AUSTRALIAN PI – CHIROCAINE®
LEVOBUPIVACAINE INJECTION

1 NAME OF THE MEDICINE

Levobupivacaine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levobupivacaine ampoules contain levobupivacaine hydrochloride equivalent to 2.5 mg/mL, 5.0 mg/mL, and 7.5 mg/mL of levobupivacaine, and the levobupivacaine bags for infusion contain levobupivacaine hydrochloride equivalent to 0.625 mg/mL and 1.25 mg/mL of levobupivacaine. Both presentations contain sodium chloride for isotonicity, and Water for Injections. Sodium hydroxide and/or hydrochloric acid may have been added to adjust pH.

3 PHARMACEUTICAL FORM

Levobupivacaine is a sterile, non-pyrogenic, colourless solution (pH 4.0 - 6.5). Levobupivacaine is preservative free and is available in 10 mL single dose injection ampoules and 100 mL and 200 mL injection bag.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ampoules

1. Adults

Levobupivacaine is indicated in adults for:

Surgical Anaesthesia

Major: Epidural (including for caesarean section), intrathecal, peripheral nerve block.

Minor: Local infiltration, oral, peribulbar block in ophthalmic surgery.

For caesarean section, the 7.5 mg/mL concentration is not recommended, see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Pain Management

Continuous epidural infusion, single or multiple bolus administration for post-operative, labour or chronic pain.

For continuous epidural analgesia, levobupivacaine may be administered in combination with epidural fentanyl, morphine or clonidine.

For labour analgesia, the 7.5 mg/mL concentration is not recommended, see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS PRECAUTIONS FOR USE.

2. Children

Levobupivacaine is indicated in children greater than 6 months of age, for infiltration analgesia (ilioinguinal/iliohypogastric blocks) see 4.2 DOSE AND METHOD OF ADMINISTRATION.

3. After careful consideration to alternative concentrations, the 7.5 mg/mL concentration of levobupivacaine may be considered for those procedures requiring a dense block with low volume.

The 7.5 mg/mL concentration should not be considered for paediatric use.

Bag for Infusion

1. Adults

Pain management

Continuous epidural infusion for post-operative and labour analgesia.

4.2 Dose and method of administration

The rapid injection of a large volume of local anaesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered. The dose of any local anaesthetic differs with the anaesthetic procedure, the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, the intensity of the block, the degree of muscle relaxation required, the duration of the anaesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors, such as impaired cardiovascular function, advanced liver disease, or severe renal dysfunction, require special attention.

To reduce the risk of potentially serious adverse reactions, attempts should be made to optimise the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly. Use an adequate test dose (3 to 5 mL) of a short-acting local anaesthetic solution containing adrenaline prior to induction of complete nerve block. This test dose should be repeated if

the patient is moved in such a fashion as to have displaced the epidural catheter. It is recommended that adequate time be allowed for the onset of anaesthesia following administration of each test dose.

The use of levobupivacaine is not recommended for more than 24 hours (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Disinfecting agents containing heavy metals, which cause release of ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and oedema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the container surface thoroughly with cotton or gauze that has been moistened with the recommended alcohol prior to use.

Ampoules:

Shelf Life After First Opening: Product should be used immediately.

Shelf Life After Dilution: The chemical and physical in-use stability of the diluted product has been demonstrated for seven days at 20°C- 22°C. Chemical and physical in-use stability with clonidine, morphine or fentanyl has been demonstrated for 40 hours at 20°C- 22°C.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C- 8°C for not more than 24 hours.

Infusion Bags:

Shelf Life After First Opening: Product should be used immediately.

To reduce microbiological hazard, use as soon as practicable after opening. If storage is necessary, hold at 2°C- 8°C for not more than 24 hours.

All products are for one dose in one patient only. Contains no antimicrobial agent. Use once only and discard any residue.

Dilution Stability

Levobupivacaine diluted to 0.625 - 2.5 mg levobupivacaine per mL in 0.9% Sodium Chloride Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2^{o}C-8^{o}C for not more than 24 hours. Aseptic technique should be used to prepare the diluted products. Admixtures of levobupivacaine should be prepared for single patient use only and used within 24

hours of preparation. The unused portion of diluted levobupivacaine should be discarded after each use.

Note: Parenteral products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Solutions that are not clear and colourless should not be used.

Table 1: Dosage Recommendations

	Concentration **mg/mL**	**Dose (mL)**	**Dose (mg)**	**Motor Block**
Surgical Anaesthesia				
Epidural for Surgery	5.0 - 7.5	10 - 20	50 -150	Moderate to Complete
Epidural for Caesarean Section	5	15 - 30	75 - 150	Moderate to Complete
Peripheral Nerve	2.5 - 5.0	1 - 40	maximum 150	Moderate to Complete
Intrathecal	5	3	15	Moderate to Complete
Ophthalmic	7.5	5 - 15	37.5 - 112.5	Moderate to Complete
Local Infiltration - Adults	2.5	60	150	Not applicable
Local Infiltration - Children > 6 months and < 12 years [c]	2.5	0.5 mL/kg/side	1.25 mg/kg/side	Not applicable
	5	0.25 mL/kg/side	1.25 mg/kg/side	Not applicable
Dental	5.0 - 7.5	5 - 10	25 - 75	Not applicable

Table 1: Dosage Recommendations				
	Concentration **mg/mL**	**Dose (mL)**	**Dose (mg)**	**Motor Block**
Pain Management [a] [b]				
Labour Analgesia (epidural bolus)	2.5	10 - 20	25 - 50	Minimal to Moderate
Labour Analgesia (epidural infusion)	0.625 1.25	10 - 15 mL/hr 4 - 10 mL/hr	6.25 – 9.375 mg/hr 5 - 12.5 mg/hr	Minimal to Moderate
Peri- and Post-Operative Analgesia (epidural infusion)	0.625 1.25 2.5	10 – 15 mL/hr 10 – 15 mL/hr 5 - 7.5 mL/hr	6.25 – 9.375 mg/hr 12.5 - 18.75 mg/hr 12.5 - 18.75 mg/hr	Minimal to Moderate
[a] In pain management levobupivacaine can be used epidurally with fentanyl, morphine or clonidine.				
[b] In cases where levobupivacaine is combined with other agents e.g. opioids in pain management, the levobupivacaine dose should be reduced as use of a lower concentration (e.g. 1.25 mg/mL) is preferable.				
[c] No data are available in paediatric population < 6 months of age (see 4.1 THERAPEUTIC INDICATIONS)				
Dilutions of levobupivacaine standard solutions should be made with preservative free 0.9% saline according to standard hospital procedures for sterility.				
The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur.				

Maximum Dose

Experience to date indicates that the following maximum doses appear to be well tolerated:

- Epidural doses of up to 375 mg have been administered incrementally to patients during a surgical procedure.

- The maximum dose in 24 hours for intra-operative block and post-operative pain management was 695 mg.
- The maximum dose administered as a post-operative epidural infusion over 24 hours was 570 mg.
- The maximum dose administered to patients as a single fractionated injection was 300 mg for brachial plexus block.
- The maximum dosage must be determined by evaluating the size and physical status of the patient.
- The recommended maximum single dose is 150mg for epidural block. Where sustained motor and sensory block are required for a prolonged procedure, additional doses may be required.
- The maximum recommended dose during a 24 hour period is 400mg.
- For post-operative pain management, the dose should not exceed 18.75mg/hour.
- For labour analgesia by epidural infusion, the dose should not exceed 18.75 mg/hour.

Children

The safety and efficacy of levobupivacaine bag for infusion in children for pain management has not been established.

Special Populations

Debilitated, elderly or acutely ill patients should be given reduced doses of levobupivacaine commensurate with their physical status.

In the management of post-operative pain, the dose given during surgery must be taken into account.

4.3 Contraindications

Levobupivacaine is contraindicated in patients with a known hypersensitivity to levobupivacaine or to any local anaesthetic agent of the amide type.

Levobupivacaine solutions are contraindicated for use in paracervical block in obstetrics, and for intravenous regional anaesthesia (e.g. Bier Block).

The 7.5 mg/mL solution is contraindicated for any obstetric use due to an enhanced risk of cardiotoxic events based on experience with bupivacaine. There is no experience of levobupivacaine 7.5 mg/mL in obstetric surgery.

Levobupivacaine solutions are contraindicated in patients with severe hypotension such as cardiogenic or hypovolaemic shock (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 Special warnings and precautions for use

In performing levobupivacaine blocks, unintended intravenous injection is possible and may result in cardiac arrest (some cases fatal). Despite rapid detection and appropriate treatment, prolonged resuscitation may be required. The resuscitability relative to bupivacaine is unknown at this point in time as it has not been studied. As with all local anaesthetics of the amide type, levobupivacaine should be administered in incremental doses. Cases of severe bradycardia, hypotension and respiratory compromise with cardiac arrest (some of them fatal), have been reported in conjunction with local anaesthetics, including levobupivacaine. Since levobupivacaine should not be injected rapidly in large doses, it is not recommended for emergency situations, where a fast onset of surgical anaesthesia is necessary.

Local anaesthetics should only be administered by clinicians who are well versed in the diagnosis and management of drug-related toxicity and other acute emergencies which might arise from the block being administered. The immediate availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies must be ensured (see also 4.8 ADVERSE EFFECTS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Delay in proper management of drug-related toxicity, underventilation from any cause, and/or altered sensitivity may lead to the development of acidosis, cardiac arrest, and possibly death.

When contemplating a peripheral nerve block, where large volumes of local anaesthetic are needed, caution should be exercised when using the higher mg/mL concentrations of levobupivacaine. Animal studies demonstrate CNS and cardiac toxicity that is dose related, thus, equal volumes of higher concentration will be more likely to produce cardiac toxicity.

The safe and effective use of local anaesthetics depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

Resuscitative equipment, oxygen, and resuscitative drugs should be available for immediate use (see 4.8 ADVERSE EFFECTS). The lowest dosage that results in effective anaesthesia should be used to avoid high plasma or dermatomal levels and serious adverse effects. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed

before and during each supplemental injection. During the administration of epidural anaesthesia, it is recommended that a test dose of a local anaesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anaesthetic solutions that contain adrenaline for the test dose because circulatory changes compatible with adrenaline may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative.

Systemic adverse reactions following overdose or accidental intravascular injection reported with long acting local anaesthetic agents involve both CNS and cardiovascular effects. Levobupivacaine should be used with caution in conditions associated with impaired cardiovascular function (see 4.3 CONTRAINDICATIONS).

Injection of repeated doses of local anaesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Local anaesthetics should also be used with caution in patients with hypotension, hypovolaemia, or impaired cardiovascular function, especially heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anaesthetic injection. The clinician must be aware that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early signs of central nervous system toxicity.

Local anaesthetics should be used with caution in patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with prolonged A-V conduction caused by these drugs.

Many drugs used during the conduct of anaesthesia are considered potential triggering agents for malignant hyperthermia. Amide-type local anaesthetics are not known to trigger this reaction.

In the management of post-operative pain, the dose given during surgery must be taken into account.

Epidural Anaesthesia

During epidural anaesthesia, levobupivacaine should be administered in incremental volumes of three to five millilitres (3 to 5mL), with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous catheter techniques. An intravascular injection is still possible even if aspirations are negative. During the administration of epidural

anaesthesia, it is recommended that a test dose is administered initially and the effects monitored before the full dose is given. A test dose of a short-acting amide anaesthetic, such as three millilitres (3 mL) of lignocaine, is recommended to detect unintentional intrathecal administration. This will be manifested within a few minutes by signs of a subarachnoid block (e.g. decreased sensation of the buttocks, paresis of the legs or, in the sedated patient, absent knee jerk). Unintentional intrathecal injection of local anaesthetics can lead to very high spinal anaesthesia, possibly apnoea, severe hypotension and loss of consciousness. An intravascular or intrathecal injection is still possible, even if the results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, extensive subarachnoid block, or cardiovascular effects.

Epidural anaesthesia with any local anaesthetic may cause hypotension and bradycardia. All patients must have intravenous access established. The availability of appropriate fluids, vasopressors, resuscitation equipment and expertise must be ensured.

Levobupivacaine should be used with caution for epidural anaesthesia in patients with impaired cardiovascular function e.g. serious cardiac arrythmias.

Epidural Analgesia

There are limited clinical trial data with levobupivacaine therapy for periods exceeding 24 hours. There have been post-marketing reports of cauda equina syndrome and events indicative of neurotoxicity (see 4.8 ADVERSE EFFECTS) temporally associated with the use of levobupivacaine for greater than or equal to 24 hours for epidural analgesia. These events were more severe and in some cases led to permanent sequelae when levobupivacaine was administered for greater than 24 hours. Therefore, the use of levobupivacaine is not recommended for more than 24 hours.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anaesthetic, both before the original dose and all subsequent doses, to avoid intravascular or intrathecal injection. However, a negative aspiration does not ensure against intravascular or intrathecal injection. Levobupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects of these drugs are additive.

Use in Head and Neck Area

Small doses of local anaesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anaesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their respirations and circulation monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions

should be immediately available. Dosage recommendations should not be exceeded (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

Information for the Patient

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anaesthetised part of the body following correct administration of the regional anaesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the levobupivacaine package insert.

Identified precautions

Special Populations

Debilitated, elderly or acutely ill patients should be given reduced doses of levobupivacaine commensurate with their physical status.

Use in hepatic impairment

No special studies were conducted in hepatic failure patients. Levobupivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Amide-type local anaesthetics, such as levobupivacaine, are metabolised by the liver, therefore, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolise local anaesthetics normally, are at a greater risk for developing toxic plasma concentrations.

Use in renal impairment

No special studies were conducted in renal failure patients. Unchanged levobupivacaine is not excreted in the urine. Although there is no evidence that levobupivacaine accumulates in patients with renal failure, some of its metabolites may accumulate because they are primarily excreted by the kidney.

Use in the elderly

Of the total number of subjects in clinical studies of levobupivacaine, 16% were 65 years and over, while 8% were 75 years and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Paediatric use

The safety and efficacy of levobupivacaine bag for infusion in children for pain management has not been established.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Levobupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics since the toxic effects of these drugs could be additive. *In-vitro* studies indicate that the CYP3A4 isoform (and, to a lesser extent, the CYP1A2 and CYP2C9 isoforms) mediate the metabolism of levobupivacaine. Although no clinical studies have been conducted, it is likely that the metabolism of levobupivacaine may be affected by the concomitant administration of known CYP3A4 inducers (such as phenytoin, phenobarbitone, rifampicin), CYP3A4 inhibitors (azole antimyotics, e.g. ketoconazole; certain protease inhibitors, e.g. ritonavir; macrolide antibiotics, e.g. erythromycin; and calcium channel antagonists, e.g. verapamil), CYP1A2 inducers (omeprazole), CYP1A2 inhibitors (clarithromycin), CYP2C9 inducers (phenytoin, phenobarbitone, rifampicin) and CYP2C9 inhibitors (cimetidine, fluvoxamine). Dosage adjustments may be warranted when levobupivacaine is concurrently administered with inhibitors of CYP3A4, CYP1A2 or CYP2C9, as systemic levobupivacaine levels may rise, resulting in toxicity.

Levobupivacaine should be used with caution in patients receiving anti-arrhythmic agents with local anaesthetic activity, e.g. mexilitine, or class III anti-arrhythmic agents since their use may be additive.

No clinical studies have been completed to assess levobupivacaine in combination with adrenaline.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There was no effect on fertility or general reproductive performance in male and female rats following administration of levobupivacaine at subcutaneous doses up to 30 mg/kg/day from prior to mating through to day 17 of pregnancy. At this dose, respective estimated exposures (plasma AUC) to total and unbound drug were less than, and 4-fold, mean human exposure at an epidural dose of 112.5 mg. This dose of 30 mg/kg/day (180 mg/m^2/day) is about 40% of the maximum human dose of 695 mg, based on body surface area (459 mg/m^2 in a 50 kg person).

Use in pregnancy

(Category B3)

Levobupivacaine and/or its metabolites cross the placenta in rats, rabbits and sheep. Reproductive toxicity studies in animals suggest that levobupivacaine can disturb embryo-foetal development without having a clear teratogenic liability. Increased incidences of foetal variations/malformations were found following subcutaneous administration of levobupivacaine to female rats, at doses of 30 mg/kg/day from prior to mating through to day 17 of pregnancy, and at dose of 5.3 and 16 mg/kg/day during the period of organogenesis, without significant maternotoxicity. Doses up to 30 mg/kg/day from late pregnancy to weaning had no significant adverse effects. At 30 mg/kg/day, respective estimated exposures (plasma AUC) to total and unbound drug were less than, and 4-fold, mean human exposure at an epidural dose of 112.5 mg. Malformations were also seen following subcutaneous administration of levobupivacaine to rabbits during the period of organogenesis at dose of 5-20 mg/kg/day, with an equivocal relationship to treatment; respective estimated exposures (plasma AUC) to total and unbound drug were 0.2-2 fold, and 4-39 fold, mean human exposure at an epidural dose of 112.5 mg. The relevance of these animal findings for the safe use of levobupivacaine during early human pregnancy is unknown, and there are no adequate and well-controlled studies in pregnant women of the effects of levobupivacaine on the developing foetus. Levobupivacaine should be used during pregnancy only if the benefit outweighs the potential risk.

Labour and Delivery

Local anaesthetics, including levobupivacaine, rapidly cross the placenta, and, when used for epidural block, can cause varying degrees of maternal, foetal, and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, foetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function. Maternal hypotension, foetal bradycardia and foetal decelerations have resulted from regional anaesthesia with levobupivacaine for obstetrical pain relief. Local anaesthetics produce vasodilation by blocking sympathetic nerves. Administration of intravenous fluids, elevation of the patient's legs and left uterine displacement will help prevent decreases in blood pressure. The foetal heart rate should also be monitored continuously and electronic foetal monitoring is highly advisable.

Historically, pregnant patients were reported to have a high risk for cardiac arrhythmias, cardiac/circulatory arrest and death when bupivacaine was inadvertently rapidly injected intravenously. For caesarean section, the 5 mg/mL (0.5%) levobupivacaine solution in doses up to 150 mg is recommended.

The 7.5 mg/mL solution is not recommended for obstetric use due to an enhanced risk for cardiotoxic events based on experience with bupivacaine. There is no experience of levobupivacaine 7.5 mg/mL in obstetric surgery.

Solutions of levobupivacaine should not be used for the production of obstetrical paracervical block anaesthesia. There are no data to support such use and there is additional risk of foetal bradycardia and death.

Use in lactation

Levobupivacaine and/or its metabolites are excreted in milk in rats, but this has not been studied in humans. There were no significant adverse effects in rats or their offspring following administration of levobupivacaine at subcutaneous doses up to 30 mg/kg/day from late pregnancy to weaning. Caution should be exercised when levobupivacaine is administered to a breast feeding woman.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after anaesthesia. The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

Reactions to levobupivacaine are characteristic of those associated with other amide-type anaesthetics. A major cause of the adverse reactions to this group of drugs is associated with excessive

plasma levels, or high dermatomal levels, which may be due to overdose, unintentional intravascular injection, or slow metabolic degradation. The reported adverse events are derived from studies conducted in the United States and Europe. The reference drug was primarily bupivacaine. The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying lengths. A total of 1220 were exposed to levobupivacaine. Each patient was counted once for each type of adverse event.

In Phase II/III studies, 78% of patients who received levobupivacaine reported at least one adverse event. Of those patients who received the 7.5mg/mL levobupivacaine concentration, 85% reported at least one adverse event.

Table 2: Adverse Events That Occurred In >5% Of All Levobupivacaine Treated Patients In Phase II/III Studies (n=1141)	
Hypotension (31%)	Pruritis (9%)
Nausea (21%)	Pain (8%)
Post-operative pain (18%)	Headache (7%)
Fever (17%)	Constipation (7%)
Vomiting (14%)	Dizziness (6%)
Anaemia (12%)	Foetal distress (5%)

Table 3: Adverse Events Reported With An Incidence of 1% In The Phase II/III Bupivacaine Controlled Studies				
Event	Levobupivacaine n=509		Bupivacaine n=453	
Hypotension	100	(19.6)	93	(20.5)
Nausea	59	(11.6)	66	(14.6)
Anaemia	49	(9.6)	37	(8.2)
Post-Operative Pain	37	(7.3)	37	(8.2)

Table 3: Adverse Events Reported With An Incidence of 1% In The Phase II/III Bupivacaine Controlled Studies

Event	Levobupivacaine n=509		Bupivacaine n=453	
Vomiting	42	(8.3)	30	(6.6)
Back Pain	29	(5.7)	19	(4.2)
Fever	33	(6.5)	35	(7.7)
Dizziness	26	(5.1)	22	(4.9)
Foetal Distress	49	(9.6)	41	(9.1)
Headache	23	(4.5)	18	(4.0)
Delayed Delivery	32	(6.3)	31	(6.8)
Pruritis	19	(3.7)	26	(5.7)
Pain	18	(3.5)	17	(3.8)
ECG Abnormal	16	(3.1)	17	(3.8)
Abdomen Enlarged	15	(2.9)	12	(2.6)
Albuminemia	15	(2.9)	6	(1.3)
Rigors	15	(2.9)	12	(2.6)
Constipation	14	(2.8)	20	(4.4)
Diplopia	13	(2.6)	14	(3.1)
Hypoesthesia	13	(2.6)	15	(3.3)
Flatulence	12	(2.4)	11	(2.4)
Abdominal Pain	11	(2.2)	6	(1.3)
Hypothermia	11	(2.2)	6	(1.3)

Table 3: Adverse Events Reported With An Incidence of 1% In The Phase II/III Bupivacaine Controlled Studies

Event	Levobupivacaine n=509		Bupivacaine n=453	
Bradycardia	11	(2.2)	10	(2.2)
Dyspepsia	10	(2.0)	11	(2.4)
Haematuria	10	(2.0)	5	(1.1)
Haemorrhage in Pregnancy	9	(1.8)	12	(2.6)
Paraesthesia	9	(1.8)	2	(0.4)
Tachycardia	9	(1.8)	7	(1.5)
Urine Abnormal	9	(1.8)	6	(1.3)
Purpura	7	(1.4)	4	(0.9)
Wound Drainage Increased	7	(1.4)	13	(2.9)
Coughing	6	(1.2)	3	(0.7)
Leukocytosis	6	(1.2)	3	(0.7)
Somnolence	6	(1.2)	4	(0.9)
Urinary Incontinence	6	(1.2)	1	(0.2)
Anaesthesia Local	5	(1.0)	5	(1.1)
Anxiety	5	(1.0)	6	(1.3)
Breast Pain (Female)	5	(1.0)	4	(0.9)
Hypertension	5	(1.0)	8	(1.8)
Urine Flow Decreased	5	(1.0)	3	(0.7)
Urinary Tract Infection	5	(1.0)	3	(0.7)

Table 3: Adverse Events Reported With An Incidence of 1% In The Phase II/III Bupivacaine Controlled Studies		
Event	Levobupivacaine n=509	Bupivacaine n=453
Diarrhoea	5 (1.0)	6 (1.3)

The following adverse events were reported during the levobupivacaine clinical program in more than one patient and occurred at an overall incidence of <1%, and were considered clinically relevant.

Table 4: Adverse Events Reported With An Incidence of <1% during the clinical program, considered clinically relevant	
Body as a Whole	Asthenia, oedema
Cardiovascular Disorders, General	Postural hypotension, decreased cardiac output, ECG changes (e.g. heart block, bradycardia, ventricular tachyarrythmias), cardiac arrest
Central and Peripheral Nervous System Disorders	Hypokinesia, involuntary muscle contraction, spasm (generalised), tremor, syncope, numbness of the tongue, light headedness, dizziness, blurred vision, drowsiness, convulsions, unconsciousness
Heart Rate and Rhythm Disorders	Arrhythmia, extrasystoles, fibrillation (atrial), cardiac arrest
Gastrointestinal System Disorders	Ileus
Liver and Biliary System Disorders	Elevated Bilirubin
Psychiatric Disorders	Confusion
Respiratory System Disorders	Apnoea, bronchospasm, dyspnoea, pulmonary oedema, respiratory insufficiency, respiratory arrest
Skin and Appendage Disorders	Increased sweating, skin discolouration

Reactions to levobupivacaine are characteristic of those associated with other amide-type local anaesthetics. Systems involved may include the central nervous system, the cardiovascular system, and the respiratory system (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.9 OVERDOSE sections).

The incidences of adverse neurological reactions associated with the use of local anaesthetics may be related to the total dose of anaesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anaesthetic techniques, with or without contribution from the drug.

Neurologic damage is a rare but well recognised consequence of regional and particularly epidural and spinal anaesthesia. It may be due to direct injury to the spinal cord or spinal artery syndrome, injection of an irritant substance or an injection of a non-sterile solution. These may result in localised areas of paraesthesia or anaesthesia, motor weakness, loss of sphincter control and paraplegia. Rarely, these may be permanent.

Allergic-type reactions are rare and may occur as a result of sensitivity to the local anaesthetic. These reactions are characterised by signs such as urticaria, pruritis, erythema, angioneurotic oedema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anaesthetic group have been reported.

Post-marketing Reports

Anaphylaxis has been reported.

Very rare reports of convulsions have occurred following accidental intravenous administration.

There have been reports of prolonged weakness or sensory disturbance, some of which may have been permanent, in association with levobupivacaine therapy. It is difficult to determine whether the long-term effects were the result of medication toxicity or unrecognized trauma during surgery or other mechanical factors, such as catheter insertion and manipulation.

Reports have been received of cauda equina syndrome or signs and symptoms of potential injury to the base of the spinal cord or spinal nerve roots (including lower extremity paraesthesias, weakness or paralysis, loss of bowel control and/or bladder control and priapism) associated with levobupivacaine administration. These symptoms were more severe, and in some cases led to permanent sequelae, when levobupivacaine was administered for greater than 24 hours (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). However, it cannot be determined whether these events are due to an effect of levobupivacaine, mechanical trauma to the spinal cord or spinal nerve roots, or blood collection at the base of the spine.

There have also been reports of transient Horner's syndrome (ptosis, miosis, enophthalmus, unilateral sweating and/or flushing) in association with use of regional anaesthetics, including levobupivacaine. This event resolves with discontinuation of therapy.

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 http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Acute emergencies from local anaesthetics are generally related to high plasma levels or high dermatomal levels ("high spinal") encountered during therapeutic use of local anaesthetics or to unintended intrathecal or intravascular injection of local anaesthetic solution (see 4.8 ADVERSE EFFECTS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). There was one case of suspected unintentional intravascular injection which occurred during the clinical trial program. That patient received 19 mL of 7.5 mg/mL levobupivacaine (142.5 mg) and experienced CNS excitation which was treated with thiopental. No abnormal cardiac changes were observed and the patient recovered without sequelae.

Management of Local Anaesthetic Emergencies

The first consideration is prevention, best accomplished by incremental injection of levobupivacaine, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anaesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered, and further measures as warranted.

Accidental intravascular injection of local anaesthetics may cause immediate toxic reactions. In the event of overdose, peak plasma concentrations may not be reached until 2 hours after administration depending upon the injection site and, therefore, signs of toxicity may be delayed.

Systemic adverse reactions following overdose or accidental intravascular injection reported with long acting local anaesthetic agents involve both CNS and cardiovascular effects.

CNS Effects

Convulsions should be treated immediately with intravenous thiopentone or diazepam titrated as necessary. Thiopentone and diazepam also depress central nervous system, respiratory and cardiac function. Therefore their use may result in apnoea. Neuro-muscular blockers may be used only if the clinician is confident of maintaining a patent airway and managing a fully paralysed patient.

If not treated promptly, convulsions with subsequent hypoxia and hypercarbia plus myocardial depression from the effects of the local anaesthetic on the heart, may result in cardiac arrhythmias, ventricular fibrillation or cardiac arrest.

Cardiovascular Effects

Hypotension may be prevented or attenuated by pre-treatment with a fluid load and/or the use of vasopressors. If hypotension occurs it should be treated with intravenous crystalloids or colloids and/or incremental doses of a vasopressor such as ephedrine 5-10 mg. Any coexisting causes of hypotension should be rapidly treated.

If severe bradycardia occurs, treatment with atropine 0.3 - 1.0 mg will normally restore the heart rate to an acceptable level.

Cardiac arrhythmia should be treated as required and ventricular fibrillation should be treated by cardioversion.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Levobupivacaine is a member of the amino amide class of local anaesthetics. Local anaesthetics block the generation and the conduction of nerve impulses by increasing the threshold for electrical excitation in the nerve, by slowing propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anaesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibres. Clinically, the order of loss of nerve function is as follows: 1) pain; 2) temperature; 3) touch; 4) proprioception; and 5) skeletal muscle tone.

Levobupivacaine can be expected to share the pharmacodynamic properties of other local anaesthetics. Systemic absorption of local anaesthetics can produce effects on the central nervous system and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance have been reported. Toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in death. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anaesthetics can produce central nervous system stimulation, depression, or both. Apparent central nervous system stimulation is usually manifested as restlessness, tremors, and shivering, progressing to convulsions. Ultimately central nervous system depression may progress to coma and cardio-respiratory arrest. However, the local anaesthetics have a primary depressant effect on the medulla and on higher centres. The depressed stage may occur without a prior excited stage.

In preclinical studies of relative potency, evidence suggests that levobupivacaine is equipotent with bupivacaine at clinically relevant concentrations.

Clinical trials

A study in human volunteers was designed to assess the effects of levobupivacaine and bupivacaine on the electroencephalogram (EEG) following an intravenous dose (40 mg) that was predicted to be below the threshold to cause central nervous system (CNS) symptoms. In this study, levobupivacaine decreased high alpha power in parietal, temporal and occipital regions, but to a lesser extent than bupivacaine. Levobupivacaine had no effect on high alpha power in the frontal and central regions, nor did it produce the increase in theta power observed at some electrodes following bupivacaine. In another study, 14 subjects received levobupivacaine or bupivacaine infusions intravenously until significant CNS symptoms occurred (occurrence of numbness of the tongue, light-headedness, tinnitus, dizziness, blurred vision, or muscle twitching). The mean dose at which CNS symptoms occurred was 56 mg (range 17.5 - 150 mg) for levobupivacaine and 48 mg (range 22.5 - 110 mg) for bupivacaine. The primary endpoints of the study were cardiac contractility and standard electrocardiographic parameters. Both drugs produced transient increases in heart rate and systolic and diastolic pressure, but the change in diastolic pressure was significantly less with levobupivacaine than with bupivacaine. Cardiac function measured by transthoracic electrical bioimpedance showed significant differences in that levobupivacaine produced a lesser reduction in stroke index, the acceleration index, and the ejection fraction.

A double-blind, randomised, parallel group trial was conducted on 22 healthy male volunteers to compare the effects of levobupivacaine and bupivacaine on QT dispersion and signal averaged ECG. The objective of the trial was to determine the effect of levobupivacaine and bupivacaine on myocardial depolarisation and repolarisation as measured by the QRS duration of signal-averaged ECGs, QT dispersion, and other ECG variables. During double-blind dosing, subjects received either levobupivacaine or bupivacaine in tolerated doses ranging from 30 mg to 120 mg. The results showed that ten of eleven bupivacaine subjects experienced CNS symptoms compared with six of eleven levobupivacaine subjects. In those subjects who received more than 75 mg of randomised drug, the maximum changes from baseline QTc interval was statistically significantly lower for levobupivacaine (3 ± 11 msec) than bupivacaine (24 ± 17 msec, p=0.022). No other statistically significant changes were seen in cardiac parameters.

The clinical trial program included 1220 patients and subjects who received levobupivacaine in 31 clinical trials. Levobupivacaine has been studied as a local anaesthetic in adults administered as an epidural block for surgical cases, including caesarean section; in peripheral neural blockade; and for post-operative pain control. Clinical trials have demonstrated that levobupivacaine and bupivacaine exhibit similar anaesthetic effects.

Central Administration

Epidural Administration in Caesarean Section

In one study, levobupivacaine and bupivacaine, 5.0 mg/mL were evaluated as an epidural block in 62 patients undergoing caesarean section in a randomised, double-blind comparative trial. The mean (±SD) time to sensory block measured at T4 to T6 was 10 ± 8 minutes for levobupivacaine and 6 ± 4 minutes for bupivacaine. The mean duration of sensory block and motor block was 8 ± 1 and 4 ± 1 hours for levobupivacaine and 7 ± 1 and 4 ± 1 hours for bupivacaine, respectively. Ninety-four percent of patients receiving levobupivacaine and 100% of patients receiving bupivacaine achieved a block adequate for surgery. In a second bupivacaine-controlled caesarean section study involving 62 patients, the mean time to onset of T4 to T6 sensory block for levobupivacaine and bupivacaine was 10 ± 7 minutes and 9 ± 7 minutes, respectively, with 94% of levobupivacaine patients and 91% of bupivacaine patients achieving a bilateral block adequate for surgery. The mean time to complete regression of sensory block was 8 ± 2 hours for both treatments.

Epidural Administration During Labour and Delivery

Levobupivacaine 2.5 mg/mL was evaluated as intermittent injections via an epidural catheter in 68 patients during labour in a randomised, double-blind comparative trial to bupivacaine 2.5 mg/mL. The median duration of pain relief in the subset of patients receiving 2.5 mg/mL levobupivacaine who had relief was 49 minutes; for bupivacaine patients the median duration was 51 minutes. Following the first top-up injections, 91% of patients receiving levobupivacaine and 90% of patients receiving bupivacaine achieved pain relief.

Epidural Administration for Surgery

Levobupivacaine concentrations of 5.0 mg/mL and 7.5 mg/mL administered by epidural injection were evaluated in 85 patients undergoing lower limb or major abdominal surgery in randomised, double-blind comparisons to bupivacaine. Anaesthesia sufficient for surgery was achieved in almost all patients on either treatment. In patients having abdominal surgery, the mean (±SD) time to onset of sensory block was 14 ± 6 minutes for levobupivacaine and 14 ± 10 minutes for bupivacaine. With respect to the duration of block, the time to complete regression was 551 ± 88 minutes for levobupivacaine and 506 ± 71 minutes for bupivacaine.

Post-Operative Pain Management

Post-operative pain control was evaluated in 324 patients in four studies including one dose-ranging study and three studies assessing levobupivacaine in combination with epidural fentanyl, morphine or clonidine. The dose-ranging study evaluated levobupivacaine in concentrations of 0.625 mg/mL, 1.25 mg/mL and 2.5 mg/mL in patients undergoing orthopaedic surgery; the highest concentration was significantly more effective than were the other two concentrations. The levobupivacaine combination studies in post-operative pain management tested 1.25 mg/mL levobupivacaine in combination with 4 mcg/mL fentanyl, 1.25 mg/mL levobupivacaine in combination with clonidine 50 mcg/hour in orthopaedic surgery, and 2.5 mg/mL levobupivacaine and 0.005% morphine in abdominal surgery. In these studies, the efficacy variable was time to first request for rescue analgesia during the 24-hour epidural infusion period. In the studies, the combination treatment provided better pain control than clonidine, opioid or local anaesthetic alone.

There is limited safety experience with levobupivacaine therapy for periods exceeding 24 hours. Therefore, use of levobupivacaine is not recommended for more than 24 hours.

Peripheral Nerve Administration

Levobupivacaine has been evaluated for its anaesthetic efficacy when used as a peripheral nerve block. These clinical trials include brachial plexus (by supraclavicular approach) block study, infiltration anaesthesia studies (for inguinal hernia repair), and peribulbar block studies.

Brachial Plexus Block: Levobupivacaine 2.5 mg/mL and 5.0 mg/mL were compared with 5.0 mg/mL bupivacaine in 74 patients receiving brachial plexus (supraclavicular) block for elective surgery. In the levobupivacaine 2.5 mg/mL treated group, 68% of patients achieved satisfactory block and in the levobupivacaine 5.0 mg/mL treated group, 81% of patients achieved satisfactory block for surgery. In the bupivacaine 5.0 mg/mL treated group, 74% of patients achieved satisfactory block for surgery.

Infiltration Anaesthesia: Levobupivacaine 2.5 mg/mL was evaluated in 68 patients in two randomised, double blind, bupivacaine controlled clinical trials for infiltration anaesthesia during surgery and for post-operative pain management in patients undergoing inguinal hernia repair. No clear differences between treatments were seen.

Peribulbar Block Anaesthesia: Two clinical trials were conducted to evaluate 7.5 mg/mL levobupivacaine and bupivacaine in 110 patients for peribulbar block for anterior segment ophthalmic surgery, including cataract, glaucoma, and graft surgery, and for post-operative pain management. In one study, a ten mL (10 mL) injection of 7.5 mg/mL levobupivacaine or bupivacaine produced a block adequate for surgery at a median time of ten minutes. In the second study, a five mL (5 mL) dose of 7.5 mg/mL levobupivacaine or bupivacaine injected in a technique more closely resembling a

retrobulbar block resulted in a median time to adequate block of two minutes for both treatments. Post-operative pain was reported in fewer than ten percent of patients overall.

5.2 Pharmacokinetic properties

Table 5: Pharmacokinetic parameter values of levobupivacaine after administration of 40 mg levobupivacaine, and those of racemic bupivacaine, R(+)- and S(-)- enantiomers after the administration of 40 mg bupivacaine intravenously in healthy volunteers (mean ± SD).

Parameter	**Levobupivacaine**	**Bupivacaine Racemate**	**R(+)- Bupivacaine**	**S(-)- Bupivacaine**
C_{max}, mcg/mL	1.445 ± 0.237	1.421 ± 0.224	0.629 ± 0.100	0.794 ± 0.131
$AUC_{0-\infty}$ mcg hour/mL	1.153 ±0.447	1.166 ±0.400	0.478 ± 0.166	0.715 ± 0.261
$t_{1/2}$, hour	1.27 ± 0.37	1.15 ± 0.41	1.08 ± 0.17	1.34 ± 0.44
$V_{d,}$ Litre	66.91 ± 18.23	59.97 ± 17.65	68.58 ± 21.02	56.73 ± 15.14
Cl, Litre/hour	39.06 ± 13.29	38.12 ± 12.64	46.72 ± 16.07	46.72 ± 16.07

After IV infusion of equivalent doses of levobupivacaine and bupivacaine, the mean clearance, volume of distribution, and terminal half-life values of levobupivacaine were similar. No detectable levels of R(+)-bupivacaine were found after the administration of levobupivacaine.

A comparison of the estimates for plasma AUC and C_{max} between levobupivacaine and bupivacaine in two Phase III clinical trials involving short duration administration of either agent found that neither total plasma exposure nor C_{max} differed between the two drugs when compared within studies. Between study values differed somewhat, likely due to differences in injection sites, volume, and total dose administered in each of the studies. These data suggest that levobupivacaine and bupivacaine have a similar pharmacokinetic profile. Pharmacokinetic data from the two Phase III studies are presented in Table 6.

Table 6: Pharmacokinetic parameter values of levobupivacaine and bupivacaine in patients administered the respective drugs epidurally and for brachial plexus block.

Route	**Epidural**			**Brachial Plexus Block**		
	Levobupivacaine		**Bupivacaine**	**Levobupivacaine**		**Bupivacaine**
Conc. (mg/mL)	5.00	7.5	5.00	2.5	5.00	5.00
Dose Received	75mg	112.5mg	75mg	1mg/kg	2mg/kg	2mg/kg
n	9	9	8	10	10	9
C_{max} (mcg/mL)	0.582	0.811	0.414	0.474	0.961	1.029
T_{max} (hour)	0.52	0.44	0.36	0.50	0.71	0.68
$AUC_{(0-t)}$ (mcg.h/mL)	3.561	4.930	2.044	2.999	5.311	6.832

Between 5.0 mg/mL and 7.5 mg/mL levobupivacaine given epidurally at doses of 75 mg and 112.5 mg respectively, the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional. Similarly, between 2.5 mg/mL and 5.0 mg/mL levobupivacaine used for brachial plexus block at doses of 1 mg/kg and 2 mg/kg respectively, the mean C_{max} and AUC_{0-24} of levobupivacaine were approximately dose-proportional. The plasma concentration of levobupivacaine following therapeutic administration depends on dose and also on route of administration, because absorption from the site of administration is affected by the vascularity of the tissue. Peak levels in blood were reached approximately 30 minutes after epidural administration, and doses up to 150 mg resulted in mean C_{max} levels of up to 1.2 mcg/mL.

Plasma protein binding of levobupivacaine evaluated *in vitro* was found to be >97% at concentrations between 0.1 and 1 mcg/mL. The association of levobupivacaine with human blood cells was very low (0 - 2%) over the concentration range 0.01 – 1 mcg/mL and increased to 32% at 10 mcg/mL. The volume of distribution of levobupivacaine after intravenous administration was 67 litres.

Levobupivacaine is extensively metabolised with no unchanged levobupivacaine detected in urine and faeces. *In vitro* studies using [^{14}C] levobupivacaine showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. *In vivo*, the 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulfate conjugates. Metabolic inversion of levobupivacaine to R(+)-bupivacaine was not evident in both *in vitro* and *in vivo*.

Following intravenous administration, recovery of the radiolabelled dose of levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and faeces in 48 hours. Of this 95%, about 71% was in urine while 24% was in faeces. The mean elimination half-life of total radioactivity in plasma was 3.3 hours. The mean clearance and terminal half-life of levobupivacaine after intravenous infusion were 39 litres/hour and 1.3 hours, respectively.

Elderly

The limited data available indicate that while there are some differences in T_{max}, C_{max}, and AUC with regards to age (between age groups of <65, 65 - 75, and >75 years), these differences are small and vary depending on the site of administration.

Gender

The small number of subjects in either of the male and female groups and the different routes of administration (data could not be pooled) in the different studies did not permit the assessment of gender differences in the pharmacokinetics of levobupivacaine.

Paediatrics

No pharmacokinetic data of levobupivacaine are available in the paediatric population.

Maternal/Foetal Ratio

The ratio of umbilical venous and maternal concentration of levobupivacaine ranged from 0.252-0.303 after the epidural administration of levobupivacaine for caesarean section. These are within the range normally seen for bupivacaine.

Breastfeeding Mothers

It is known that some local anaesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a breastfeeding woman. The excretion of levobupivacaine or its metabolites in human milk has not been studied (see 4.6 FERTILITY, PREGNANCY AND LACTATION).

Hepatic Failure

Levobupivacaine should be used with caution in patients with severe hepatic disease, and repeated doses may need to be reduced due to delayed elimination (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.3 Preclinical safety data

Genotoxicity

There was no evidence of mutagenicity with levobupivacaine in bacterial and mammalian gene mutation assays, or of clastogenicity in human lymphocytes *in vitro* or mouse bone marrow *in vivo*.

Carcinogenicity

Long-term animal studies of most local anaesthetics (including levobupivacaine) to evaluate carcinogenic potential have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refer to section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION

6.2 Incompatibilities

Levobupivacaine may not be compatible with alkaline solutions having a pH greater than 8.5. Studies have shown that levobupivacaine is compatible with 0.9% Sodium Chloride Injection USP and with saline solutions containing morphine, fentanyl, and clonidine. Compatibility studies with other parenteral products have not been studied.

In pain management, levobupivacaine can be used epidurally with 8.4 micrograms/mL clonidine, 50 micrograms/mL morphine, 2 micrograms/mL fentanyl or 0.4 micrograms/mL sufentanyl.

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. Refer to 4.2 DOSE AND METHOD OF ADMINISTRATION for information on storage after opening and after dilution.

6.4 Special precautions for storage

Ampoule

Store below 30^{o} C.

Bag for Infusion

Store below 25°C.

The Chirocaine 0.625 mg/mL and 1.25 mg/mL solution for infusion bags are packaged in an integral foil overpouch. Inside the integral foil overpouch there is a gradient in relative humidity between that of the solution bag headspace and the space between the bag and overpouch. Due to this phenomenon, a small amount of condensation or water beadlets between the foil overpouch and the

bag surfaces may be observed on opening the foil overpouch and is considered normal for this product. In line with the product user instructions for parenteral medicinal products, the primary bag should be checked for leaks on removal of the overpouch. If a leak is confirmed, discard the solution bag, as the sterility may be impaired.

6.5 Nature and contents of container

10 mL, single use, plastic ampoules containing levobupivacaine 25 mg/10mL, 50 mg/10mL and 75 mg/10mL.

100 mL, single use solution, in a 100 mL flexible polymeric bag in an aluminium foil overpouch, containing levobupivacaine 62.5 mg/100mL and 125 mg/100mL.*

200 mL, single use solution, in a 250 mL flexible polymeric bag in an aluminium foil overpouch, containing levobupivacaine 250 mg/200mL.

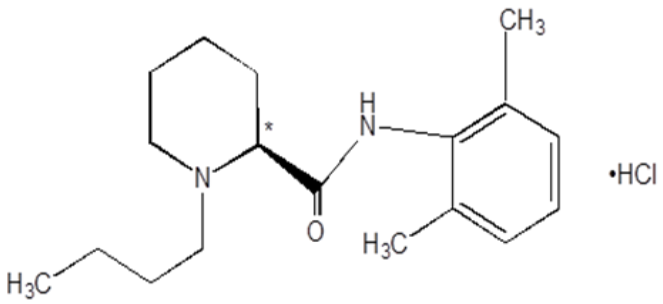
* Not marketed in Australia

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



* Indicates the chiral centre

Levobupivacaine injection contains a single enantiomer of bupivacaine hydrochloride which is chemically described as (S)-1-butyl-2-piperidylformo-2', 6'-xylidide hydrochloride and it is related chemically and pharmacologically to the amino amide class of local anaesthetics.

Levobupivacaine hydrochloride, the S-enantiomer of bupivacaine, is a white crystalline powder with a molecular formula of $C_{18}H_{28}N_2O.HCl$ and a molecular weight of 324.9.

The solubility of levobupivacaine hydrochloride in water is about 100mg per mL at 20°C, the partition coefficient (oleyl alcohol/water) is 1624 and the pKa is 8.09. The pKa of levobupivacaine hydrochloride is the same as that of bupivacaine hydrochloride and the partition coefficient is very similar to that of bupivacaine hydrochloride (1565).

CAS number

27262-48-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine - Schedule 4

8 SPONSOR

AbbVie Pty Ltd
241 O'Riordan Street
Mascot NSW 2020
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Tel: 1800 043 460

9 DATE OF FIRST APPROVAL

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Summary table of changes

Section Changed	Summary of new information
All sections	Reformat to align with revised TGA PI requirements
All sections	Minor editorial changes including correction of typographical errors, conversion of US to Australian spelling and grammatical corrections.