

PART II**SUMMARY OF PRODUCT CHARACTERISTICS****1. NAME OF THE MEDICINAL PRODUCT**

Bupivacaine Hydrochloride Injection BP 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**

In the production of local or regional anaesthesia where a prolonged effect is required.

4.2 Posology and Method of Administration

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

Recommended dosage: A maximum dose of 2mg/kg should not be exceeded in any four-hour period.

Elderly & debilitated patients, children: Dosage should be reduced.

Caudal block in children:

Age 1 to 10 years: Up to lower thoracic (T10)
0.25% (2.5mg/ml) 0.75 to 1mg/kg

Mid-thoracic
0.25% (2.5mg/ml) 1.0 to 1.25mg/kg

If total amount greater than 20ml, reduce concentration to 0.2%

4.2 **Posology and Method of Administration (Cont/d)**

The table below is intended as a guide for dosage in healthy adults.

Obstetrical Procedure	Conc. (%)	Dose	
		(ml)	(mg)
Lumbar epidural anaesthesia	0.25	6 – 12	15 – 30
	0.5	6 – 12	30 – 60
Caudal epidural anaesthesia	0.25	15 – 30	37.5 – 75
	0.5	10 – 20	50 – 100

Surgical Procedure	Conc. (%)	Dose	
		(ml)	(mg)
Local infiltration anaesthesia	0.25	Up to 60	Up to 150
Peripheral nerve block	0.25	5 – 60	12.5 – 150
	0.5	2.5 – 30	12.5 – 150
Lumbar epidural anaesthesia	0.25	15 – 20	37.5 – 50
	0.5	10 – 20	50 – 100
Caudal epidural anaesthesia	0.25	15 – 40	37.5 – 100
	0.5	15 – 30	75 – 150
Sympathetic	0.25	20 – 50	50 – 125

4.3 **Contraindications**

Injection into inflamed or infected areas.

Hypersensitivity to the active ingredient or to the components of the formulation.

Use intravenously.

Use for obstetrical paracervical block.

4.4 Special Warnings and Special 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.

Great caution must be exercised to avoid overdose 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 may give rise to allergic manifestations.

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.

4.5 Interactions with Other Medicaments 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.

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.

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

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.

Allergic reactions to bupivacaine may occur but are rare.

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 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.

4.9 Overdosage

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.

4.9 Overdosage (Cont/d)

Such reactions involve the central nervous system and the cardiovascular system.

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. 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

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 occurs. 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 rate 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
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 metals ions may cause swelling at the site of injection.

6.3 Shelf Life

3 years.
If only part of an ampoule is used, discard the remaining solution.

6.4 Special Precautions for Storage

Protect from light.
Store below 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 Instructions for Use and Handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Limited
Roscrea
Co Tipperary

8. MARKETING AUTHORISATION NUMBER

PA 73/91/9

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

21st September 1995/21st September 2000

10. DATE OF REVISION OF THE TEXT