

<p style="text-align: center;">Bupivacaine 0.25% w/v solution for injection Summary of Product Characteristics</p>
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1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine 0.25% w/v solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains bupivacaine hydrochloride 2.64 mg equivalent to anhydrous bupivacaine hydrochloride 2.5 mg.

Each 10 ml contains bupivacaine hydrochloride 26.4 mg equivalent to anhydrous bupivacaine hydrochloride 25 mg.

The product contains sodium chloride.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless or almost colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine 0.25% w/v and 0.5% w/v solution for injection are used for the production of local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anaesthesia is required. Because sensory nerve block is more marked than motor block, bupivacaine is especially useful in the relief of pain, e.g. during labour.

A list of indications and the suggested dose and strength of solution appropriate for each are shown in the table below.

4.2 Posology and method of administration

The utmost care should be taken to prevent an accidental intravascular injection, always including careful aspiration. For epidural anaesthesia, a test dose of 3-5 ml of bupivacaine containing adrenaline should be administered, since an intravascular injection of adrenaline will be quickly recognised by an increase in heart rate

Verbal contact and repeated measurement of heart rate should be maintained throughout a period of 5 minutes following the test dose. Aspiration should be repeated prior to administration of the total dose. The main dose should be injected slowly, 25-50 mg/min, in incremental doses under constant contact with the patient. If mild toxic symptoms occur, the injection should be stopped immediately.

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.

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 total dose of up to 500 mg bupivacaine over 24 hours, which does not include the initial bolus dose, has been used routinely for many years without reports of toxicity. The dosages in the following table are recommended as a guide for use in the average adult. For young, elderly or debilitated patients, these doses should be reduced.

TYPE OF BLOCK	% CONC.	EACH DOSE		MOTOR BLOCK*
		ML	MG	
<u>LOCAL INFILTRATION</u>	0.25	UP TO 60	UP TO 150	-
<u>LUMBAR EPIDURAL</u>				
SURGICAL OPERATIONS	0.5	10 TO 20	50 TO 100	MODERATE TO COMPLETE
ANALGESIA IN LABOUR	0.5	6 TO 12	30 TO 60	MODERATE TO COMPLETE
	0.25	6 TO 12	15 TO 30	MINIMAL
<u>CAUDAL EPIDURAL</u>				
SURGICAL OPERATIONS	0.5	15 TO 30	75 TO 150	MODERATE TO COMPLETE
CHILDREN (AGED UP TO 10 YEARS)				
UP TO LOWER THORACIC (T10)	0.25	0.3 - 0.4 ml/kg	0.75 - 1.0 mg/kg	
UP TO MID- THORACIC (T6)	0.25	0.4 - 0.6 ml/kg	1.0 - 1.5 mg/kg	
IF TOTAL AMOUNT GREATER THAN 20 ML REDUCE CONCENTRATION TO 0.2%.				

<u>ANALGESIA IN LABOUR</u>	0.5	10 TO 20	50 TO 100	MODERATE TO COMPLETE
	0.25	10 TO 20	25 TO 50	MODERATE
<u>PERIPHERAL NERVES</u>	0.5	UP TO 30	UP TO 150	MODERATE TO COMPLETE
	0.25	UP TO 60	UP TO 150	SLIGHT TO MODERATE
<u>SYMPATHETIC BLOCKS</u>	0.25	20 TO 50	50 TO 125	-

*With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block for intra-abdominal surgery.

4.3 Contraindications

Bupivacaine hydrochloride solutions are contra-indicated in patients with a known hypersensitivity to local anaesthetic agents of the amide type or to other components of the injectable formulation.

Solutions of bupivacaine hydrochloride are contra-indicated for intravenous regional anaesthesia (Bier's-block).

Epidural anaesthesia, regardless of the local anaesthetic used, has its own contra-indications which include:

Active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, sub-acute combined degeneration of the cord due to pernicious anaemia and cerebral and spinal tumours; tuberculosis of the spine; pyogenic infection of the skin at or adjacent to the site of lumbar puncture; cardiogenic or hypovolaemic shock; coagulation disorders or ongoing anticoagulation treatment.

4.4 Special warnings and precautions for use

There have been reports of cardiac arrest during the use of bupivacaine for epidural anaesthesia or peripheral nerve blockade where resuscitative efforts have been difficult, and were required to be prolonged before the patient responded. However, in some instances resuscitation has proven impossible despite apparently adequate preparation and appropriate management.

Like all local anaesthetic drugs, bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems if utilised for local anaesthetic procedures resulting in high blood concentrations of the drug. This is especially the case after unintentional intravascular administration. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine.

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.

Before any nerve block is attempted, intravenous access for resuscitation purposes should be established. Clinicians should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see 4.9).

Adequate resuscitation equipment should be available whenever local or general anaesthesia is administered. The clinician responsible should take the necessary precautions to avoid intravascular injection (see 4.2).

Overdosage or accidental intravenous injection may give rise to toxic reactions.

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 physical status.

Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects may be additive.

Only in rare cases have amide local anaesthetics been associated with allergic reactions (in most severe instances anaphylactic shock).

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.

Local anaesthetics should be used with caution for epidural anaesthesia in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow.

The physiological effects generated by a central neural blockade are more pronounced in the presence of hypotension. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia. Epidural anaesthesia should therefore be avoided or used with caution in patients with untreated hypovolaemia or significantly impaired venous return.

Epidural anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include pre-loading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10-15 mg intravenously. Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration, or aorto-caval occlusion in patients

with massive ascites, large abdominal tumours or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation.

Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia.

Epidural anaesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicaemia can increase the risk of intraspinal abscess formation in the postoperative period.

Paracervical block may have a greater adverse effect on the foetus than other nerve blocks used in obstetrics. Due to the systemic toxicity of bupivacaine special care should be taken when using bupivacaine for paracervical block.

Small doses of local anaesthetics injected into the head and neck, including retrobulbar, dental and stellate ganglion blocks, may produce systemic toxicity due to inadvertent intra-arterial injection.

Retrobulbar injections may very rarely reach the cranial subarachnoid space causing serious/severe reactions, including temporary blindness, cardiovascular collapse, apnoea, convulsions.

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.

Each 10 ml of Bupivacaine 0.25% w/v solution for injection contains approximately 1.47 mmol (33.8 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

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-arrhythmics, such as lidocaine, 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 4.4)

4.6 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 is administered in pregnancy. Bupivacaine 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 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

Serious systemic adverse reactions are rare, but may occur in connection with overdosage (see 4.9) or unintentional intravascular injection.

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. Pronounced acidosis or hypoxia may increase the risk and severity of toxic reactions. Such reactions involve the central nervous system (CNS) 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 related to depression of the conduction system of the heart and myocardium leading to decreased cardiac output, heart block, hypotension, bradycardia and sometimes ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation and cardiac arrest. Usually these will be preceded or accompanied by major CNS toxicity, i.e. convulsions, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Epidural anaesthesia itself can cause adverse reactions regardless of the local anaesthetic agent used. These include hypotension and bradycardia due to sympathetic blockade and/or vasovagal fainting.

In severe cases cardiac arrest may occur.

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

Neurological damage is a rare but well recognised consequence of regional and particularly epidural and spinal anaesthesia. It may be due to several causes, e.g. direct injury to the spinal cord or spinal nerves, anterior 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. Occasionally these are permanent.

Hepatic dysfunction, with reversible increases of SGOT, SGPT, alkaline phosphates and bilirubin, has been observed following repeated injections or long-term infusions of

bupivacaine. If signs of hepatic dysfunction are observed during treatment with bupivacaine, the drug should be discontinued.

4.9 Overdose

Acute Systemic Toxicity

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 a 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. In severe cases apnoea may occur. Acidosis, hyperkalaemia 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.

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 to 200 mg or diazepam 5 to 10 mg. Alternatively succinylcholine 50 mg – 100 mg IV may be used providing the clinician is capable of performing endotracheal intubation and managing a fully paralysed patient.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required.

Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and resuscitation must be continued energetically for a prolonged period.

High or total spinal blockade causing respiratory paralysis and hypotension during epidural anaesthesia should be treated by ensuring and maintaining a patent airway and giving oxygen by assisted or controlled ventilation.

Hypotension should be treated by the use of vasopressors, e.g. ephedrine 10-15 mg intravenously and repeated until the desired level of arterial pressure is reached. Intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 intercostal 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.

5.3 Preclinical safety data

No other information other than that which is included in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

10 ml polypropylene ampoules.
Pack size: 20 ampoules x 10 ml

6.6 Special precautions for disposal

For single use only.
Use immediately after opening.
Discard any unused solution

7. MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Ltd.,
Lourdes Road,
Roscrea,
County Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

PL 20910/0008

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Legal Status

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