SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

EXPAREL liposomal 133 mg/10 mL prolonged-release dispersion for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 13.3 mg bupivacaine in a multivesicular liposomal dispersion.

Each vial of 10 mL prolonged-release dispersion for injection contains 133 mg bupivacaine.

Excipient(s) with known effect

Each 10 mL vial contains 21 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release dispersion for injection.

White to off-white aqueous liposomal dispersion.

The dispersion has a pH between 5.8 and 7.8 and is isotonic (260 - 330 mOsm/kg).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EXPAREL liposomal is indicated (see section 5.1):

- in adults as a brachial plexus block or femoral nerve block for treatment of post-operative pain;

- in adults and children aged 6 years or older as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds.

4.2 Posology and method of administration

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

Posology

The recommended dose of EXPAREL liposomal in adults and children aged 6 years or older is based on the following factors:

- Size of the surgical site
- Volume required to cover the area
- Individual patient factors

A maximum dosage of 266 mg (20 mL of undiluted medicinal product) must not be exceeded.

Field block (infiltration around small- to medium-sized surgical wounds)

- In patients undergoing bunionectomy, a total of 106 mg (8 mL) of EXPAREL liposomal was administered, with 7 mL infiltrated into the tissues surrounding the osteotomy and 1 mL infiltrated into the subcutaneous tissue.

- In patients undergoing haemorrhoidectomy, a total of 266 mg (20 mL) of EXPAREL liposomal was diluted with 10 mL of normal saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

- In paediatric patients aged 6 years and older, EXPAREL liposomal should be administered at a dose of 4 mg/kg (maximum not to exceed 266 mg). EXPAREL liposomal may be either administered ‘as is’ or expanded with normal (0.9%) saline to increase the volume up to a final concentration of 0.89 mg/mL (i.e., 1:14 dilution by volume). The total volume of expansion will be dependent on the incision length. Examples are given in section 6.6.

Peripheral nerve block (femoral and brachial plexus)

- In patients undergoing total knee arthroplasty (TKA), a total of 266 mg (20 mL) of EXPAREL liposomal was administered as a femoral nerve block.

- In patients undergoing total shoulder arthroplasty or rotator cuff repair, a total of 133 mg (10 mL) of EXPAREL liposomal was diluted with 10 mL of normal saline, for a total volume of 20 mL, was administered as a brachial plexus nerve block.

Co-administration with other local anaesthetics

The toxic effects of local anaesthetics are additive and their co-administration, taking into account the dose of local anaesthetic and the extended pharmacokinetic profile of EXPAREL liposomal, should be used with caution including monitoring for neurologic and cardiovascular effects related to local anaesthetic systemic toxicity. See section 4.5.

EXPAREL liposomal is a liposomal preparation and should not be used interchangeably with any other formulations of bupivacaine. Bupivacaine hydrochloride (immediate release formulations) and EXPAREL liposomal may be administered simultaneously in the same syringe as long as the ratio of the milligram dose of bupivacaine solution to EXPAREL liposomal does not exceed 1:2. If preparing admixture, the total amount of bupivacaine used (EXPAREL liposomal + bupivacaine HCl) should not exceed 400 mg equivalents of bupivacaine HCl in adults. For more information, see section 4.4.

Special populations

Elderly patients (65 years of age or older)

Care should be taken in dose selection of EXPAREL liposomal in elderly patients because bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. No dosage adjustment is required; however, greater sensitivity of some older individuals cannot be ruled out (see sections 5.1 and 5.2).

The risk of falls may increase for the elderly patients.

Renal impairment

Bupivacaine or its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Impaired renal function should be considered when performing dose selection of EXPAREL liposomal (see sections 4.4 and 5.2).

Hepatic impairment

Bupivacaine is metabolized by the liver. No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5-6) or moderate hepatic impairment (Child Pugh score 7-9). There are insufficient data to recommend the use of EXPAREL liposomal in patients with severe (Child-Pugh score $\geq$10) hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of EXPAREL liposomal have not yet been established for administration as a field block in children aged 1 to less than 6 years of age, nor as a nerve block in children aged 1 to less than 18 years of age. No data are available.

EXPAREL liposomal should not be used in children aged less than 1 year of age because neonates and infants have a decreased ability to metabolize anaesthetics due to an immature hepatic system.

Method of administration

EXPAREL liposomal is for administration by infiltration or perineural use only.

EXPAREL liposomal is intended for single-dose administration only.

EXPAREL liposomal should be injected slowly (generally 1 to 2 mL per injection) with frequent aspiration, when clinically appropriate, to check for blood and minimize the risk of inadvertent intravascular injection.

EXPAREL liposomal is to be administered with a 25 gauge or larger bore needle to maintain the structural integrity of the liposomal bupivacaine particles.

For instructions on the preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to local anaesthetic medicinal products of the amide type.
- Obstetrical paracervical block anaesthesia due to risk of foetal bradycardia or death.
- Intravascular administration.
- Intraarticular administration (see section 4.4).

4.4 Special warnings and precautions for use

Efficacy and safety have not been established in major abdominal, vascular and thoracic 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.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of bupivacaine. Restlessness, anxiety, incoherent speech, light headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Toxic local anaesthetic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmia, and cardiac arrest, which can be fatal. In addition, toxic local anaesthetic blood concentrations depress myocardial contractility and cause peripheral vasodilation, leading to decreased cardiac output and arterial blood pressure.

Acute emergencies due to neurological or cardiovascular toxicity from local anaesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anaesthetics or due to unintended intravascular injection of local anaesthetic solution (see sections 4.3 and 4.9).

Injection of multiple doses of bupivacaine and other amide-containing products may cause significant increases in plasma concentrations with each repeated dose due to slow accumulation of the active substance or its metabolites or due to slow metabolic degradation. Tolerance to elevated blood concentrations varies with the status of the patient.

Potential cases of LAST have been observed in the post-marketing setting. Although the majority with a recorded time to onset were observed within less than 1 hour of EXPAREL liposomal administration, a small number with a time to onset greater than 24 hours was reported. No correlation of cases of potential LAST with surgical procedure or route of administration has been found with EXPAREL liposomal, but redosing of EXPAREL liposomal, overdose, or concomitant use with other local anaesthetics may increase the risk of LAST (see section 4.5).

Neurologic effects

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitation may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may include nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anaesthetics varies with the procedure used and the total dose administered.

Neurologic effects following field block may include persistent anaesthesia, paraesthesias, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Cardiovascular function impairment

Bupivacaine should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of atrioventricular conduction produced by these medicinal products.

Hepatic impairment

Bupivacaine is metabolised by the liver, so it should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations because of their inability to metabolise local anaesthetics normally. Increased monitoring for local anaesthetic systemic toxicity should be considered in subjects with moderate to severe hepatic disease (see sections 4.2 and 5.2).

Renal impairment

Only 6% of bupivacaine is excreted unchanged in the urine. Bupivacaine metabolites are known to be extensively excreted by the kidney. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Acidifying the urine hastens the renal elimination of local anaesthetics. Various pharmacokinetic parameters of local anaesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow. Thus, the risk of toxic reactions to this medicinal product may be greater in patients with impaired renal function.

Allergic reactions

Allergic-type reactions may rarely occur as a result of hypersensitivity to the local anaesthetic or to other formulation ingredients. These reactions are characterised by

signs such as urticaria, pruritus, erythema, angioneurotic oedema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anaesthetic group has been reported. Allergic symptoms should be treated symptomatically.

Chondrolysis

Intra-articular infusions of local anaesthetics, including EXPAREL liposomal, following arthroscopic and other surgical procedures are contraindicated (see section 4.3). There have been post-marketing reports of chondrolysis in patients receiving such infusions.

Methaemoglobinaemia

Cases of methaemoglobinaemia have been reported in association with local anaesthetic use. Although all patients are at risk for methaemoglobinaemia, infants under 6 months of age and patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methaemoglobinaemia, cardiac or pulmonary compromise, or concurrent exposure to oxidizing agents or their metabolites (see section 4.5) are more susceptible to developing clinical manifestations of the condition. If local anaesthetics must be used in these patients, close monitoring for symptoms and signs of methaemoglobinaemia is recommended.

Signs and symptoms of methaemoglobinaemia may occur immediately or may be delayed some hours after exposure and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methaemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse reactions, including seizures, coma, arrhythmias, and death. Bupivacaine should be discontinued as well as any other oxidizing medicinal product. Depending on the severity of the symptoms, patients may respond to supportive care (i.e. oxygen therapy, hydration). More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Warnings and precautions specific to EXPAREL liposomal

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL liposomal and vice versa. No substitution with other bupivacaine containing products should be made.

Caution is advised when co-administering EXPAREL liposomal and bupivacaine HCl, particularly when administering to highly vascular areas where higher systemic absorption is expected. Admixing of EXPAREL with other local anaesthetics has not been studied in children and is not recommended.

Using EXPAREL liposomal followed by other bupivacaine formulations has not been studied in clinical trials. However, based on the clinical situation, bupivacaine hydrochloride may be administered, taking into account the relevant PK profiles and individual patient considerations. As with all local anaesthetics, physicians need to evaluate local anaesthetic systemic toxicity risk based on total dose with respect to time of administration.

EXPAREL liposomal has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration:

- epidural
- intrathecal

EXPAREL liposomal is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan (see section 4.7). Sensory and/or motor loss may occur with EXPAREL liposomal use, however, this is temporary and degree of loss and duration varies depending on the site of injection and dosage administered. As seen during clinical trials, any temporary sensory and/or motor loss may last for up to 5 days.

Excipients with known effect

Sodium

This medicinal product contains 21 mg sodium per 10 mL vial, equivalent to 1.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Use of EXPAREL liposomal with other local anaesthetics

The addition of local anaesthetics administered within 96 hours following administration of EXPAREL liposomal should take into account the total bupivacaine exposure.

EXPAREL liposomal 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.

Other bupivacaine products

The impact on pharmacokinetic and/or physicochemical properties of EXPAREL liposomal when it is co-administered with bupivacaine HCl is concentration dependent. Therefore, bupivacaine HCl can be administered simultaneously in the same syringe as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL liposomal does not exceed 1:2. The total amount of bupivacaine HCl and

EXPAREL liposomal being co-administered should not exceed 400 mg equivalents of bupivacaine HCl in adults (see sections 4.4 and 6.6).

Non-bupivacaine local anaesthetics

EXPAREL liposomal should only be admixed with bupivacaine as admixing with either lidocaine, ropivacaine or mepivacaine has been shown to cause an immediate release of bupivacaine from the multivesicular liposomes of the medicine delivery system. When EXPAREL liposomal is admixed with lidocaine, lidocaine binds to the liposomes, leading to an immediate displacement and release of bupivacaine. This displacement can be prevented by ensuring that EXPAREL liposomal is administered at least 20 minutes after administering lidocaine. There are no data to support administration of other local anaesthetics prior to administration of EXPAREL liposomal.

Oxidizing medicinal products

Patients that are administered local anaesthetics may be at increased risk of developing methaemoglobinamia when concurrently exposed to the following oxidizing medicinal products:

- Nitrates/Nitrites - nitroglycerin, nitroprusside, nitric oxide, nitrous oxide
- Local anaesthetics - benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine, ropivacaine
- Antineoplastic medicinal products - cyclophosphamide, flutamide, rasburicase, isofamide, hydroxyurea
- Antibiotics - dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid
- Antimalarials - chloroquine, primaquine
- Anticonvulsants - phenytoin, sodium valproate, phenobarbital
- Other medicinal products - acetaminophen, metoclopramide, sulfa medicines (e,g., sulfasalazine), quinine

Other medicinal products

When a topical antiseptic, such as povidone iodine, is applied, the site should be allowed to dry before EXPAREL liposomal is administered into the site. EXPAREL liposomal should not be allowed to come into contact with antiseptics such as povidone iodine in solution (see also section 6.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of bupivacaine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

EXPAREL liposomal is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

Bupivacaine and its metabolite, pipecoloxylidide, are present in human milk at low levels. There is no available information on effects of the medicinal product in the breastfed infant or effects of the medicinal product on milk production. Because of the potential for serious adverse reactions in breastfed infants a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from EXPAREL liposomal therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of EXPAREL liposomal on fertility.

4.7 Effects on ability to drive and use machines

Bupivacaine could have a major influence on the ability to drive and use machines. Patients should be informed in advance that bupivacaine liposomal dispersion can cause temporary loss of sensation or motor function. The potential sensory and/or motor loss with EXPAREL liposomal is temporary and varies in degree and duration depending on the site of injection, route of administration (i.e. field block or nerve block) and dosage administered, and may last for up to 5 days as seen in clinical trials.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (≥ 5%) associated with EXPAREL liposomal in clinical trials were dysgeusia (6.0%) and hypoaesthesia oral (6.5%).

The most important serious adverse reactions associated with EXPAREL liposomal were systemic toxic reactions. Systemic toxic reactions usually present shortly after administration of bupivacaine but may be delayed in some cases. Severe central nervous system toxicity due to EXPAREL liposomal may result in convulsions

(< 0.001% from post-marketing data). Severe cardiac toxicity due to EXPAREL liposomal may result in serious dysrhythmia (0.7% in clinical trials), serious hypotension (0.7% in clinical trials), and/or cardiac arrest (< 0.001% from post-marketing data).

Tabulated list of adverse reactions in adults

The adverse reactions associated with EXPAREL liposomal in adults from clinical trials and post-marketing surveillance are presented below in Table 1 according to the MedDRA System Organ Classification and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000) and frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Table of adverse drug reactions (ADRs) in adults

System organ class	Frequency	Adverse drug reactions
Immune system disorders	Not known	Hypersensitivity
Psychiatric disorders	Rare	Confusional state, anxiety
Nervous system disorders	Common	Dysgeusia
	Uncommon	Motor dysfunction, sensory loss, dizziness, somnolence, hypoaesthesia, burning sensation, headache
	Rare	Syncope, monoplegia, presyncope, lethargy
	Not known	Seizure, palsy
Eye disorders	Rare	Visual impairment, vision blurred
Ear and labyrinth disorders	Rare	Diplacusis
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Rare	Atrial fibrillation, tachyarrhythmia, sinus tachycardia
	Not known	Cardiac arrest
Vascular disorders	Uncommon	Hypotension
	Rare	Hypertension, flushing
Respiratory, thoracic, and mediastinal disorders	Rare	Apnoea, hypoxia, atelectasis, dyspnoea, oropharyngeal pain
Gastrointestinal disorders	Common	Vomiting, constipation, hypoaesthesia oral, nausea
	Rare	Haematochezia, dysphagia, abdominal distension, abdominal discomfort, abdominal pain upper, diarrhoea, salivary hypersecretion, dry mouth, dyspepsia, oral pruritus, paraesthesia oral
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, pruritus generalised, pruritus, skin irritation
	Rare	Drug eruption, hyperhidrosis, erythema, rash, nail discolouration
Musculoskeletal and connective tissue disorders	Uncommon	Mobility decreased, muscular weakness, muscle spasms, muscle twitching, arthralgia
	Rare	Joint swelling, groin pain, joint stiffness, musculoskeletal chest pain, pain in extremity
Renal and urinary disorders	Not known	Urinary retention
General disorders and administration site conditions	Uncommon	Pyrexia
	Rare	Peripheral swelling, non-cardiac chest pain, chills, feeling hot, injection site pain, pain

System organ class	Frequency	Adverse drug reactions
	Not known	Lack of efficacy
Investigations	Uncommon	Blood creatinine increased, alanine aminotransferase increased, aspartate aminotransferase increased
	Rare	Electrocardiogram ST segment elevation, hepatic enzyme increased, white blood cell count increased
Injury, poisoning, and procedural complications	Uncommon	Contusion, post procedural oedema, fall
	Rare	Muscle injury, seroma, wound complication, incision site erythema, procedural pain
	Not known	Local anaesthetic systemic toxicity (LAST)

Tabulated list of adverse reactions in the paediatric population

Adverse reactions associated with EXPAREL liposomal in paediatrics from clinical trials and post-marketing surveillance are presented below in Table 2 according to the MedDRA System Organ Classification and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000) and frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Table of adverse drug reactions (ADRs) in children

System organ class	Frequency	Adverse drug reactions
Blood and lymphatic system disorders	Very common	Anaemia
Immune system disorders	Common	Hypersensitivity
Psychiatric disorders	Common	Anxiety
Nervous system disorders	Common	Hypoaesthesia, paraesthesia, burning sensation, dizziness, dysgeusia and syncope
	Not known	Somnolence
Eye disorders	Common	Visual impairment, vision blurred
Ear and labyrinth disorders	Common	Hypoacusis
Cardiac disorders	Very common	Tachycardia
	Common	Bradycardia
Vascular disorders	Very common	Hypotension
	Common	Hypertension
Respiratory, thoracic, and mediastinal disorders	Common	Dyspnoea, tachypnoea
Gastrointestinal disorders	Very common	Vomiting, constipation, nausea
	Common	Abdominal pain, diarrhoea, hypoaesthesia oral, dyspepsia
Skin and subcutaneous tissue disorders	Very common	Pruritus
	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Muscle twitching
	Common	Musculoskeletal chest pain, pain in extremity, muscular weakness, muscle spasms
General disorders and administration site conditions	Common	Chest pain, pyrexia
Injury, poisoning, and	Common	Delayed recovery from anaesthesia,

System organ class	Frequency	Adverse drug reactions
procedural complications		seroma, fall
	Not known	Local anaesthetic systemic toxicity (LAST)

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Rare reports of overdose with EXPAREL liposomal alone or in combination with another local anaesthetic have been received. Systemic toxic reactions, primarily involving the central nervous system and the cardiovascular system may occur following high blood concentrations of local anaesthetics. Approximately 30% of overdose reports were associated with adverse reactions.

Signs and symptoms of overdose may include CNS symptoms (perioral paraesthesia, dizziness, dysarthria, confusion, mental obtundation, sensory and visual disturbances, and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia, and asystole).

Management of overdose

At the first sign of local anaesthetic overdose, oxygen should be administered.

The first step in the management of convulsions, as well as hypoventilation 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. 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, dysrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation employing medicinal products 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.

Lipid emulsion has been used to treat some cases of overdose in the post-marketing setting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, amides, ATC code: N01BB01

Mechanism of action

Bupivacaine is related chemically and pharmacologically to the amide-type local anaesthetics. It is a homologue of mepivacaine and is related chemically to lidocaine.

Local anaesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.

Pharmacodynamic effects

Systemic absorption of local anaesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with normal therapeutic doses and route of administration, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic local anaesthetic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, which can be fatal. In addition, toxic local anaesthetic blood concentrations depress myocardial contractility and cause peripheral vasodilation, leading to decreased cardiac output and arterial blood pressure.

Plasma levels of bupivacaine associated with toxicity can vary. Although concentrations of 2,000 to 4,000 ng/mL have been reported to elicit early subjective CNS symptoms of bupivacaine toxicity, symptoms of toxicity have been reported at levels as low as 800 ng/mL.

Clinical efficacy and safety

Clinical studies confirming efficacy

The efficacy of EXPAREL liposomal was evaluated in four double-blind, controlled trials involving 703 patients with moderate-to-severe acute pain (pain intensity of ≥ 4 on a 0-10 scale). Acute pain was assessed for 24 hours after bunionectomy, 48 hours after total shoulder arthroplasty/rotator cuff repair and 72 hours after haemorrhoidectomy and total knee arthroplasty. Of the 703 patients, 352 received EXPAREL liposomal treatment, 351 received placebo. Patients were of appropriate sex to the type of surgery (men/women ratio 329/374), mean age was 53.4 years (range 18-88 years [23.2% (n = 163) are ≥ 65 years, and 6.3% (n = 44) are ≥ 75 years (i.e. elderly)], BMI 27.9 kg/m^2 (range 18.7-43.9), race was predominately White (82.9%). Primary endpoint for all pivotal studies was area under the curve (AUC) of pain intensity score. Rescue pain therapy was available in all studies and was tailored to surgical type and the clinical practice at the time of study conduct.

Table 3 Summary of key pain endpoint results in Phase 3 studies

Study / Surgery Type	EXPAREL liposomal Dose (n) / Control (n)	Primary Endpoint	Treatment Difference (95% CI)	P-value[a]
Summary of key pain endpoint results in local analgesia studies				
Field Block / Haemorrhoidectomy	266 mg (94) / Placebo (93)	AUC NRS-R_{0-72}	-61 (-90, -31)	<0.0001
Field Block / Bunionectomy	106 mg (97) / Placebo (96)	AUC NRS-R_{0-24}	-22 (-35, -10)	0.0005
Summary of key pain endpoint results in regional analgesia studies				
Femoral Nerve Block / TKA[b]	266 mg (92) / Placebo (91)	AUC NRS-R_{0-72}	-96.5 (-144, -49)	<0.0001
Brachial Plexus Nerve Block / TSA/RCR	133 mg (69) / Placebo (71)	AUC VAS_{0-48}	-118 (-151, -84)	<0.0001

[a]: non-inferiority p-value; b: TKA study was a combined Phase 2 (Part 1) and Phase 3 (Part 2) study; only Phase 3 results are displayed here.

AUC: area under the curve; NRS-R: numeric rating scale at rest; TKA: total knee arthroplasty; VAS: visual analogue scale; TSA: total shoulder arthroplasty; RCR: rotator cuff repair; (n): number of subjects.

Table 4 Summary of key opioid endpoint results in Phase 3 studies

Block Type / Surgery Type	EXPAREL liposomal Dose / Control	Opioid Rescue Medication Use	Opioid-free Subjects
Summary of key opioid related endpoint results in local analgesia studies			
Field Block / Haemorrhoidectomy	266 mg / Placebo	Geometric LS mean: 9.9 vs 18.2 MME (45% reduction in geometric LS mean ratio through 72 hours; p=0.0006)	Opioid free through 72 hours: (26/94) in EXPAREL liposomal arm vs (9/93) in placebo arm (p=0.0007)
Field Block / Bunionectomy	106 mg / Placebo	LS mean 3.8 vs 4.7 tablets (19% reduction in	Opioid free through 24 hours: (7/97) in

Block Type / Surgery Type	EXPAREL liposomal Dose / Control	Opioid Rescue Medication Use	Opioid-free Subjects
		the mean number of Percocet tablets (5 mg oxycodone / 325 mg paracetamol) used through 24 hours; p=0.0077)	EXPAREL liposomal arm vs (1/96) in placebo arm (p=0.040)
Summary of key opioid related endpoint results in regional analgesia studies			
Femoral Nerve Block[a]/ TKA	266 mg / Placebo	Geometric LS mean: 93.2 vs 122.1 MME (26% reduction in geometric LS mean ratio through 72 hours; p=0.0016)	No subjects opioid free at 72 hours in either group
Brachial Plexus Nerve Block / TSA/RCR	133 mg / Placebo	LS mean: 25.0 vs 109.7 MME (77% reduction in geometric LS mean ratio through 48 hours; p<0.0001)	Opioid free at 48 hours: (9/69) in EXPAREL liposomal arm vs (1/71) in placebo arm (p=0.008)

[a]: TKA study was a combined Phase 2 (Part 1) and Phase 3 (Part 2) study.
TKA: total knee arthroplasty; TSA: total shoulder arthroplasty; RCR: rotator cuff repair;
MME = Methods-of-Moments; LS = Least square.

Of the 1645 patients in the EXPAREL liposomal field block and peripheral nerve block clinical studies, 469 patients were 65 years of age or older and 122 patients were 75 years of age or older.

The safety and pharmacokinetics of EXPAREL when used as a field block in paediatric patients aged 6 years and older is supported by data from study 319, a Phase 3, open-label, multi-centre study to evaluate EXPAREL when administered via infiltration in paediatric subjects aged 12 to less than 17 years undergoing spine surgery (Group 1, n=61) and in paediatric subjects aged 6 to less than 12 years undergoing spine surgery or cardiac surgery (Group 2, n=34). In Group 1, subjects were randomized 1:1 to receive a single dose of either EXPAREL 4 mg/kg (maximum 266 mg) or bupivacaine HCl 2 mg/kg (maximum 175 mg). In Group 2, all subjects received a single dose of EXPAREL 4 mg/kg (maximum 266 mg). The primary objective of the study was to evaluate the pharmacokinetics of EXPAREL in children 6 years and older.

5.2 Pharmacokinetic properties

EXPAREL liposomal is bupivacaine encapsulated in the multivesicular liposomal drug delivery system. Upon administration, bupivacaine is slowly released from the liposomes over an extended period of time.

Absorption

Administration of EXPAREL liposomal results in detectable systemic plasma levels of bupivacaine through 96 hours after local infiltration and through 120 hours after nerve block. In general, peripheral nerve blocks have shown systemic plasma levels of bupivacaine for extended duration when compared to local infiltration. Systemic plasma levels of bupivacaine following administration of EXPAREL liposomal are not correlated with local efficacy. The rate of systemic absorption of bupivacaine is dependent upon the total dose of medicine administered, the route of administration, and the vascularity of the administration site.

Descriptive statistics of pharmacokinetic parameters of representative EXPAREL liposomal doses in field block and peripheral nerve block in adults are provided in Table 5 and Table 6, respectively.

Table 5 Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL liposomal via Field Block in Adults

Parameters	**Surgical Site Administration**	
	Bunionectomy 106 mg (8 mL)	**Hemorrhoidectomy 266 mg (20 mL)**
	(N=26)	**(N=25)**
C_{max} (ng/mL)	166 (92.7)	867 (353)
T_{max} (h)	2 (0.5-24)	0.5 (0.25-36)
$AUC_{(0-t)}$ (h•ng/mL)	5864 (2038)	16,867 (7868)
$AUC_{(inf)}$ (h•ng/mL)	7105 (2283)	18,289 (7569)
$t_{½}$ (h)	34 (17)	24 (39)

AUC_{0-t} = the area under the plasma concentration-versus-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf} = the area under the plasma concentration-versus-time curve from time 0 extrapolated to infinity;
C_{max} = maximum plasma concentration; T_{max} = time to reach C_{max}; $t_{1/2}$ = apparent terminal elimination half-life.

Table 6 Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL liposomal via Peripheral Nerve Block in Adults

Parameters	Peripheral Nerve Block (Surgery)			
	Femoral Nerve Block (Total Knee Arthroplasty)		Brachial Plexus Nerve block (Total Shoulder Arthroplasty)	
	133 mg (10 mL)	266 mg (20 mL)	133 mg (10 mL)	266 mg (20 mL)
	(N = 19)	(N = 21)	(N = 32)	(N = 32)
C_{max} (ng/mL)	282 (127)	577 (289)	209.35 (121)	460.93 (188)
T_{max} (h)	72	72	48	49
$AUC_{(0-t)}$ (h•ng/mL)	11,878 (7,870)	22,099 (11,137)	11426.28 (7855)	28669.07 (13205)
$AUC_{(inf)}$ (h•ng/mL)	18,452 (12,092)	34,491 (5,297)	12654.57 (8031)	28774.03 (13275)
$t_{½}$ (h)	29.0 (24)	18.2 (6.)	11 (4)	15 (6)

AUC_{0-t} = the area under the plasma concentration-versus-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf} = the area under the plasma concentration-versus-time curve from time 0 extrapolated to infinity;
C_{max} = maximum plasma concentration; T_{max} = time to reach C_{max}; $t_{1/2}$ = apparent terminal elimination half-life.

Distribution

With EXPAREL liposomal, bupivacaine is released from the liposomal matrix by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time. After bupivacaine has been released from EXPAREL liposomal and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation.

Bupivacaine is distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. The rate and degree of diffusion is governed by the degree of plasma protein binding, the degree of ionization, and the degree of lipid solubility. Bupivacaine has a high protein binding capacity (95%) predominantly to α1-acid glycoprotein and also albumin at higher concentrations. The plasma protein binding of bupivacaine is concentration-dependent. A hepatic extraction ratio of 0.37 has been reported for bupivacaine in the literature after IV administration. A volume of distribution at steady state of 73 l has been reported for bupivacaine.

Metabolism

Amide-type local anaesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Bupivacaine is extensively metabolised as evidenced by the minimal amount of parent drug in the urine. Pipecolylxylidine (PPX) is the major metabolite of bupivacaine; approximately 5% of bupivacaine is converted to PPX. The primary liver enzyme in formation of PPX was shown to be CYP3A4 using liver microsomes, although CYP2C19 and CYP2D6 may play a minor

role. Hydroxylation of the aromatic ring is also a principal route of metabolism resulting in minor metabolites. It is presumed that lipid components of the liposome undergo similar metabolism pathway as the naturally occurring lipids.

Elimination

The kidney is the main excretory organ for most local anaesthetics and their metabolites. Only 6% of bupivacaine is excreted unchanged in the urine. Various pharmacokinetic parameters of the local anaesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow. Based on this knowledge, clinicians should practice caution when administering any local anaesthetics in patients with renal disease, including EXPAREL liposomal. From population pharmacokinetics models based on EXPAREL liposomal clinical studies, apparent clearance ranges from 22.9 L/h for wound infiltration studies to 10.6 L/h in regional analgesia, and due to the flip-flop kinetics it reflects the rate of absorption.

Special populations

Paediatric population

The pharmacokinetic profiles of bupivacaine after administration of EXPAREL as a single-dose field block were similar in paediatric and adult subjects in matching surgical procedures. The summary of bupivacaine pharmacokinetic parameters when EXPAREL administered as a field block in spinal or cardiothoracic procedures in paediatric patients aged 6 years or older is given in Table 7.

Table 7 Summary of Bupivacaine Pharmacokinetic Parameters with EXPAREL and Bupivacaine HCl

Study No.	**Population**	**Study Drug (Dose)**	**Global Cmax (ng/mL)**	**Global Tmax(h)**	**AUC (0-t) (ng*h/mL)**	**AUC (0-inf) (ng*h/mL)**
			Mean (SD)	**Median (min, max)**	**Mean (SD)**	**Mean (SD)**
Spinal Procedures						
319	Group 1: 12 to <17 years (N=16)	EXPAREL 4 mg/kg	357 (121)	1.1 (0.3, 26.1)	9,043 (3,763)	14,246 (9,119)
	Group 1: 12 to <17 years (N=15)	Bupivacaine 2 mg/kg	564 (321)	0.9 (0.3, 2.5)	5,233 (2,538)	5,709 (3,282)
	Group 2: 6 to <12 years (N=2)	EXPAREL 4 mg/kg	320 (165)	7.4 (2.4, 12.3)	10,250 (5,957)	11,570 (7,307)
Cardiothoracic procedures						
319	Group 2: 6 to <12 years (N=21)	EXPAREL 4 mg/kg	447 (243)	22.7 (0.2, 54.5)	16,776 (7,936)	26,164 (28,038)

Elderly

In population pharmacokinetic models based on nerve block and wound infiltration clinical studies, approximately 29% decrease in clearance was observed in elderly patients which was not considered clinically relevant.

Hepatic impairment

Various pharmacokinetic parameters of the local anaesthetics can be significantly altered by the presence of hepatic disease. A study of EXPAREL liposomal administration in patients with mild to moderate hepatic disease found that dosage adjustment in these patients is not required. However, based on what is known about amid-type local anaesthetics such as bupivacaine, clinicians should consider that patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anaesthetics.

Renal impairment

Population PK analysis on clinical trial data for EXPAREL liposomal in nerve block settings showed no effect of mild or moderate renal impairment. EXPAREL liposomal was not studied in subjects with severe renal impairment.

Population pharmacokinetics

Based on the population PK analysis for peripheral nerve block, age, sex, body weight and race had no clinically meaningful effect on EXPAREL liposomal pharmacokinetics.

5.3 Preclinical safety data

Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine have not been conducted. The mutagenic potential of bupivacaine has not been determined.

Bupivacaine crosses the placenta. Bupivacaine produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. An increase in embryo-foetal deaths in rabbits and decreased survival of the offspring in rats was observed. The effect on fertility of bupivacaine has not been determined.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dierucoylphosphatidylcholine (DEPC)

Dipalmitoylphosphatidylglycerol (DPPG)

Cholesterol for parenteral use

Tricaprylin

Sodium chloride

Phosphoric acid

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

EXPAREL liposomal must not be diluted with water or other hypotonic agents as it will result in disruption of the liposomal particles.

Topical antiseptics, such as povidone-iodine, demonstrated a strong interaction with EXPAREL liposomal when the solutions are admixed. This is due to the surface-active nature of antiseptics interacting with lipids. However, if topical antiseptics are applied to the skin surface and allowed to dry prior to local administration of EXPAREL liposomal, no interactions are expected in normal clinical practice (see section 4.5).

6.3 Shelf life

Unopened vials: 2 years.

<u>After first opening</u>

Chemical and physical in-use stability of EXPAREL liposomal withdrawn from vials and transferred into polypropylene syringes has been demonstrated for 48 hours when stored in a refrigerator (2°C to 8°C), or 6 hours when stored at room temperature (below 25°C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C unless opening has taken place in controlled and validated aseptic conditions.

<u>After dilution</u>

Chemical and physical in-use stability of EXPAREL liposomal when admixed with other formulations of bupivacaine has been demonstrated for 24 hours at room temperature (below 25°C). When admixed with 9 mg/mL (0.9%) sodium chloride or lactated Ringer's solution, chemical and physical in-use stability has been demonstrated for 4 hours when stored in a refrigerator (2°C to 8°C) and at room temperature (below 25°C). From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened vials: Store in a refrigerator (2°C to 8°C). Do not freeze.

Unopened vials may also be stored at room temperature (below 25°C) for up to 30 days. Vials should not be re-refrigerated.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL or 20 mL, single-use Type I glass vials with an ethylenetetrafluoroethylene-faced grey butyl rubber stopper, and an aluminium/polypropylene flip-tear-up seal.

Available in packs of 4 or 10 vials.

6.6 Special precautions for disposal

EXPAREL liposomal vials are intended for single use only.

EXPAREL liposomal vials should be visually inspected prior to administration. They should be gently inverted multiple times to re-suspend the particles in the dispersion immediately prior to withdrawal from the vial.

EXPAREL liposomal should be administered with a 25 gauge or larger bore needle to maintain the structural integrity of the liposomal bupivacaine particles.

EXPAREL liposomal can be administered in the ready to use dispersion or diluted to a concentration of up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with 9 mg/ml (0.9%) sodium chloride or lactated Ringer's solution.

The median infiltrated volume for spinal procedures in Study 319 (31 cm x 2 sides x 3 layers / 1.5 mL infiltrate every 1 cm) was 124 mL. The median infiltrated volume for cardiac procedures in Study 319 (13 cm x 2 sides x 3 layers / 1.5 mL infiltrate every 1 cm) was 52 mL.

Bupivacaine hydrochloride (immediate release formulations) can be administered simultaneously in the same syringe, as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL liposomal does not exceed 1:2. The total amount of bupivacaine HCl and EXPAREL liposomal being co-administered should not exceed 400 mg equivalents of bupivacaine HCl in adults. Bupivacaine amount in EXPAREL liposomal is expressed as the free base of bupivacaine, thus, when calculating the total dose of bupivacaine for coadministration, the amount of bupivacaine from EXPAREL liposomal should be converted to the equivalent of bupivacaine HCl by multiplying EXPAREL liposomal dose with a factor of 1.128.

If preparing an admixture of EXPAREL liposomal with bupivacaine or saline or both, the order in which the components are combined does not matter.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 34175/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/08/2025

10 DATE OF REVISION OF THE TEXT

15/08/2025