

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine Hydrochloride Injection BP 0.25% w/v.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution contains 2.5mg anhydrous bupivacaine hydrochloride.

3. PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Local or regional anaesthesia with bupivacaine is indicated for:

- Surgical operations, including obstetric operations such as Caesarean section.
- Acute pain relief, including labour or postoperative pain.
- Diagnosis and treatment of chronic pain, e.g. sympathetic nerve blocks.

Bupivacaine can be used for different anaesthetic techniques including local infiltration, minor and major nerve blocks and epidural blockade.

4.2 Posology and method of administration

Care should be taken in order to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and intermittently during the injection is recommended. For epidural anaesthesia, a test dose of 3 - 5ml of bupivacaine containing adrenaline is recommended, since an intravascular injection of an adrenaline-containing solution may be recognised by an increase in heart rate. Verbal contact with the patient and repeated measurements of heart rate (ECG) should be maintained following the test dose. Aspiration should be repeated prior to administration of the main dose. The main dose should be injected slowly in incremental doses of 4 - 5ml while keeping in constant contact with the patient. If toxic symptoms or signs of an intrathecal blockade occur, the injection should be stopped immediately.

Unnecessarily high doses of local anaesthetics are to be avoided. In general, complete blockade of all nerve fibres in large nerves, requires high concentrations of drug. For thinner nerves, or when only a sensory blockade is required (e.g. in the relief of labour

pain), the lower concentrations producing less motor blockade are indicated. The volume of drug used will affect the extent of spread of anaesthesia.

For prolongation of the blockade, an indwelling catheter through which local anaesthetic drug can be injected or infused, may be used. This is common for epidural anaesthesia, but can also be used, for example, for brachial plexus anaesthesia and interpleural analgesia.

The following table is a guide to dosage for the more commonly used techniques. The clinician's experience and knowledge of the patient's physical status are of importance in calculating the required dose. When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the potential problem of increasing systemic concentrations must be addressed. Experience to date indicates that 400mg administered over 24 hours is well tolerated in average adults.

Children require smaller doses and dosage should be calculated on a weight basis up to 1.5mg/kg (see table).

Dosage recommendations for Bupivacaine

The dosages in the table are those considered to be necessary for the production of a successful block and should be regarded as guidelines for use in the average adult. There are wide individual variations in the time to onset and the duration of anaesthesia and it is impossible to be precise. For other regional local anaesthetic techniques consult standard textbooks.

N.B. Risk of systemic effects of adrenaline with large volumes of adrenaline-containing solutions.

Type of block	Conc. Mg/ml	Dose				Onset (min)	Duration (Hours)		Indication	Comments
		Without Adrenaline		With Adrenaline			Without adrenaline	With Adrenaline		
		ml	mg	ml	mg					
Local Infiltration	2.5	40	100	40	100	1-3	3-4	≈	Surgical procedures and post-negative analgesia “	
Digital Block	5.0	20	100	20	100	1-3	4-8	≈		
	2.5	≤5	12.5	-	-	5-10	3-4	NR	Surgical procedures	
Peripheral nerves	2.5	≤10	25	≤10	25	5-10	3-4	≈	Surgical procedures and post-operative analgesia “	
	5.0	≤10	50	≤10	50	5-10	4-8	≈		

≤ -Up to

NR -Not recommended

Type of block	Conc. Mg/ml	Dose				Onset (min)	Duration (hours)		Indications	Comments
		Without adrenaline		With Adrenaline			Without adrenaline	With adrenaline		
		ml	mg	ml	mg					
Intercostal (per nerve)	5.0	2-3	10-15	2-3	10-15		4-8	≈	Pain relief for surgery, post-operative and trauma	
[CAUTION: Beware of drug overdose if many intercostals are to be blocked]										
Interpleural	2.5	20-30	50-75	-	-	10-20	3-4	NR	Post-operative analgesia	
	5.0	20	100	-	-	10-20	4-8	NR		
Brachial plexus	5.0	30	150	30	150	15-30	4-8	≈	Surgical procedures	
Sciatic	5.0	10-20	50-100	10-20	50-100	15-30	4-8	≈		
3 in 1 (Femoral, obturator and lateral cutaneous)	5.0	20-30	100-150	20-30	100-150	15-30	4-8	≈	Surgical procedure	
Knee arthroscopy	2.5	≤30	75	≤30	75	5-10	2-4 hours after washout		Arthroscopy	

≤ -Up to

NR -Not recommended

Type of block	Conc. Mg/ml	Dose				Onset (min)	Duration (hours)		Indication	Comments
		Without adrenaline		With adrenaline			Without adrenaline	With adrenaline		
		ml	mg	ml	mg					
Lumbar epidural	5	≤30	150	≤30	150	1.5-30	1.5-3	≈	Surgical procedures including obstetrics	
	2.5	6-12	15-30	6-12	15-30	2.5	1.2	≈	Labour and post-operative pain relief	Dose repeated when pain reappears Total <400mg/24h
Lumbar epidural-continuous infusion	2.5	5-7.5/h	12.5-18.75/h	-	-	-	-	-	Post-operative or labour pain	Initial bolus dose of bupivacaine 2.5 or 5.0mg/ml required. Total <400mg/24h
Thoracic epidural	5.0	5-10	25	5-10	25	10-15	2-3	≈	Surgical procedures	
	2.5	5-15	50	5-15	50					
Thoracic epidural-continuous infusion	2.5	4-10/h	10-25/h	-	-	-	-	-	Post operative pain after thoracic and upper abdominal procedures	Initial bolus dose of bupivacaine 2.5 or 5.0mg/ml required Total <400mg/24h

≤ =Up to

NR =Not recommended

Type of block	Conc. Mg/ml	Dose				Onset (min)	Duration (hours)		Indication	Comments
		Without adrenaline		With adrenaline			Without adrenaline	With adrenaline		
Caudal epidural adults	5	≤30	150	≤30	150	15-30	2-3	≈	Surgical procedures and post-operative pain relief	Blocks to T10
	2.5	≤30	75	≤30	75	20-30	1-2	≈		
Caudal epidural children	2.5	0.3-0.5/kg	0.75-1.25/kg	0.3-0.5/kg	0.75-1.25/kg	10-15	2-3	≈	Surgical procedures	Blocks to T6
		0.4-0.6/kg	1.0-1.5/kg	0.4-0.6/kg	1.0-1.5/kg				“	

≤ =Up to

NR =Not recommended

4.3 Contraindications

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 tumors. 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 tumor, cyst or abscess, which may, if the intracranial pressure is suddenly altered, cause obstruction to the cerebrospinal fluid or blood circulation (the pressure cone).

Bupivacaine should be used with caution in patients receiving agents structurally related to local anaesthetics, for instance tocainide, since the toxic effects are additive.

4.4 Special warnings and 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.

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 & 4.8).

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.

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 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.

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. 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, severe renal dysfunction, 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, toxæmia 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 function, such as patients with a fixed cardiac output (severe valvular stenosis, partial or complete 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. 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 treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects may be additive.

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.

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.

When bupivacaine is administered as 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.

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.

Retrobulbar injections may very rarely reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc.

Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available as with all other regional procedures.

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.

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 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. (Refer section 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 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

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. Depending on dosage, 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

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

The adverse reaction profile for Bupivacaine hydrochloride is similar to those for other long acting local anaesthetics. Adverse reactions caused by the drug per se are difficult to distinguish from the physiological effects of the nerve block (e.g., decrease in blood pressure, bradycardia), events caused directly (e.g., nerve trauma) or indirectly (e.g., epidural abscess) by needle puncture.

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.

The adverse reactions considered at least possibly related to treatment with Bupivacaine hydrochloride from clinical trials with related products and post-marketing experience are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (1/10), common (1/100, < 1/10), uncommon (1/1,000, < 1/100), rare (1/10,000, < 1/1,000) including isolated reports, or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Table of Adverse Drug Reactions (ADR)

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic reaction/shock (see section 4.4)
Nervous system disorders	Common	paraesthesia, dizziness
	Uncommon	Signs and symptoms of CNS toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria,

		muscle twitching)
	Rare	Neuropathy, peripheral nerve injury, arachnoiditis, paresis and paraplegia
Eye disorders	Rare	Diplopia
Cardiac disorders	Common	Bradycardia (see section 4.4)
	Rare	Cardiac arrest (see section 4.4), cardiac arrhythmias
Vascular disorders	Very Common	Hypotension (see section 4.4)
	Common	Hypertension (see section 4.5)
Respiratory disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Renal and Urinary	Common	Urinary retention

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.

4.8.1 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.

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 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.

4.8.2 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).

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

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.

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.

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.

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 slower increase in local anaesthetic blood concentration. (see sections 4.8.1 and 4.8.2)

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B51

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 occur. These include effects on the C.N.S, the autonomic ganglia, the neuromuscular junction and all forms of muscle fibres. At high doses it produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia) with less pronounced motor block. 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, force of contraction and eventually cardiac arrest.

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. In adults, the terminal half-life of Bupivacaine is 2.7 hours. In neonates and some young infants, terminal elimination half-lives could be as long as 8 to 12 hours. The maximum blood concentration varies with the site of injection.

Amide local anaesthetics including Bupivacaine have been shown to have diminished clearance in neonates and infants less than 3 months of age, with steady maturation until they reach levels of adult clearance at about 8 months of age. Although clearance is similar in older children and adolescents, the steady state volume of distribution (VD_{ss}) is increased in children compared to that in adults. 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 Preclinical safety data

Bupivacaine hydrochloride is a well established active ingredient.

6.1 List of excipients

Sodium chloride, sodium hydroxide, water for injections.

6.2 Incompatibilities

Bupivacaine Hydrochloride Injection should not be mixed with other drugs unless their compatibility is known.

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 (36 months).

6.4 Special precautions for storage

Protect from light.
Store below 25°C.

6.5 Nature and contents of container

10ml and 20ml translucent plastic ampoules made from polypropylene Ph.Eur.
Pack sizes: 10, 20, 50 and 100.

6.6 Instructions for use/handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.
Roscrea
Co. Tipperary
Ireland

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PL 02848 / 0178

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