1 BUPIVACAINE-BAXTER (solution for injection)

Bupivacaine-Baxter 0.25% (2.5mg/mL) solution for injection.

Bupivacaine-Baxter 0.5% (5mg/mL) solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

There are four presentations in two concentrations and two vial sizes:

- 2.5mg/mL (0.25%)
  Bupivacaine Hydrochloride Ph Eur 25mg in 10mL and 50mg in 20mL
- 5mg/mL (0.5%)
  Bupivacaine Hydrochloride Ph Eur 50mg in 10mL and 100mg in 20mL.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Bupivacaine-Baxter is a clear, colourless, particle-free, sterile, isotonic, pH adjusted solution of Bupivacaine Hydrochloride Ph Eur conforming to Bupivacaine Injection BP.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 four presentations i.e. 25mg in 10mL, 50mg in 20mL, 50mg in 10mL and 100mg in 20mL makes it possible to vary the degree of motor blockade.

4.2 Dose and method of administration

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 medicine used will affect the extent of spread of anaesthesia.

Bupivacaine-Baxter injection solutions are intended for single use only. Any solution remaining from an opened container should be discarded.

Recommended dosage

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

Adults

Recommended dosages for bupivacaine solutions for various anaesthetic procedures in the average healthy 70kg adult patient.

Recommended dosage for surgical anaesthesia:

Surgical anaesthesia	concentration (%)	volume (mL)	dose (mg)
Lumbar epidural[1]	0.5	15 – 30	75 – 150[1]
Thoracic Epidural[1]	0.25 0.5	5 – 15 5 – 10	12.5 – 37.5[1] 25 – 50[1]
Caudal Epidural (Adults)[1]	0.5	20 – 30	100 – 150[1]
Local infiltration in surgery	0.25 0.5	≤ 60 ≤ 30	≤ 150 ≤ 150
Digital Block	0.25	1 – 5	2.5 – 12.5
Retrobulbar Peribulbar	0.5 0.5	2 – 4 6 – 10	10 – 20 30 – 50
Intercostal (per nerve)	0.5	2 – 3	10 – 15
Brachial Plexus[2]	0.5	30	150
Sciatic[2]	0.5	10 – 20	50 – 100
3 in 1[2] - Femoral, obturator, lateral cutaneous	0.5	20 – 30	100 – 150
Intra-articular block	0.25	≤ 40	≤ 100

Recommended dosage for analgesia, including continuous infusion

Analgesia	concentration (%)	volume (mL)	dose (mg)
Lumbar epidural	0.25	6 – 15	15 – 37.5[1]
Lumbar epidural (continuous infusion) [Initial bolus of 2.5 or 5mg/mL required. Max ≤ 400mg/24 hr]	0.125[3] 0.25	10 – 15/hr 5 – 7.5/hr	12.5 – 18.75/hr 12.5 – 18.75/hr
Thoracic epidural (continuous infusion) [Initial bolus of 2.5 or 5mg/mL required. Max ≤ 400mg/24 hr]	0.125[3] 0.25	5 – 10/hr 4 – 7.5/hr	6.25 – 12.5/hr 10 – 18.75/hr
Caudal epidural (Adults)	0.25 0.5	20 – 30 20 – 30	50 – 75[1] 100 – 150[1]
Local infiltration	0.25 0.5	≤ 60 ≤ 30	≤ 150 ≤ 150
Intercostal (per nerve)	0.5	2 – 3	10 – 15
Interpleural	0.25 0.5	20 – 30 20	50 – 75 100

Notes

1. Dose includes test dose.
2. The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used (refer to section 4.4).
3. This solution is often used for epidural administration in combination with a suitable opioid for pain management. For further details of procedures please consult the current standard textbooks.

Test dose

For epidural anaesthesia, a test dose of 3 to 5mL, prepared from bupivacaine injection mixed with a sterile solution containing 15mcg of adrenaline, 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 may have further advantages in that an intravascular injection of adrenaline 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 spinal block.

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

Paediatrics

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 2mg/kg. The addition of adrenaline will prolong the duration of the block by 50 to 100%.

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.

Use in pregnancy

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

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. (refer to section 4.4).

4.3 Contraindications

Allergy or hypersensitivity to amide type local anaesthetics to any excipients (see section 6.1).

Bupivacaine is contraindicated in obstetric paracervical block, intravenous regional anaesthesia (Bier's block) and all intravenous infusions.

4.4 Special warnings and precautions for use

The safety and effectiveness of bupivacaine depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures. The lowest dosage that results in effective anaesthesia should be used (refer to section 4.2). Repeated injection of bupivacaine 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. Debilitated, elderly or young 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. N.B. Regional

anaesthesia is frequently indicated in these patients. Rather than subjecting them to general anaesthesia, attempts should be made to optimise the patient's condition before major nerve blocks.

When any local anaesthetic agent is used, resuscitative equipment and medicines, including oxygen, should be immediately available to manage possible reactions involving the cardiovascular, respiratory or central nervous systems. 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.

Injections should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection which can produce toxic effects. 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 rapid systemic absorption which can lead to high plasma concentrations. There have been reports of cardiac arrest or death during 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.

In view of the risk of inadvertent intravascular injection bupivacaine should be given with great caution to patients with epilepsy, severe bradycardia, cardiac conduction disturbances, severe shock or severe 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 medicines class III (e.g. amiodarone) should be under close surveillance and ECG monitoring since cardiac effects may be additive.

Patients with uncorrected hypotension, coagulation disorders or in patients receiving anti- coagulant treatment should receive epidural local anaesthetics with caution.

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.

Bupivacaine should be used with caution in patients with known agent sensitivities.

Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological or neuromuscular disease, e.g. myasthenia gravis.

Use with extreme caution in epidural and caudal 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.

Since bupivacaine is metabolised in the liver and excreted via the kidneys, the possibility of bupivacaine accumulation should be considered in patients with hepatic and/or renal impairment.

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 i.e. cardiovascular collapse, CNS depression and respiratory arrest. 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, medicines 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 peri-bulbar injections of local anaesthetics have a low risk of persistent ocular muscle dysfunction. The primary reasons include trauma and/or local toxic effects to muscles and/or nerves. The severity of such tissue reactions is related to the degree of trauma, concentration of the local anaesthetic and duration of exposure of the tissue to local anaesthetic. Therefore, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors and other additives may worsen tissue reactions, and should be used only when indicated.

Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart is necessary.

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 is not an approved indication for bupivacaine injection.

Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced either by preloading the circulation or by injecting a vasopressor. Hypotension should be treated promptly with e.g. ephedrine 5 to 10mg intravenously and repeated if necessary. Children should be given ephedrine doses commensurate with their age and weight.

When bupivacaine is administered as intra-articular injection, caution is advised when recent major intra-articular trauma is suspected or extensive raw surfaces with the joint have been created by the surgical procedure, as that may accelerate absorption and result in higher plasma concentrations.

4.5 Interaction with other medicines and other forms of interaction

Bupivacaine should be used with caution in patients receiving agents structurally related to local anaesthetics, e.g. certain anti-arrhythmics, such as lignocaine, mexiletine and tocainide, since the systemic toxic effects are additive. Specific interaction studies with bupivacaine and anti-arrhythmic medicines class III (e.g. amiodarone) have not been performed, but caution should be advised (refer to section 4.4).

Cases of severe hypotension are reported when clonidine was mixed with local anaesthetics like bupivacaine in blocks. Combinations with ketamine may cause neurotoxicity.

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.

The vials are intended for single use only, any unused portions of solutions should be discarded. The solution should be used immediately after opening. Solutions showing discolouration or containing particulate matter should be discarded.

Bupivacaine is compatible when admixed with 0.9% w/v sodium chloride injection, Ringer Lactate Solution and Sufentanil Citrate 50mcg/mL.

4.6 Fertility, pregnancy and lactation

Fertility

No fertility data are available.

Pregnancy (Category A)

Assigned Category A in the Australian Categorisation of risk system. Category A refers to medicines which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

It is reasonable to assume that a large number of pregnant women and women of childbearing age have been given bupivacaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations.

Bupivacaine has been effectively used for obstetric analgesia and adverse effects on the course of labour or delivery are rare. Local anaesthetics cross the placental barrier rapidly. Total plasma concentration is less in the foetus than in the mother.

Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the foetus (see section 4.4).

Breast feeding

Like other local anaesthetics bupivacaine may enter the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate.

At maternal serum levels of up to 0.45mcg/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 0.02mcg/mL).

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and co-ordination even in the absence of overt central nervous system toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

The adverse reaction profile for bupivacaine is similar to those for other long acting local anaesthetics. Adverse reactions caused by the drug per se are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture. Neurological damage is a rare but well recognised consequence of regional, and particularly epidural and spinal anaesthesia.

Incidence of adverse drug reactions

Very common (> 1 in 10)

Vascular disorders: hypotension

Gastrointestinal disorders: nausea

Common (from 1 in 100 to 1 in 10)
Nervous system disorders: paraesthesia, dizziness
Cardiac disorders: bradycardia
Vascular disorders: hypertension
Gastrointestinal disorders: vomiting
Renal and urinary disorders: urinary retention

Uncommon (from 1 in 1,000 to 1 in 100)
Nervous system disorders: signs and symptoms of CNS toxicity (convulsions, paraesthesia circumoral, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria)

Rare (<1 in 1,000)
Immune system disorders: allergic reactions, anaphylactic reaction/shock
Nervous system disorders: neuropathy, peripheral nerve injury, arachnoiditis, paresis and paraplegia
Eye disorders: diplopia
Cardiac disorders: cardiac arrest, cardiac arrhythmias Respiratory disorders: respiratory depression

Systemic and functional categorisation
Central nervous system
CNS manifestations are excitatory and/or depressant and may be characterised by lightheadedness, 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 medicine 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 medicines available to manage such patients (refer to section 4.9).

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 (refer to section 4.9).

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 medicine used, the route of administration and the physical status of the patient. In 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 cardiovascular system (refer section 4.9). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Allergic
Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactic reactions. Allergy to amide-type local anaesthetics is very rare.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphv.otago.ac.nz/reporting/

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 (refer to Adverse effects and Warnings and precautions).

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.

Signs and symptoms
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, 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 hypercarbia occur rapidly following convulsions due to the 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 medicine from the central nervous system and metabolism. Recovery may be rapid unless large amounts of the medicine have been injected.

Signs of cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, decreased cardiac output, heart block, arrhythmia, and even 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

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 a 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 advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code

N01BB01: member of N01BB - amides, a subset of N01B – anaesthetics, local.

Actions

Bupivacaine is a long acting, amide-type local anaesthetic 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. Onset and duration of the local anaesthetic effect of bupivacaine depends on the dose and site of administration.

Bupivacaine like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. The sodium channel of the nerve membrane is 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 medicine reach the systemic circulation, symptoms and signs of toxicity may appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity 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.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration depending on the extent of the concomitant sympathetic block.

In concentrations of 5mg/mL, bupivacaine 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 blockade is slower than with lignocaine, especially when anaesthetising large nerves. When used in low concentrations (2.5mg/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.

5.2 Pharmacokinetic properties

Bupivacaine has a pKa of 8.2 and a partition coefficient of 346 (25°C n-octanol/phosphate buffer pH 7.4).

Absorption

The plasma concentration of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site. The therapeutic effect varies with the type of block, dose and concentration.

After injection of bupivacaine solutions for caudal, epidural or peripheral nerve block in man, peak plasma levels of bupivacaine in the blood are attained within 30 to 45 minutes, followed by a decline to insignificant levels during the next 3 to 6 hours.

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

Bupivacaine shows complete and biphasic absorption from the epidural space with half-lives in the order of 7 min and 6 h respectively. 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 volume of distribution at steady state of 73 litres after IV administration. It is mainly bound to alpha-1-acid glycoprotein in plasma with a plasma binding of 96%.

Bupivacaine readily crosses the placenta and equilibrium with regard to the unbound concentration is rapidly attained. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

Biotransformation

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. Bupivacaine is extensively metabolised in the liver, predominately by aromatic hydroxylation to 4-hydroxy- bupivacaine and N-dealkylation to PPX, both mediated by cytochrome P4503A4. About 1% of bupivacaine is excreted in the urine as unchanged drug in 24 h and approximately 5% as PPX. The plasma concentrations of PPX and 4-hydroxy-bupivacaine during and after continuous administration of bupivacaine are low compared to the parent drug. Metabolites of bupivacaine have a lower pharmacological activity than the parent drug.

Elimination
Bupivacaine has a total plasma clearance of 0.58 l/min, an elimination half-life of 2.7h and an intermediate hepatic extraction ratio of 0.438 after IV administration.

Special patient considerations
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 and certain concomitant medication.

In children between 1 to 7 years the pharmacokinetics are similar to that in adults. An increase in total plasma concentration has been observed during continuous epidural infusion. This is related to a postoperative increase in alpha-1-acid glycoprotein. The unbound, i.e. pharmacologically active, concentration is similar before and after surgery.

5.3 Preclinical safety data
Based on conventional studies with bupivacaine on safety pharmacology, single and repeated toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards from humans were identified other than those which can be expected on the basis of the pharmacodynamic action of high doses of bupivacaine (e.g. CNS signs and cardiotoxicity).

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride, Hydrochloric acid, Sodium hydroxide, water for injections (pH adjusted from 4.0 to 6.5).

Sodium content is 3.15mg/mL. Solution osmolarity is 290mOsmol per litre.

6.2 Incompatibilities
Bupivacaine may precipitate in alkaline solutions with pH above 6.5 and should not be diluted or co-administered with sodium bicarbonate injections.

6.3 Shelf life
Batches manufactured at Clarion 1 Site: 36 months
Batches manufactured at Clarion 2 Site: 30 months.

6.4 Special precautions for storage
Unopened container
Store below 30°C.
Do not refrigerate or freeze. Protect from light.

Opened container
For immediate use only. Discard any residue.

6.5 Nature and contents of container
10mL vials – packs of 5 vials.
20mL vials – single-vial packs and 5-vial packs

Vial stopper is composed entirely of siliconised synthetic bromobutyl rubber.

6.6 Special precautions for disposal and other handling

Disposal

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

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

Bupivacaine-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

Bupivacaine-Baxter 0.25% 19 April 2012.
Bupivacaine-Baxter 0.5% 19 April 2012.

10 DATE OF REVISION OF THE TEXT

9 April 2019.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
ALL	Trade name updated to **Bupivacaine-Baxter**.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.