

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine Hydrochloride Injection BP 0.25% w/v, 10ml & 20ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains bupivacaine hydrochloride BP equivalent to 0.25% w/v anhydrous Bupivacaine Hydrochloride.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless aqueous sterile solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Bupivacaine 0.25% and 0.5% solutions 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 areas where prolonged anaesthesia is indicated. Bupivacaine without adrenaline may also be used for intradural spinal anaesthesia. Bupivacaine is particularly useful for pain relief e.g. during labour, as its sensory nerve block is more marked than its motor block. A list of indications and suggested dose and strength of solution appropriate for each are shown in the table under 'Posology and method of administration'.

4.2. Posology and Method of Administration

Great care must be taken in order to prevent an accidental intravascular injection, always including careful aspirations. For epidural anaesthesia, a test dose of 3 - 5ml 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 frequent measurements of the heart rate, preferably by electrographic (ECG) monitoring, should be maintained throughout a period of 5 minutes following the test dose.

Aspiration should be repeated prior to the administration of the total dose. The main dose should be injected slowly, 25 - 50mg/min., in incremental doses under constant contact with the patient. If mild toxic symptoms develop, the injection must be immediately stopped.

The lowest dosage required to achieve effective anaesthesia should be given. However, the dose will vary, and will be dependent on 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. 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 150mg bupivacaine hydrochloride. Doses of up to 50mg 2-hourly may subsequently be used. 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.

<i>Type of block</i>	<i>% Conc</i>	<i>Each dose</i>		<i>Motor block⁺</i>
		<i>ml</i>	<i>mg</i>	
LOCAL INFILTRATION	0.25	Up to 60	Up to 150	-
LUMBAR EPIDURAL				
Surgical operations	0.50	10 to 20	50 to 100	Moderate to complete
Analgesia in labour	0.50	6 to 12	30 to 60	Moderate to complete
	0.25	6 to 12	15 to 30	Minimal
CAUDAL EPIDURAL				
Surgical operations	0.50	15 to 30	75 to 150	Moderate to complete
Children (aged up to 10yrs): Up to lower thoracic (T10)	0.25	0.3 - 0.4	0.75 - 1.0	
		(ml/kg)	(mg/kg)	
Up to mid-thoracic (T6)	0.25	0.4 - 0.6	1.0 - 1.5	-
		(ml/kg)	(mg/kg)	
If total amount greater than 20ml, reduce concentration to 0.2%				
Analgesia in labour	0.50	10 to 20	50 to 100	Moderate to complete
	0.25	10 to 20	25 to 50	Moderate
PERIPHERAL NERVES	0.50	Up to 30	Up to 150	Moderate to complete
	0.25	Up to 60	Up to 150	Slight to moderate
SYMPATHETIC BLOCKS	0.25	20 to 50	50 to 125	-
*SPINAL ANAESTHESIA FOR SURGERY				
Average Adult	0.5	2 to 4	10 to 20	

⁺ 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.

* Bupivacaine without adrenaline. 4ml maximum dose.

4.3. Contra-Indications

Bupivacaine hydrochloride solutions are contraindicated in patients with a known hypersensitivity to local anaesthetic agents of the amide group or to other components of the injectable formulation. Solutions of bupivacaine hydrochloride are contraindicated for intravenous regional anaesthesia (Bier's block).

Epidural anaesthesia, regardless of the local anaesthetic used, has its own contraindications which include: Active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, subacute combined degeneration of the cord due to pernicious anaemia, and cerebral or 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 anticoagulant therapy. Epidural and spinal anaesthesia is contraindicated in patients with an expanding cerebral lesion, a tumour, cyst or abscess, which may, if the intracranial pressure is suddenly altered, cause obstruction to the cerebrospinal fluid or blood circulation (the pressure cone).

4.4. Special Warnings and Special Precautions for Use

Before any nerve block is attempted, an open vein must be guaranteed (by an indwelling needle, cannula, drip etc.). Adequate resuscitative equipment (oxygen, suction, means of intubation and appropriate emergency drugs) must be available. Epidural and spinal block techniques should only be carried out by clinicians with the necessary knowledge and experience.

There have been reports of cardiac arrest with difficult resuscitation or death during the use of bupivacaine for epidural anaesthesia in obstetrical patients. Resuscitation has been difficult or impossible despite adequate preparation and appropriate management. Cardiac arrest has occurred after convulsions resulting from systemic toxicity presumably following inadvertent intravascular injection. Regardless of the site of injection or overdose, inadvertent 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.

Only in rare cases have amide local anaesthetics been associated with allergic reactions (with anaphylactic shock developing in most severe instances). Patients allergic to ester-type local anaesthetics such as procaine have not shown cross-sensitivity to amide-type agents 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. Local anaesthetics should be used with caution for epidural or spinal anaesthesia in the following situations: severe shock, hypovolaemia, dehydration, hypotension below 90mm systolic or a level less than 30% of their average systolic blood pressure, gross hypotension, marked obesity, senility, cerebral atheroma, myocardial degeneration, toxemia and severe ischaemic heart disease, (especially with a history of recent infarction) because of the dangers of hypotension.

Similar caution is required in cases of impaired cardiovascular conduction, such as patients with a fixed cardiac output (severe valvular stenosis, heart block, beta-blocking therapy), resulting in decreased ability to respond to dilatation of the vascular bed or to compensate for functional changes associated with the prolongation of A-V conduction produced by local anaesthetics.

Epidural and spinal anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include preloading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with posture, pressor drugs e.g. ephedrine 10 - 15mg intravenously in divided doses, intravenous infusions, atropine or glycopyrrolate in the presence of severe bradycardia and oxygen. Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration or aorta-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 may develop sudden and severe hypotension during epidural or spinal anaesthesia.

Epidural and spinal anaesthesia, properly performed, is generally well tolerated by obese patients and by those with obstructive lung disease. However, patients with a splinted diaphragm which interferes with breathing, such as those with hydramnios, large ovarian or uterine tumours, pregnancy, ascites or omental obesity are at risk from hypoxia due to respiratory inadequacy and aortocaval compression due to tumour mass. Lateral tilt, oxygen and mechanical ventilation should be used when indicated. Dosage should be reduced in such patients. Patients who are breathless from any cause e.g. pleural effusion, may become hypoxic, especially if the level of anaesthesia is so high as to cause paralysis of the intercostal muscles.

Septicaemia can increase the risk of intraspinal abscess formation in the post operative 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 para cervical 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. Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anaesthetic injection. Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available as with all other regional procedures.

4.5. Interactions with other Medicinal Products and other Forms of Interaction

Bupivacaine should be used with care in patients receiving anti-arrhythmic drugs with local anaesthetic activity, e.g. lignocaine, since their toxic effects may be additive.

4.6. Pregnancy and Lactation

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

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 bradycardia may occur following paracervical nerve block. Labour may be prolonged leading to the need for caesarian section.

4.7. Effects on Ability to Drive and Use Machines

In general, it is sufficient to allow 2 - 4 hours post nerve block or until full functions have returned following regional nerve block. In many situations, patients receive a sedative or other C.N.S. depressant drug e.g. diazepam, midazolam to allow the block to be performed. One must allow adequate time for the effects of these drugs to clear.

4.8. Undesirable Effects

Serious systemic adverse reactions are rare, but may occur in connection with overdosage 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 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 subarachnoid 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 phosphatase and 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.

4.9. Overdose

Overdosage with bupivacaine causes systemic toxicity similar to that observed with other local anaesthetic agents. Pronounced acidosis or hypoxia may increase the risk and severity of toxic reactions. 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.

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Treatment of 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 thiopentone 100 to 200mg or diazepam 5 to 10mg. Alternatively, succinyl choline 50 to 100mg I.V. may be used providing the clinician is capable of performing endotracheal intubation and managing a fully paralysed patient.

When convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required. However, if hypotension is present a vasopressor, preferably one with inotropic activity such as ephedrine 15 to 30mg in divided doses, should be given intravenously. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and resuscitation must be continued energetically for a long period.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Bupivacaine has a similar mechanism of action to other local anaesthetics in nerve axons in the peripheral nervous system. It also interferes with the function of all organs in which conduction or transmission of impulses occurs. These include effects on the C.N.S., the autonomic ganglia, the neuromuscular junction and all forms of muscle fibres. Following absorption, bupivacaine may cause stimulation of the C.N.S. followed by depression and, in the cardiovascular system; it acts primarily on the myocardium where it may decrease electrical excitability, conduction rate and force of contraction.

5.2. Pharmacokinetic Properties

Like other local anaesthetics, the rate of systemic absorption of bupivacaine is dependent upon the total dose and concentration administered, the route of administration and the vascularity of the tissue locally. Bupivacaine is about 95% bound to plasma proteins, mainly to alpha-1-acid glycoprotein at low concentrations and to albumin at high concentrations.

Foetal concentrations are lower than maternal concentrations because only the free, unbound drug is available for placental transfer. Local anaesthetics are distributed to some extent to all body tissues, with higher concentrations found in highly perfused organs such as liver, heart and brain.

Bupivacaine is metabolised in the liver and is excreted in the urine mainly as metabolites, with only 5 to 6% as unchanged drug.

5.3. Pre-clinical Safety Data

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

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

3 years.

6.4. Special Precautions for Storage

Protect from light.
Store below 25°C.

6.5. Nature and Contents of Container

Clear glass ampoules, glass type 1 Ph Eur. packed in cardboard cartons to contain 10 unwrapped or sterile wrapped ampoules.

Pack sizes: 10 x 10ml sterile wrapped ampoules
 10 x 20ml sterile wrapped ampoules
 10 x 10ml unwrapped ampoules
 10 x 20ml unwrapped ampoules.

6.6. Instruction for Use, Handling and Disposal

If only part used, discard the remaining solution.

7. MARKETING AUTHORISATION HOLDER

Antigen International Limited.,
Roscrea,
Co. Tipperary.

8. MARKETING AUTHORISATION NUMBER

PL 02848/0116

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first product licence: 3/9/88.
Date of last renewal: 19/1/95.

10. DATE OF (PARTIAL) REVISION OF THE TEXT

May 2002