AUSTRALIAN PRODUCT INFORMATION – BUPIVACAINE INJECTION BP and BUPIVACAINE INJECTION (Bupivacaine hydrochloride monohydrate)

NOT FOR INTRAVENOUS ADMINISTRATION UNDER ANY CIRCUMSTANCES

1. NAME OF THE MEDICINE

Bupivacaine hydrochloride monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Bupivacaine Injection contains bupivacaine hydrochloride (as monohydrate) 50 mg or 100 mg.

Each ampoule of Bupivacaine Injection contains bupivacaine hydrochloride (as monohydrate) 50 mg.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Bupivacaine Injection is a sterile, isotonic, preservative-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine Injection is indicated for the production of local or regional anaesthesia and analgesia in individuals as follows:

Surgical anaesthesia

- Epidural block for surgery.
- Field block (minor and major nerve blocks and infiltration).

Analgesia

- Continuous epidural infusion or intermittent bolus epidural administration for analgesia in postoperative pain or labour pain.
- Field block (minor nerve block and infiltration).

The choice of 2 strengths, 0.25% and 0.5%, makes it possible to vary the degree of motor blockade.

4.2 Dose and method of administration

Dosage

As with all local anaesthetics, the dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anaesthesia and degree of muscle relaxation required, individual tolerance, the technique of anaesthesia, and the physical condition of the patient.

The lowest dosage that results in effective anaesthesia should be used. In general, surgical anaesthesia requires the use of higher concentrations and doses than those required for analgesia. The volume of the drug used will affect the extent of spread of anaesthesia.

The presentations of Bupivacaine Injection are intended for single use only. Any solution remaining from an opened container should be discarded.

The following tables are a guide to dosage. The clinician's experience and knowledge of the patient's physical status are of importance in deciding the dose. Experience to date indicates that 400 mg administered over 24 hours is well tolerated in average adults.

The normal recommended dose of plain bupivacaine injections for various anaesthetic procedures in the average, healthy 70 kg adult patient are as follows:

RECOMMENDED DOSAGE FOR SURGICAL ANAESTHESIA

SURGICAL ANAESTHESIA	**Conc mg/mL**	**Dose**	
		mg	**mL**
Lumbar Epidural Abdominal, pelvic and lower limb surgery, including Caesarean section	5.0	75 to 150	15 to 30
Thoracic Epidural	2.5	12.5 to 37.5	5 to 15
Upper abdominal and thoracic surgery	5.0	25 to 50	5 to 10
Caudal Epidural	2.5	37.5 to 100	15 to 40
	5.0	75 to 125	15 to 25
Other Blocks			
Local infiltration	2.5	12.5 to 150	5 to 60
	5.0	25 to 150	5 to 30
Intercostal (per segment)	2.5	10 to 20	4 to 8
	5.0	15 to 25	3 to 5
Brachial plexus	5.0	100 to 150	20 to 30
Sciatic	5.0	50 to 100	10 to 20

SURGICAL ANAESTHESIA	Conc mg/mL	Dose	
		mg	mL
3 in 1 (femoral, obturator and lateral cutaneous)	5.0	50 to 100	10 to 20
Pudendal	2.5 to 5.0	7.5 to 100	3 to 20 each side

RECOMMENDED DOSAGE FOR ANALGESIA, INCLUDING CONTINUOUS INFUSION

ANALGESIA	Conc mg/mL	Dose	
		mg	mL
Caudal Epidural Postoperative pain management	2.5	50 to 75 mg bolus	20 to 30 mL bolus
Lumbar Epidural Bolus (incl. labour pain management)	2.5 to 5.0	15 to 60 mg bolus followed by	6 to 12 mL bolus followed by
Continuous infusion (incl. labour pain and postoperative pain management)	2.5	12.5 to 18.75 mg/hour	5 to 7.5 mL/hour
Thoracic Epidural Continuous infusion for postoperative pain management	2.5	6.25 to 12.5 mg/hour	2.5 to 5 mL/hour

Notes

- ***Recommended doses:*** tolerability varies widely between patients and toxic effects may occur after any local anaesthetic procedure. Careful observation of the patient must therefore be maintained. It is recommended that the dose of bupivacaine at any time should not exceed 2 mg/kg. However, the dose administered must be tailored to the individual patient and procedure, and the maximum dose quoted here should be used as a guide only.

- ***Hypotension:*** during thoracic, lumbar and caudal epidural anaesthesia, a marked fall in blood pressure and/or intercostal paralysis may occur, possibly due to the use of excessive doses, improper positioning of the patient or accidental disposition of the anaesthetic within the subarachnoid space. Hypotension and bradycardia may occur as a result of sympathetic blockade.

Method of administration

- ***Injection:*** injection of repeated doses of bupivacaine may cause significant increase in blood levels with each repeated dose, due to accumulation of the drug or its metabolites, or due to slow metabolic degradation.

  The rapid injection of a large volume of local anaesthetic solution should be avoided and fractional doses should be used when feasible. For most indications the duration of bupivacaine is such that a single dose is sufficient.

- ***Test dose:*** for epidural anaesthesia, a 3 to 5 mL test dose of local anaesthetic solution, preferably containing up to 15 micrograms adrenaline (epinephrine), should be administered. Verbal contact and repeated monitoring of the heart rate and blood pressure should be maintained for 5 minutes after the test dose after which, in the absence of signs of subarachnoid or intravascular injection, the main dose may be given.

  Use of a test dose containing adrenaline (epinephrine) may have further advantages in that an intravascular injection of adrenaline (epinephrine) will be quickly recognised by an increase in heart rate, usually within about 40 seconds. To detect this, the heart rate and rhythm should be monitored with an electrocardiogram.

  An accidental intrathecal injection may be recognised by signs of a spinal block.

  Before administration of the total dose, aspiration should be repeated. The main dose should be injected **slowly** at a rate of 25 to 50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms or signs occur, the injection should be stopped immediately.

- ***Prolonged blocks:*** When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing a local neural injury must be considered.
- Bupivacaine solutions contain no antimicrobial agent and should be used only once and any residue discarded.
- Solutions showing discolouration and unused portions of solutions from ampoules and vials should be discarded.

Dosage adjustment

Use in children

Experience with bupivacaine in children under the age of 12 is limited. The dosage in children should be calculated on a weight basis up to 2 mg/kg.

Use in pregnancy

It should be noted that the dose should be reduced in patients in the late stages of pregnancy.

Use in debilitated or elderly patients

Debilitated or elderly patients, including those with partial or complete heart block, advanced liver disease or severe renal dysfunction should be given a reduced dosage commensurate with their physical condition (see Section 4.4 Special warnings and precautions for use).

4.3 Contraindications

- Allergy or hypersensitivity to local anaesthetics of the amide type. Detection of suspected hypersensitivity by skin testing is of limited value.
- Local anaesthetic techniques must not be used when there is infection in the region of the proposed injection and/or in the presence of septicaemia.
- Obstetrical paracervical block, intravenous regional anaesthesia (Bier's block) and all intravenous infusions.

- Epidural and spinal anaesthesia in patients with uncorrected hypotension.
- General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

4.4 Special warnings and precautions for use

During administration of bupivacaine, it is mandatory to have emergency resuscitative equipment (including oxygen) and drugs immediately available to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems (CNS).

Because of the possibility of hypotension and bradycardia following major blocks, an IV cannula should be inserted before the local anaesthetic is injected. Delay in proper management of dose related toxicity, under-ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and death.

The safety and effectiveness of bupivacaine depend upon proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted for specific techniques and precautions for various regional anaesthetic procedures.

- Injections should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection which can produce toxic effects (see Section 4.2 Dose and method of administration - Test dose).

- Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

- The use of local anaesthetics for major peripheral nerve block may involve the administration of large volumes in highly vascularised areas, often close to large blood vessels. As such there is an increased risk of intravascular injection and/or systemic absorption which can lead to high plasma concentrations. There have been reports of cardiac arrest or death during the use of bupivacaine for epidural anaesthesia or peripheral nerve blockade. In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and management.

- Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function. Epidural anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly.

- Low molecular weight heparins and heparinoids (spinal/epidural haematomas) – When neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet

inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

- The lowest dosage that results in effective anaesthesia should be used (see Section 4.2 Dose and method of administration). Repeated injection of Bupivacaine Injection may cause accumulation of bupivacaine or its metabolites and result in toxic effects.

  Tolerance to elevated blood levels varies with the status of the patient. Elderly, young or debilitated patients, including those with partial or complete conduction block, advanced liver disease or severe renal impairment, should be given reduced doses commensurate with their age and physical condition.

- 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 drug. This is especially the case after unintentional intravascular administration. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine.

- Bupivacaine should be given with caution to patients with epilepsy, impaired cardiac conduction, bradycardia, severe shock or digitalis intoxication. It should also be administered with caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by bupivacaine. Patients being treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and electrocardiogram (ECG) monitoring since cardiac effects may be additive.

  In patients with Stokes-Adams syndrome or Wolff-Parkinson-White syndrome extreme care should be taken to avoid accidental arterio-venous injection.

- Local anaesthetics should be given with great caution (if at all) to patients with pre-existing neurological or neuromuscular disease e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

- Patients with hyperthyroidism are also more susceptible to toxicity with bupivacaine.

- Inadvertent intravascular or subarachnoid injection of small doses of local anaesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Injections made inadvertently into an artery may cause immediate cerebral symptoms even at low doses.

  Clinicians who perform retrobulbar blocks should be aware that there have been reports of cardiovascular collapse and apnoea following the use of local anaesthetic injections for retrobulbar block. Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available as with all other regional procedures. Retrobulbar injections may very occasionally reach the subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.

Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and /or local toxic effects on muscles or nerves. The severity of such tissue reactions is related to the degree of the trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose should be used. Vasoconstrictors may aggravate tissue reaction and should be used only when indicated.

- Fetal bradycardia/tachycardia frequently follows paracervical block with some amide-type local anaesthetics and may be associated with fetal acidosis and hypoxia. Added risk appears to be present in prematurity, toxaemia of pregnancy and fetal distress. Careful monitoring of the fetal heart rate is necessary (see Section 4.3 Contraindications).

- Bupivacaine should be used with caution in patients with known drug sensitivities.

- Hepatic dysfunction, with reversible increases of alanine aminotransferase (ALT), alkaline phosphates (ALP) and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. Association between bupivacaine use and the development of drug-induced liver injury (DILI) has been reported in a small number of literature reports especially with prolonged use. While the pathophysiology of this reaction remains unclear, immediate withdrawal of bupivacaine has shown rapid clinical improvement. If signs of hepatic dysfunction are observed during administration with bupivacaine, the medicinal product should be discontinued.

Use in hepatic impairment

Bupivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Bupivacaine has an intermediate clearance which depends on its unbound fraction and intrinsic metabolic clearance. Bupivacaine should therefore be used with caution in patients with severe hepatic disease.

Use in renal impairment

Bupivacaine should be used with caution in patients with severe renal dysfunction because acidosis and reduced plasma protein concentration, which are frequently seen in these patients, may increase the risk of systemic toxicity.

Use in the elderly

Please see Section 4.2 Dose and method of administration - Use in debilitated or elderly patients.

Paediatric use

Caution should be used when administering bupivacaine to children under 12 years of age.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Antiarrhythmic drugs

Local anaesthetics of the amide type, such as bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain antiarrhythmic drugs such as mexiletine and lidocaine (lignocaine), since potentiation of cardiac effects may occur. Specific interaction studies with bupivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution should be advised (see Section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Effects on fertility

Effects on fertility have not been determined.

Use in pregnancy - Category A

After epidural administration of bupivacaine to women in labour, bupivacaine crosses the placental barrier. However, concentrations in umbilical veins are lower than those found in the maternal circulation.

Bupivacaine has been effectively used for obstetrical analgesia and adverse effects on the course of labour or delivery are rare. It has been suggested that blood glucose levels should be checked in newborns after obstetric regional anaesthesia.

Fetal adverse effects due to bupivacaine, such as fetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the fetus (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

The safe use of bupivacaine during pregnancy, other than labour, has not been established. Although bupivacaine has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or fetus, there are no adequate and well controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. It is known that local anaesthetics cross the placenta rapidly. It should therefore be used cautiously during pregnancy other than labour.

Use in lactation

Bupivacaine passes into breast milk. The amount of bupivacaine appearing in breast milk from a breastfeeding mother receiving parenteral bupivacaine is unlikely to lead to a significant accumulation of the parent drug in the breast-fed infant.

At maternal serum levels of up to 0.45 microgram/mL produced by the epidural use of bupivacaine for vaginal delivery, bupivacaine could not be detected in breast milk during the first 24 hours after delivery (detection limit 0.02 microgram/mL).

The possibility of an idiosyncratic or allergic reaction in the breast-fed infant from bupivacaine remains to be determined.

4.7 Effects on ability to drive and use machines

Depending on the dosage, local anaesthetics may have a mild effect on mental function and coordination and may temporarily impair locomotion and coordination.

4.8 Adverse effects (undesirable effects)

Adverse reactions to bupivacaine are rare in the absence of overdosage, exceptionally rapid absorption or inadvertent intravascular injection. These adverse reactions are similar in character to those observed with other amide-type local anaesthetics and pertain mainly to the central nervous system and the cardiovascular system. Adverse reactions to bupivacaine are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption, delayed elimination, altered metabolism, inadvertent intravascular injection or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Serious adverse experiences are generally systemic in nature. Ventricular arrhythmias, ventricular fibrillation, sudden cardiovascular collapse and death have been reported when bupivacaine has been utilised for local anaesthetic procedures that may result in high systemic concentrations of bupivacaine (see Section 4.4 Special warnings and precautions for use).

Pronounced acidosis, hyperkalaemia, hypocalcaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

Central nervous system

CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, diplopia, nausea, vomiting, sensations of heat, cold or numbness, urinary retention, paraesthesia circumoral, paraesthesia, hyperacusis, twitching, tremors, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, numbness of the tongue, difficulty swallowing and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following administration of bupivacaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients, circulatory collapse should be watched as CNS effects may not be apparent as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant drugs available to manage such patients (see Section 4.9 Overdose - Treatment of overdosage).

Cardiovascular

Cardiovascular manifestations following inadvertent intravascular injection are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest (see Section 4.9 Overdose).

Haemodynamic

Regional anaesthesia may lead to maternal hypotension.

Neurologic

The incidences of adverse reactions associated with the use of local anaesthetics may be related to the total dose of local anaesthetic administered and are also dependent on the particular drug used, the route of administration and the physical status of the patient.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally.

These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anaesthetic procedures.

Paresis, paraplegia, neuropathy, peripheral nerve injury and arachnoiditis have been observed.

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see Section 4.9 Overdose). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Allergic

Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Allergy to amide-type local anaesthetics is rare. If such a reaction occurs, it should be managed by conventional means.

The detection of sensitivity by skin testing is of doubtful value.

Musculoskeletal

Although intra-articular continuous infusions of local anaesthetics following arthroscopic and other surgical procedures is an unapproved use, there have been post-marketing reports of chondrolysis in patients receiving such infusions. Symptoms include joint pain, stiffness and loss of motion.

Currently, there is no effective treatment for chondrolysis. Patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement. Therefore, bupivacaine should not be used for post-operative intra-articular continuous infusion.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels, or to unintended subarachnoid injection of the local anaesthetic solution (see Sections 4.8 Adverse effects (undesirable effects) and 4.4 Special warnings and precautions for use).

With accidental intravascular injections of local anaesthetics, the toxic effects will be obvious within 1 to 3 minutes. With overdosage, peak plasma concentrations may not be reached for 20 to 30 minutes, depending on the site of injection, and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

Symptoms of acute toxicity

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbances and muscular 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. These may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

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

Signs of cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, decreased cardiac output, heart block, arrhythmia and even ventricular arrhythmias, ventricular fibrillation and cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepines or barbiturates.

Treatment of overdosage

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.

If convulsions occur then immediate attention is required for the maintenance of patent airway and assisted or controlled ventilation with oxygen, via a positive airway pressure delivery system mask. Adequacy of the circulation should then be evaluated, bearing in mind that drugs used to treat convulsions depress the circulation when administered intravenously.

Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, appropriate anticonvulsant medication such as an ultra-short acting barbiturate (e.g. thiopentone) or a benzodiazepine (e.g. diazepam) may be administered IV.

The clinician should be familiar with these anticonvulsant drugs prior to use of local anaesthetics.

Suxamethonium will stop the muscle convulsions rapidly but will require tracheal intubation and controlled ventilation, and should only be used by those familiar with these procedures.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, inotropic agents and/or lipid emulsion should be considered. Children should be given doses commensurate with age and weight.

If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation, and circulatory support as well as treatment of acidosis are of vital importance.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Bupivacaine is classed as a membrane stabilising agent and is a local anaesthetic of the amide type.

Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Local anaesthetic drugs may have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous system and the cardiovascular system.

Central nervous system toxicity usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

Indirect cardiovascular effects, e.g. hypotension and bradycardia, may occur after epidural or spinal administration depending on the extent of the concomitant sympathetic block.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Bupivacaine is a long acting, amide-type local anaesthetic chemically related to lignocaine and mepivacaine. Its potency and toxicity is approximately four times that of lignocaine.

In concentrations of 5 mg/mL it has a long duration of action, from 2 to 5 hours following a single epidural injection and up to 12 hours after peripheral nerve blocks. The onset of the blockade is slower than with lignocaine, especially when anaesthetising large nerves.

When used in low concentrations (2.5 mg/mL or less) there is less effect on motor nerve fibres and the duration of action is shorter. Low concentrations may, however, be used with advantage for prolonged pain relief, e.g. in labour or postoperatively.

The plasma concentration of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site. The addition of a vasoconstrictor such as adrenaline (epinephrine) may decrease the rate of absorption and prolong the duration of action.

Following injection of bupivacaine solutions for caudal, epidural or peripheral nerve block, peak plasma levels of bupivacaine are reached within 30 to 45 minutes and decline to insignificant concentrations during the next 3 to 6 hours.

Intercostal blocks give the highest peak plasma concentration due to rapid absorption (maximum plasma concentrations in the order of 1 to 4 mg/L after a 400 mg dose), while subcutaneous abdominal injections give the lowest plasma concentrations. Epidural and major plexus blocks are intermediate. In children rapid absorption (plasma concentrations are in the order of 1 to 1.5 mg/L after a dose of 3 mg/kg) is seen with caudal block. Absorption may be slowed by the addition of adrenaline (epinephrine).

Absorption of bupivacaine from the epidural space occurs in 2 phases; the first phase is in the order of 7 minutes and the second is in 6 hours. The slow absorption is rate-limiting in the elimination of bupivacaine, which explains why the apparent elimination half-life after epidural administration is longer than after intravenous administration.

Distribution

Bupivacaine has a total plasma clearance of 0.58 L/min, a volume of distribution at steady-state of 73 L, an elimination half-life of 2.7 hours (range 1.5 to 5.5 hours) and an intermediate hepatic extraction ratio of 0.40 following experimental IV administration in adults. The terminal elimination half-life is prolonged in the newborn to approximately 8 hours (range 8.1 to 14.0 hours). In children aged over 3 months the elimination half-life is similar to that in adults. Bupivacaine is mainly bound to α_1-acid glycoprotein in plasma with a plasma binding of 96%.

Metabolism and excretion

An increase in α_1-acid glycoprotein, which occurs postoperatively after major surgery, may cause an increase in the total plasma concentration of bupivacaine. The level of free drug will remain the same. This explains why total plasma concentrations above the apparent toxic threshold level of 2.6 to 3.0 mg/L are apparently well tolerated in this situation.

Bupivacaine is excreted in the urine principally as metabolites with about 6% as unchanged drug. Following epidural administration, the urinary recovery of unchanged bupivacaine is about 0.2%, of pipecolylxylidine (PPX) about 1% and of 4-hydroxy-bupivacaine about 0.1% of the administered dose.

Various pharmacokinetic parameters can be significantly altered by a number of factors including the presence of hepatic and renal disease, route of administration, age of the patient, presence or absence of adrenaline (epinephrine) in the solution and certain concomitant medication.

5.3 Preclinical safety data

Genotoxicity

Mutagenic potential have not been determined.

Carcinogenicity

Long term studies in animals of most local anaesthetics, including bupivacaine, to evaluate the carcinogenic potential, have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact between Bupivacaine solutions and metal surfaces, such as metal bowls, cannulae and syringes with metal parts.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Single use only. Discard unused portion.

6.5 Nature and contents of container

Bupivacaine Injection BP 0.25% (sterile) 50 mg in 20 mL Glass Theatre Vial (5 vials)

Bupivacaine Injection BP 0.5% (sterile) 100 mg in 20 mL Glass Theatre Vial (5 vials)

Bupivacaine Injection 0.5% (sterile) 50 mg in 10 mL Glass Vial (25 vials)

Bupivacaine Injection BP 0.5% (sterile) 50 mg in 10 mL Steriamp® Plastic Ampoule (50 ampoules)

Bupivacaine Injection BP 0.5% (sterile) 50 mg in 10 mL Steriluer® Plastic Ampoule (50 ampoules)

Not all presentations are available.

6.6 Special precautions for disposal

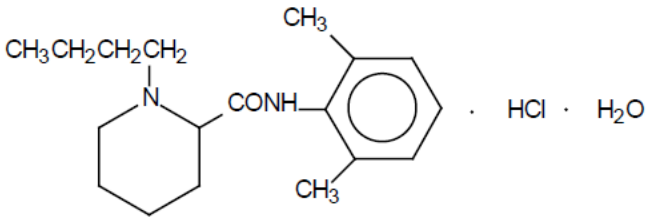
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

It appears as a white, crystalline powder or colourless crystals. It is soluble in water, freely soluble in ethanol (96%), slightly soluble in chloroform and in ether. Bupivacaine has a pKa of 8.1 and is more lipid soluble than lignocaine.

The structural formula of bupivacaine hydrochloride monohydrate is represented below.



Chemical name: (2*RS*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate.

Molecular Formula: $C_{18}H_{29}ClN_2O.H_2O$

Molecular Weight: 342.9

CAS number

73360-54-0 (bupivacaine hydrochloride monohydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedical.com.au

9. DATE OF FIRST APPROVAL

50 mg in 20 mL Glass Theatre Vials – 13 August 1991

100 mg in 20 mL Glass Theatre Vial – 13 August 1991

50 mg in 10 mL Glass Vial – 03 November 2026

50 mg in 10 mL Steriamp® Plastic Ampoule – 13 August 1991

50 mg in 10 mL Steriluer® Plastic Ampoule – 13 August 1991

10. DATE OF REVISION

03 November 2026

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Summary Table of Changes

Section changed	Summary of new information
Throughout	Removed reference to 'BP' except in relevant Product tradenames.
6.5	Addition of new presentation in 10 mL glass vial.
8	Update to sponsor medical information website.