of medicines called local anaesthetics.
- Meloxicam belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

Zynrelef will be applied during surgery by your doctor.

Zynrelef is used in adults to reduce pain from small- to medium-sized surgical wounds after surgery.

2. What you need to know before you are given Zynrelef

You must not be given Zynrelef:
- if you are in your **last trimester of pregnancy** (30 weeks onwards). See section on pregnancy;
- if you are **allergic** to **bupivacaine** and/or **meloxicam** or any of the other ingredients of this medicine (listed in section 6);
- if you are **allergic** to other local anaesthetics of the same class as bupivicaine (such as **lidocaine, mepivacaine, prilocaine, levobupivacaine**, and **ropivacaine**);
- if you have ever **developed any of the following after taking acetyl salicylic acid, a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, or other non-steroidal anti-inflammatories** :
  - wheezing, chest tightness, breathlessness (asthma)
  - nasal blockage due to swellings in the lining of your nose (nasal polyps)
  - skin rashes/nettle rash (urticaria) or serious skin reactions
  - sudden skin or mucosal swelling, such as swelling around the eyes, face, lips, mouth or throat, possibly making breathing difficult (angioneurotic oedema)
- during a **heart bypass surgery** (coronary artery bypass graft);
- if you have **severe heart failure**;

- if you have **severe liver problems**;
- if you have **severe kidney failure and not receiving dialysis**.

If you are not sure if any of the above applies to you, talk to your doctor before you are given Zynrelef.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before receiving Zynrelef:
- if you have heart problems, previous stroke or think that you might be at risk of these conditions because medicines such as meloxicam present in Zynrelef may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.
- if you have ever had bleeding from your stomach or gastro-intestinal tract, a stomach ulcer, or inflammation of the stomach (gastritis) because medicines such as meloxicam present in Zynrelef may worsen these conditions.
- if you develop signs of skin reactions, especially within the first weeks after surgery. Your doctor will closely monitor skin reactions, and Zynrelef must never be administered to you again.
- if you have impaired kidney function or kidney disease.
- if you have impaired liver function or liver disease.
- if you have high potassium levels in your blood (hyperkalaemia).
- if you are having a surgery to fix a bunion in your foot because impaired wound healing has been observed in patients following this surgery. Your doctor should be aware to avoid the administration of an excess volume of Zynrelef.

Chondrolysis (breakdown of the cartilage) has been reported in patients receiving postoperative intra-articular continuous infusion of local anaesthetics (one of the ingredients of this medicine). Your doctor should be aware that Zynrelef is not intended to be used for administration via an intra-articular route.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before you are given Zynrelef.

Children and adolescents

Zynrelef is not recommended for use in children and adolescents below 18 years of age.

Other medicines and Zynrelef

Tell your doctor if you are taking, have recently taken or might take any other medicines. This is because Zynrelef can affect the way some medicines work.

In particular, **tell your doctor** or pharmacist if you are taking/have taken or are using any of the following:
- medicines used to treat an uneven heart beat (arrhythmia), such as lidocaine and mexiletine.

Your doctor needs to know about these medicines to be able to work out the correct dose of Zynrelef for you.

Also, **tell your doctor** if you are taking any of the following medicines:
- medicines to treat heart and kidney diseases (such as ACE inhibitors, angiotensin receptor blockers, or beta-blockers);
- any diuretic medicine ("water tablets"). Your doctor may monitor your kidney function if you are taking diuretics;
- lithium - used to treat mood disorders.

If you are in doubt about any of these medicines, ask your doctor.

Pregnancy, breast-feeding and fertility

Tell your doctor immediately if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby. Meloxicam, one of the medicines in Zynrelef, may make it more difficult to become pregnant. If you have difficulties conceiving or you are undergoing investigation for fertility, your doctor will decide if Zynrelef should be given to you.

Zynrelef must not be administered if you are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected. Zynrelef should not be administered during the first 6 months of pregnancy unless absolutely necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose should be administered. If administered after 20 weeks of pregnancy, Zynrelef can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment, your doctor may recommend additional monitoring. Zynrelef is not recommended during breast-feeding.

Driving and using machines

Zynrelef may have a very mild effect on your mental function and coordination, and may temporarily impair your locomotion and alertness. After you have been given Zynrelef, you should not drive or use tools or machines until after these effects wear off.

3. How you will be given Zynrelef

Zynrelef will be applied during surgery by your doctor.
Your doctor will determine the correct dose for you depending on the type of surgery you are having.
Your doctor may decide to reduce the dose if you are elderly.

Your doctor will ensure you have the correct amount of pain relief at all times.

If you have been given too much Zynrelef

Serious side effects from getting too much Zynrelef need special treatment and the doctor treating you is trained to deal with these situations.

Seek medical help as soon as possible if you experience any of these early signs of being given too much Zynrelef:

- feeling dizzy or light-headed;
- numbness of the lips and around the mouth;
- numbness of the tongue;
- hearing problems;
- problems with your vision.

More serious side effects from being given too much Zynrelef include problems with your speech, twitching of your muscles, tremors, trembling, fits (seizures), and loss of consciousness. If any of these occur, **seek medical help immediately.**

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects to look out for:

Side effects reported in clinical studies for patients treated with Zynrelef were:

Very common (may affect more than 1 in 10 people):
- dizziness

Common (may affect up to 1 in 10 people):
- abnormally slow heart beat;
- low blood pressure;
- unpleasant body smell;
- infection of the skin (cellulitis);
- abnormal healing, including reopening of the wound, at the site of bunion surgery;
- swelling, redness, heat or infection at the site of surgery;
- swelling of your lower legs or hands;
- altered taste.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zynrelef

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

Your doctor or the hospital will normally store Zynrelef and they are responsible for the quality of the medicine when it has been opened if it is not used immediately. The medicine should be visually inspected prior to use. The solution should only be used if it is clear, practically free from particles and if the container is undamaged. Your doctor will throw away the medicine appropriately.

6. Contents of the pack and other information

What Zynrelef contains
- The active substances are bupivacaine and meloxicam. Each mL of solution contains 29.25 mg bupivacaine and 0.88 mg 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.
- The other ingredients are DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer, triacetin, dimethyl sulfoxide and maleic acid.

What Zynrelef looks like and contents of the pack

Zynrelef is a prolonged-release wound solution for intralesional use (application to surgical site). It is a clear, pale yellow to yellow solution.

Each Zynrelef pack contains 1 x 10 mL or 1 x 20 mL single-use glass vial, contained in an individual carton and sterile individually packaged components for preparation and administration:

- 60 mg bupivacaine and 1.8 mg meloxicam: one 10 mL single-dose vial, 1 vented vial spike, one 3 mL Luer lock syringe, and 1 Luer lock applicator.
- 200 mg bupivacaine and 6 mg meloxicam: one 10 mL single-dose vial, 1 vented vial spike, one 12 mL Luer lock syringe, and 1 Luer lock applicator.
- 400 mg bupivacaine and 12 mg meloxicam: one 20 mL single-dose vial, 1 vented vial spike, two 12 mL Luer lock syringes, and 2 Luer lock applicators.

Not all pack sizes may be marketed.

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

Manufacturer
Millmount Healthcare Limited
Block-7, City North Business Campus
Stamullen K32 YD60
Co. Meath
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

INSTRUCTIONS FOR USE FOR ZYNRELEF

1. Zynrelef is intended for single-dose administration only.
2. Zynrelef is supplied as a procedure pack consisting of a single-dose glass vial, and the following sterile components: Luer lock syringe(s), a vented vial spike, and Luer lock applicator(s).
3. Zynrelef is a viscous solution that should only be prepared and administered with the components provided in the Zynrelef procedure pack.
4. The contents of the Zynrelef vial are sterile. The vial exterior is not sterile. Aseptic technique must be strictly observed throughout handling of the medicinal product to keep it free from microbial contamination.

Preparation
The following 3 procedure packs are available for Zynrelef:

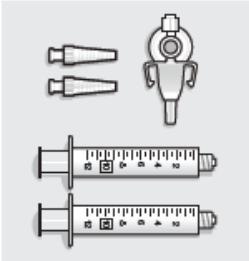
Product Presentation	Syringe size	Number of syringes	Volume to withdraw per syringe[a]	Volume administered
60 mg/1.8 mg of bupivacaine/meloxicam solution in a 10 mL vial	3 mL	1	2.3 mL	2.0 mL
200 mg/6 mg of bupivacaine/meloxicam solution in a 10 mL vial	12 mL	1	7 mL	6.7 mL
400 mg/12 mg of bupivacaine/meloxicam solution in a 20 mL vial	12 mL	2	7 mL (14 mL total)	13.5 mL

[a] Volume withdrawn includes Luer lock applicator hold-up volume.

Instructions for preparation and administration

For operating room preparation, it is recommended that a 2-person team prepares this product: one sterile (shown in blue) and one non-sterile (shown in green).

1. Prepare components



STERILE

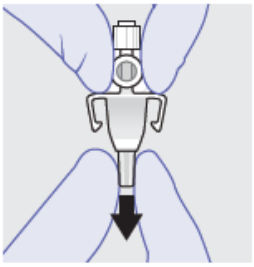
Open all components onto sterile field.
Note: Prepare all syringe(s) provided in kit.
Do not substitute any of the components.

2. Prepare vial

NON-STERILE

A) Flip cap off of vial and place onto stable non-sterile surface.
B) Cleanse septum with alcohol wipe.
C) Hold the vial in place for the sterile person to safely insert the vented vial spike.
Do not remove the stopper or attempt to pour the vial contents.

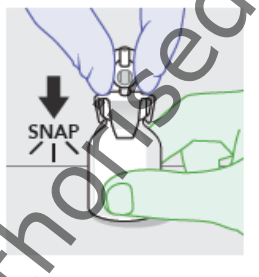
3. Remove protective sheath



STERILE

A) Remove blue protective sheath from vented vial spike.
B) Remove Luer cap.

4. Attach vented vial spike



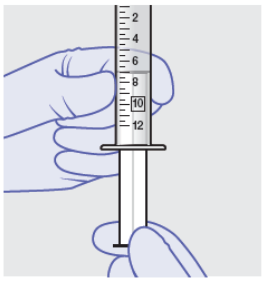
STERILE

Push the spike through the septum of the vial until it "snaps" into place.
Hold the vented vial spike by the adapter neck to maintain sterility of the vented vial spike and sterile person.

NON-STERILE

Hold the vial in place while sterile person attaches spike.
Note: It is recommended to do this on a firm, flat surface.

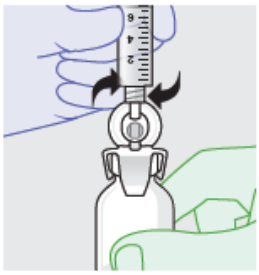
5. Prepare syringe



STERILE

Fill the syringe with the same amount of air as the amount of product you plan to withdraw. Air from syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial.

6. Prepare for withdrawal



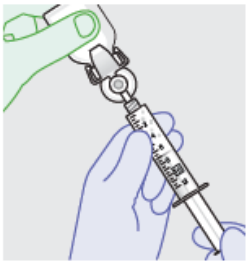
STERILE

Attach the air-filled syringe to the vented vial spike.
Note: Avoid pushing or pumping the plunger rod up and down at any point in the withdrawal process.

NON-STERILE

Hold the vial in place until the syringe is attached.

7. Withdraw product



STERILE

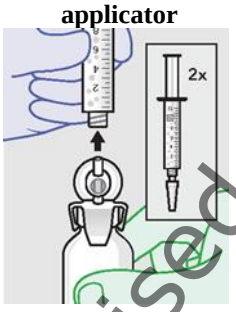
A) Invert the vial using the syringe.
B) Allow product to fill the neck of the vial.
C) Push air into vial and wait for the air bubble to rise.
D) Withdraw the product into the syringe. It is normal for there to be small air bubbles in the syringe.

Note: Product is very thick. It may take a few minutes to withdraw.

NON-STERILE

You may assist the sterile person with inverting the vial if necessary by holding the non-sterile vial.

8. Attach Luer lock applicator



STERILE

A) Return vial to non-sterile surface.
B) Remove syringe from vial and attach Luer lock applicator.
C) Place syringe on sterile surface.
D) (if needed) Repeat steps 5-8 with second syringe.

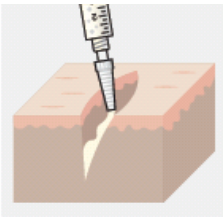
NON-STERILE

Hold the vial in place for attachment of second syringe, if needed.

This medicinal product should only be prepared immediately prior to use. This medicinal product cannot be prepared and stored in advance of use.

Administration Instructions – This information should be reviewed before using the medicinal product for the first time. Zynrelef should only be administered with the syringe and Luer lock applicator provided in the procedure pack.

1. Zynrelef is applied without a needle into the surgical site following final irrigation and suction and prior to suturing. Only apply Zynrelef after final irrigation and suction of each layer before closing, if multiple tissue layers are involved.
2. Using the Luer lock applicator attached to the syringe, apply Zynrelef to the tissues within the surgical site that could result in pain generation.
3. Use a sufficient amount to coat the tissues. For small spaces, ensure there is not an excess that could be expressed from the site during closure. Wipe off excess Zynrelef from the skin prior to or during closure of the wound. Wipe off excess Zynrelef from the skin prior to or during closure of the wound.



4. Only apply Zynrelef to the tissue layers below the skin incision and not directly onto the skin.
5. The amount of Zynrelef required depends upon the surgical area of tissue to be treated. The maximum total dose volume is approximately 14 mL. Zynrelef spreads easily and covers a large area.
6. Zynrelef does not degrade sutures. When tying knots with monofilament sutures, contact with Zynrelef may cause knots to loosen or untie due to the viscosity of Zynrelef. Minimise administration of Zynrelef near the incision line and wipe off excess Zynrelef from the skin prior to suturing. Three or more knots ending in a multi-throw knot (e.g. a Surgeon's knot) are recommended with monofilament sutures. Consider braided or barbed sutures, especially for closure of deeper layers.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ANNEX IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for bupivacaine/meloxicam, the scientific conclusions of CHMP are as follows:

In view of available data about the use of bupivacaine / meloxicam during lactation, based on the results of study HTX-011-220 (showing that bupivacaine / meloxicam is excreted in breastmilk for 6-8 days), and information about use during pregnancy, based on the PRAC advice for NSAID-containing medicinal products (EMA/CMDh/642745/2022), the PRAC considers that the product information should be strengthened accordingly. The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for bupivacaine/meloxicam the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing bupivacaine/meloxicam is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.