

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Injection BP 0.25% w/v, solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml of sterile solution for injection contains Bupivacaine Hydrochloride equivalent to 25 mg of Anhydrous Bupivacaine Hydrochloride (2.5 mg in 1 ml)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A colourless or almost colourless sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bupivacaine Hydrochloride Injection B.P. is 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.

4.2 Posology and method of administration

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

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

Every precaution should be taken to avoid an accidental intravascular injection; careful aspiration is essential. For epidural anaesthesia, a test dose of bupivacaine containing adrenaline will be quickly recognized by an increase in heart rate. Verbal contact with the patient and repeated measurement of heart rate (ECG) 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 – 50mg/min, in incremental doses under constant contact with the patient, if toxicity symptoms or signs of an intrathecal blockade occur, the injection should be stopped immediately.

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. A maximum dose of 2mg/kg should not be exceeded in any four hour period and the total dose over 24 hours should not exceed 400mg. 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	
		ml	mg
LOCAL INFILTRATION	0.25	Up to 60	Up to 150
LUMBAR EPIDURAL	0.50	10 to 20	50 to 100
Surgical operations	0.25	15 to 20	37.5 to 50
Analgesia in labour	0.50	6 to 12	30 to 60
	0.25	6 to 12	15 to 30
CAUDAL EPIDURAL	0.50	15 to 30	75 to 150
Surgical operations	0.25	15 to 40	37.5 to 100
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 20ml, reduce concentration to 0.2%			
ANALGESIA IN LABOUR (rarely used)	0.50	10 to 20	50 to 100
	0.25	10 to 20	25 to 50
PERIPHERAL NERVES	0.50	Up to 30	Up to 150
	0.25	Up to 60	Up to 150
SYMPATHETIC BLOCKS	0.25	20 to 50	50 to 125

4.3 Contraindications

Bupivacaine Hydrochloride Injection BP is contraindicated in patients with a known hypersensitivity to local anaesthetic agents of the amide group or to other components of the injection formulation. Solutions of bupivacaine hydrochloride are contraindicated for intravenous regional anaesthesia (Bier's block), paracervical block in obstetrics, and are contraindicated for injection into inflamed or infected areas.

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 the lumbar puncture. Cardiogenic or hypovolaemic shock. Coagulation disorders or ongoing anticoagulant or antiplatelet 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 precautions for use

The maximum safe dose of this agent depends on the clinical condition and physical characteristics of the patient together with the concentration of the agent and the area and route of administration and should be determined on an individual basis. The maximum recommended dose should not be exceeded.

The lowest effective dose should be used. Continuous or repeated administration of this product may give rise to cumulative toxicity with significantly increased blood levels and tachyphylaxis.

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.

Epidural blockade and large nerve plexus blocks should only be employed by those with the necessary training and experience.

Great caution must be exercised to avoid overdose as a result of repeated dose or accidental intravascular injection of this compound, since either may give rise to rapid onset of toxicity, with marked restlessness, twitching, or convulsions, followed by coma with apnoea and cardiovascular collapse. Adequate resuscitation facilities should be immediately available.

This product should be used with caution in patients with epilepsy, impaired cardiac conduction, or in those with hepatic impairment, including reduced hepatic blood flow, or renal damage.

There have been reports of cardiac arrest with difficult resuscitation or death during use of bupivacaine for epidural anaesthesia in obstetrical patients. In most cases, this has followed use of the 0.75% concentration. Resuscitation has been difficult or impossible despite apparently adequate preparations and appropriate management. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection.

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

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

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

Epidural anaesthesia with any local anaesthetic, can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken.

4.5 Interaction with other medicinal products and other forms of interaction

Other drugs which are highly protein-bound e.g. anticonvulsants or anticoagulants, or which are metabolised in the liver, e.g. cimetidine, may affect the metabolism of bupivacaine

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

4.6 Pregnancy and lactation

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

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 caesarean section. (*See section 4.3, Contraindications*).

4.7 Effects on ability to drive and use machines

Where outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is restored.

4.8 Undesirable effects

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 characterized 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).

Hepatic dysfunction, with reversible increase 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.

Very Common > 1/10)	Vascular disorders:	hypotension
	Gastrointestinal disorders:	nausea
	Nervous system disorders:	paraesthesia, dizziness
	Cardiac disorders:	bradycardia
Common > 1/100 < 1/10)	Vascular disorders:	hypertension
	Gastrointestinal disorders:	vomiting
	Renal and urinary disorders:	urinary retention
Uncommon > 1/1,000 < 1/100)	Nervous system disorders:	Signs and symptoms of CNS toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria)
	Immune system disorders:	Allergic reactions, anaphylactic reaction/shock
Rare (< 1/1,000)	Nervous system disorders:	Neuropathy, peripheral nerve injury, arachnoiditis, paresis and

Eye disorders:	paraplegia Diplopia
Cardiac disorders:	Cardiac arrest, cardiac arrhythmias
Respiratory disorders:	Respiratory depression

4.9 Overdose

Overdosage with 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. (*See section 4.8. Undesirable Effects*).

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.

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.

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. Intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and successful outcome may require prolonged resuscitative efforts.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code N01B B01

Bupivacaine Hydrochloride is a long-acting local anaesthetic of the amide type. It prevents the generation and conduction of the nerve impulse by decreasing the permeability of the nerve cell membrane to sodium ions. As well as blocking conduction in nerve axons in the peripheral nervous system, local anaesthetics interfere with the function of all organs in which conduction or transmission of impulses occur. 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. The drug crosses the placenta.

5.3 Preclinical 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 (for pH adjustment)
Water for Injections

6.2 Incompatibilities

Bupivacaine Injection BP 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

Do not store above 25°C.

Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

10ml, clear glass ampoules, glass type 1 Ph.Eur. borosilicate glass packed in cardboard cartons available as:

carton containing 10 x 10ml ampoules

carton containing 10 x 10ml individually sterile wrapped ampoules

10 x 10ml individual sterile non-reclosable lidded trays.

Not all pack sizes may be marketed

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

Do not use if the solution is discoloured.

For single use only, if only part used, discard the remaining solution.

7 MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Limited

Chandler House

Castle Street

Roscrea

Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 0073/091/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 1988

Date of last renewal: 21 January 2008

10 DATE OF REVISION OF THE TEXT

January 2010