Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Hydrochloride Injection B.P. 0.5% w/v

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupivacaine Hydrochloride BP/Ph.Eur. equivalent to 0.5% w/v anhydrous
Bupivacaine Hydrochloride.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Surgical anaesthesia in adults and children above 12 years of age
- Acute pain management in adults, infants and children above 1 year of age

The suggested dose and strength of solution appropriate for each indication are provided in Section 4.2.

4.2 Posology and method of administration

Routes of administration: Infiltration by injection. Epidural. Caudal.

The dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia used. The lowest dosage needed to provide effective anaesthesia should be administered. For most indications, the duration of anaesthesia with bupivacaine solutions is such that a single dose is sufficient.

The maximum dosage must be determined by evaluating the size and physical status of the patient and considering the usual rate of systemic absorption from a particular injection site. Experience to date indicates a single dose of up to 150 mg bupivacaine hydrochloride. Doses of up to 50 mg 2-hourly may subsequently be used. A maximum dose of 2 mg/kg should not be exceeded in any four-hour period.

When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration must be considered.

The dosages in the following table are recommended as a guide for use in the average adult. Individual variations in onset and duration occur. For young, elderly or debilitated patients, these doses should be reduced.

Dosage recommendations for adults

	Conc mg/ml	Volume ml	Dose mg	Onset min	Duration of effect Hours[7]
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration 1)					
Surgery	5	15-30	75-150	15-30	2-3

Caesarean Section	5	15-30	75-150	15-30	2-3
Thoracic Epidural Administration 1)					
Surgery	2.5	5-15	12.5-37.5	10-15	1.5-2
	5	5-10	25-50	10-15	2-3
Caudal Epidural Block 1)	2.5	20-30	50-75	20-30	1-2
	5	20-30	100-150	15-30	2-3
Major Nerve Block 2)					
(e.g. brachial plexus, femoral, sciatic)	5	10-35	50-175	15-30	4-8
Field block					
(e.g. minor nerve blocks and infiltration)	2.5	<60	<150	1-3	3-4
	5	≤30	≤150	1-10	3-8

ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Intermittent injections 3) (e.g. post-operative pain relief)	2.5	6-15; minimum interval 30 minutes	15-37.5; minimum interval 30 minutes	2-5	1-2
Continuous infusion 4)	2.5	5-7.5/h	12.5-18.8/h		
Thoracic Epidural Administration					
Continuous infusion	2.5	4-7.5/h	10-18.8/h		
Intra-Articular Block 6)					
(e.g. single injection following knee arthroscopy)	2.5	≤40	≤1005)	5-10	2-4 h after wash out
Field Block					
(e.g. minor nerve blocks and infiltration)	2.5	≤60	≤150	1-3	3-4

1) 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, see also section 4.4.
3) In total ≤500 mg/24 h.
4) This solution is often used for epidural administration in combination with a suitable opioid for pain management. In total ≤500 mg/24 h.
5) If additional bupivacaine is used by any other techniques in the same patient, an overall dose limit of 150 mg should not be exceeded.
6) There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. Bupivacaine is not approved for this indication (see also section 4.4).
7) Bupivacaine Hydrochloride without adrenaline.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When

a less intense block is required (e.g. in the relief of labour pain), the use of a lower concentration is indicated. The volume of drug used will affect the extent of spread of anaesthesia.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25–50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3–5 ml bupivacaine containing adrenaline (epinephrine) is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

Paediatric patients 1 to 12 years of age
Paediatric regional anaesthetic procedures should be performed by qualified clinicians who are familiar with this population and the technique.

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.
The lowest dose required for adequate analgesia should be used.

Dosage recommendations for children 1 to 12 years of age

	Conc. mg/ml	Volume ml/kg	Dose mg/kg	Onset min	Duration of effect hours
ACUTE PAIN MANAGEMENT (per-and postoperative)					
Caudal Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Lumbar Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Thoracic Epidural Administration[b)]	2.5	0.6-0.8	1.5-2	20-30	2-6
Field Block (eg, minor nerve blocks and infiltration)	2.5 5.0		0.5-2.0 0.5-2.0		
Peripheral Nerve Blocks (e.g ilioinguinal – iliohypogastric)	2.5 5.0		0.5-2.0 0.5-2.0	a) a)	

a) The onset and duration of peripheral nerve blocks depend on the type of block and the dose administered.
b) Thoracic epidural blocks need to be given by incremental dosage until the desired level of anaesthesia is achieved.

In children the dosage should be calculated on a weight basis up to 2 mg/kg.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose. This should be injected slowly in incremental doses, particularly in the lumbar and thoracic epidural routes, constantly and closely observing the patient's vital functions.

Peritonsillar infiltration has been performed in children above 2 years of age with bupivacaine 2.5 mg/ml at a dose of 7.5-12.5mg per tonsil.

Ilioinguinal-iliohypogastric blocks have been performed in children aged 1 year or older with bupivacaine 2.5 mg/ml at a dose of 0.1-0.5 ml/kg equivalent to 0.25-1.25 mg/kg. Children aged 5 years or older have received bupivacaine 5 mg/ml at a dose of 1.25-2 mg/kg.

For penile blocks bupivacaine 5 mg/ml has been used at total doses of 0.2-0.5 ml/kg equivalent to 1-2.5 mg/kg.

The safety and efficacy of Bupivacaine Hydrochloride Injection BP 0.5% w/v with and without adrenaline in children < 1 year of age have not been established. Only limited data are available.

Safety and efficacy of intermittent epidural bolus injection or continuous infusion have not been established. Only limited data is available.

4.3 Contraindications

Bupivacaine hydrochloride solutions are contra-indicated in patients with hypersensitivity to local anaesthetic agents of the amide type or to any of the excipients listed in section 6.1.

Solutions of bupivacaine hydrochloride are contra-indicated for injection into inflamed or infected areas and for intravenous regional anaesthesia (Bier's-block).

4.4 Special warnings and precautions for use

There have been reports of cardiac arrest or death during use of Bupivacaine Hydrochloride Injection BP 0.5% w/v for epidural anaesthesia or peripheral nerve blockade. In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management.

Like all local anaesthetic drugs, Bupivacaine Hydrochloride Injection BP 0.5% w/v may cause acute toxicity effects on the central nervous and cardiovascular systems if utilized for local anaesthetic procedures resulting in high blood concentrations of the drug. This is especially the case after unintentional intravascular administration or injection into highly vascular areas. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of Bupivacaine Hydrochloride Injection BP 0.5% w/v.

Adequate resuscitation equipment should be available whenever local or general anaesthesia is administered. Overdosage or accidental intravenous injection may give rise to toxic reactions with marked restlessness, twitching or convulsions followed by coma with apnoea and cardiovascular collapse.

Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should be in an optimal condition and have an i.v. line inserted before the blocking procedure. The doctor responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see section 4.9).

Major peripheral nerve blocks may require the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption. This may lead to high plasma concentrations.

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention in order to reduce the risk of dangerous side effects:

- The elderly and patients in poor general condition
- Patients with partial or complete heart block-due to the fact that local anaesthetics may depress myocardial conduction
- Patients with advanced liver disease or severe renal dysfunction
- Patients in late stages of pregnancy
- Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used:

- 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.
- Retrobulbar injections may very occasionally reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.
- Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The

primary causes include trauma and/or local toxic effects on muscles and/or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors may aggravate tissue reactions and should be used only when indicated.

- Injections in the head and neck regions may be made inadvertently into an artery which may cause immediate cerebral symptoms even at low doses.
- Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.
- There have been post-marketing reports of chondrolysis in patients receiving post-operative 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. Intraarticular continuous infusion is not an approved indication for Bupivacaine Hydrochloride Injection.

Hypotension and bradycardia may occur as normal physiological phenomena following sympathetic block with central neural blocks.
Epidural anaesthesia and subarachnoid block may lead to hypotension and bradycardia. The risk of such effects can be reduced either by pre-loading the circulation or by injecting a vasopressor. Hypotension should be treated promptly with e.g. ephedrine 5-10mg intravenously and repeated as necessary.

The lowest dose that produces effective anaesthesia should be used. Injection of repeated doses of bupivacaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug. Tolerance varies with the status of the patient. Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their age and physical status. The maximum recommended dose should not be exceeded.

The continuous or repeated administration of this product may give rise to cumulative toxicity and tachyphylaxis.

Bupivacaine hydrochloride should be used with caution in patients with epilepsy, impaired cardiac conduction or in those with hepatic or renal damage.

Bupivacaine hydrochloride solutions should be used with caution in persons with known drug sensitivities. Patients allergic to ester-type local anaesthetic drugs (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide-type such as bupivacaine.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow (e.g. in severe shock).

If this product is used for the production of obstetric epidural analgesia, it is advised that the mother be placed on her side or tilted laterally to avoid caval occlusion with consequent maternal hypotension and foetal acidosis.

Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural and subarachnoid anaesthesia should be used with caution in patients with impaired cardiovascular function.

Children should be given doses commensurate with their age and weight.

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

The presence of Horner’s syndrome should alert the anaesthetist to the excessive cranial spread of local anaesthetic and the possibility of the autonomic and motor complications that can arise from this.

Paediatric population

The use of Bupivacaine Hydrochloride Injection 0.5% w/v for intra-articular block in children 1 to 12 years of age has

not been documented.

The use of Bupivacaine Hydrochloride Injection 0.5% w/v for major nerve block in children 1 to 12 years of age has not been documented.

For Epidural anaesthesia children should be given incremental doses commensurate with their age and weight as especially epidural anaesthesia at a thoracic level may result in severe hypotension and respiratory impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti-arrhythmic agents such as lidocaine and mexiletine, since the systemic toxic effects are additive.

Specific interaction studies with bupivacaine and anti-arrhythmic drugs, class III (e.g. amiodarone) have not been performed, but caution should be advised. (See also section 4.4)

4.6 Fertility, pregnancy and lactation

There is no evidence of untoward effects in human pregnancy. In large doses there is evidence of decreased pup survival in rats and an embryological effect in rabbits if Bupivacaine hydrochloride is administered in pregnancy. Bupivacaine hydrochloride should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks.

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 also Section 4.4)

Bupivacaine enters the mother's milk, but in such small quantities that there is no risk of affecting the child at therapeutic dose levels.

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 CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

4.8.1 *General*

Bupivacaine causes systemic toxicity similar to that observed with other local anaesthetic agents. It is caused by high plasma concentrations as a result of excessive dosage, rapid absorption or, most commonly, inadvertent intravascular injection. Such reactions involve the central nervous system and the cardiovascular system. CNS reactions are characterised by numbness of the tongue, light-headedness, dizziness, blurred vision and muscle twitch, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest.

Cardiovascular reactions are depressant and are characterised by hypotension and myocardial depression. They may be the result of hypoxia due to convulsions and apnoea as well as a direct effect.

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.

The incidence of adverse neurologic reactions associated with the use of local anaesthetics is very low and have

included persistent anaesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control.

In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock).

SOC	Very Common (>1/10)	Common (> 1/100 to < 1/10)	Uncommon (> 1/1,000 to < 1/100)	Rare (≥1/10000 to < 1/1,000)	Not Known
Immune system disorders				Allergic reactions, anaphylactic reaction/shock (see section 4.4)	
Nervous system disorders		paraesthesia, dizziness	Signs and symptoms of CNS toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria)	Neuropathy, peripheral nerve injury, arachnoiditis, paresis and paraplegia	Following epidural injection of some local anaesthetic agents including bupivacaine, high sympathetic blockade may occasionally result in ocular and other symptoms similar to those seen in Horner's syndrome. These effects are encountered more commonly in pregnant women.
Eye disorders				Diplopia	
Cardiac disorders		bradycardia (see section 4.4)		Cardiac arrest (see section 4.4), cardiac arrhythmias	
Vascular disorders		hypertension ((see section 4.5			
Respiratory disorders				Respiratory depression	
Gastrointestinal disorders		vomiting			
Renal and urinary disorders		urinary retention			

Hepatic dysfunction, with reversible increases of SGOT, SGPT, alkaline phosphates & bilirubin, has been observed following repeated injections or infusions of bupivacaine. If signs of hepatic dysfunction are observed during treatment with bupivacaine, the drug should be discontinued.

Accidental subarachnoid injection can lead to very high spinal anaesthesia possibly with apnoea and severe hypotension.

4.8.2 Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively. Signs of toxicity in the central nervous system generally precede cardiovascular toxic effects, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepine or barbiturate.

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, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

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

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Paediatric population
Adverse drug reactions in children are similar to those in adults, however in children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during sedation or general anaesthesia.

4.8.3 Treatment of acute toxicity

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

Treatment of a patient with systemic toxicity consists of arresting convulsions and ensuring adequate ventilation with oxygen, if necessary by assisted or controlled ventilation (respiration). If convulsions occur they must be treated promptly by intravenous injection of thiopental 100-200mg or diazepam 5-10mg.

Prolonged convulsions may jeopardise the patient’s ventilation and oxygenation. If so, injection of a muscle relaxant (eg succinylcholine 1mg/kg body weight) will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation must be considered in such situations.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required. If hypotension is present however, a vasopressor, preferably one with inotropic activity, eg ephedrine 15-30mg, should be given intravenously.

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

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued

monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration. (See sections 4.8.2 & 4.8.3).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code N01B BO1
Bupivacaine is a potent amide local anaesthetic with a prolonged duration of action. It affects sensory nerves more than motor nerves and is ideal for producing analgesia without motor blockade.

5.2 Pharmacokinetic properties

In adults the terminal half-life of bupivacaine is 3.5 hours. The maximum blood concentration varies with the site of injection and is highest after intercostals nerve blockade.
Total dose, rather than concentration, is an important determinant of peak blood levels.
Bupivacaine is biodegraded in the liver and only 6% is excreted unchanged in the urine.

In children the pharmacokinetics is similar to that in adults.

5.3 Preclinical safety data

Bupivacaine hydrochloride is a well established active ingredient.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide,
Water for injections

6.2 Incompatibilities

Bupivacaine Injection should not be mixed with other drugs. The solution must not be stored in contact with metals, e.g. needles or metal parts of syringes, as dissolved metal ions may cause swelling at the site of injection.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Keep the ampoules in the outer carton.
Do not store above 25°C.

6.5 Nature and contents of container

10ml and 20ml translucent polypropylene ampoules packed in cardboard cartons to contain 10, 20, 50 and 100 x 10ml ampoules and 10, 20, 50 and 100 x 20ml ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

If only part of an ampoule is used, discard the remaining solution.
For single use only.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
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8 MARKETING AUTHORISATION NUMBER

PA0073/091/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21 September 2000

10 DATE OF REVISION OF THE TEXT

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