SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine and Adrenaline (Epinephrine) Injection 0.25% w/v, 1 in 200,000

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml of solution contains Bupivacaine Hydrochloride B.P. 26.375mg equivalent to anhydrous Bupivacaine Hydrochloride 25mg, Adrenaline Acid Tartrate B.P. 0.091mg equivalent to Adrenaline 0.05mg

Excipient(s) with known effect:

Each 10ml also contains sodium metabisulfite: 5mg

Sodium: 33.48 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. Colourless or almost colourless, aqueous, 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 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 4.2 below.

- Surgical anaesthesia in adults and children above 12 years of age.
- Acute pain management in adults, infants and children above 1 year of age

Note:
From the reviewed literature only evidence for the use of bupivacaine 1.25 - 2.5 mg/ml + 2.5 - 5μg/ml adrenaline for caudal epidural block in children > 1 year of age could be derived.
Regarding other anaesthetic techniques, the investigated paediatric population were mostly very small and a variety of different applications were studied, so that no reliable recommendations can be derived from the literature.

As for other local anaesthetics, recommendations for the adolescent population above 12 years remain included in the information for adults.

4.2 Posology and method of administration

Posology

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.

Type of block	% Conc.	Each dose		Motor block+
		ml	mg	
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

Type of block	% Conc.	Each dose		Motor block+
		ml	mg	
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	-

+ 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.

Paediatric population

Paediatric patients 1 to 12 years of age

Paediatric regional anaesthetic procedures should be performed by qualified clinicians who are familiar with this population and the technique.

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. The lowest dose required for adequate analgesia should be used.

The duration may be prolonged with the adrenaline-containing solutions.

N.B. Risk of systemic effects of adrenaline with large volumes of adrenaline containing solutions should be considered.

Table: Dosage recommendations for children 1 to 12 years of age

	Conc. mg/ml	Volume ml/kg	Dose mg/kg	Onset min	Duration of effect hours
ACUTE PAIN MANAGEMENT (per-and postoperative)					
Caudal, lumbar and thoracic Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose. This should be injected slowly in incremental doses, particularly in the lumbar and thoracic epidural routes, constantly and closely observing the patient's vital functions. Thoracic epidural blocks need to be given by incremental dosage until the desired level of anaesthesia is achieved.

The safety and efficacy of Bupivacaine and Adrenaline (Epinephrine) Injection 0.25% w/v, 1 in 200,000 in children < 1 year of age have not been established. Only limited data are available.

Safety and efficacy of intermittent epidural bolus injection or continuous infusion have not been established. Only limited data is available.

Method of administration

Epidural injection.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

Bupivacaine hydrochloride solutions are contraindicated in patients with a known hypersensitivity to local anaesthetic agents of the amide group.

Solutions of bupivacaine hydrochloride are contraindicated for intravenous regional anaesthesia (Bier's block). Solutions containing adrenaline are contraindicated in patients with thyrotoxicosis or severe heart disease particularly when tachycardia is present.

Solutions of bupivacaine containing adrenaline should not be used in connection with anaesthesia in areas of the body supplied by end arteries or otherwise having a compromised blood supply such as digits, nose, external ear or genitalia owing to the risk of tissue necrosis.

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 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).

Injection of adrenaline containing bupivacaine in areas of end arteries (e.g. penile block, Oberst block) may cause ischemic tissue necrosis.

Note: No specific contraindications were identified for paediatric patients.

4.4 Special warnings and precautions for use

Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available whenever local or general anaesthesia is administered. Patients receiving major blocks should be in an optimal condition and have an i.v. line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid overdose or intravascular injection, always including careful aspiration, and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications such as marked restlessness, twitching or convulsions followed by coma with apnoea and cardiovascular collapse.

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. 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.

Like all local anaesthetic drugs, bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems if utilized for local anaesthetic procedures resulting in high blood concentrations of the drug.

Accidental intravascular injection of bupivacaine may lead to systemic toxicity which could result in:

- Cerebral haemorrhage due to the sudden rise in blood pressure
- Convulsions leading to cardiac arrest
- Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death.

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.

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention in order to reduce the risk of dangerous side effects:

• The elderly and patients in poor general condition should be given reduced doses commensurate with their physical status.
• Patients with partial or complete heart block – due to the fact that local anaesthetics may depress myocardial conduction.
• Patients with advanced liver disease or severe renal dysfunction.
• Patients in late stages of pregnancy

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.

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

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.

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. Bupivacaine with adrenaline solutions contain sodium metabisulphite, which can cause allergic-type reactions including anaphylaxis and life threatening or less severe asthmatic episodes in certain susceptible individuals. The overall prevalence of sulphite sensitivity in the general population is unknown and

probably low. Sulphite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

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 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 hypertension, marked obesity, senility, cerebral atheroma, myocardial degeneration, toxaemia 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 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.

Epidural 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 intercostals muscles.

Septicaemia can increase the risk of intraspinal abscess formation in the post operative period.

Solutions containing adrenaline should be used with caution in patients with hyperthyroidism, diabetes mellitus, pheochromocytoma, narrow angle glaucoma, hypokalaemia, hypercalcaemia, severe renal impairment, prostatic adenoma leading to residual urine, cerebrovascular disease, organic brain

damage or arteriosclerosis, in elderly patients, in patients with shock (other than anaphylactic shock) and in organic heart disease or cardiac dilatation (severe angina pectoris, obstructive cardiomyopathy, hypertension) as well as most patients with arrhythmias.
Anginal pain may be induced when coronary insufficiency is present.
Adrenaline should be used cautiously, if at all, during general anaesthesia with halogenated hydrocarbon anaesthetics (See section 4.5).

Prolonged use of Adrenaline can result in severe metabolic acidosis because of elevated blood concentrations of lactic acid.

Paediatric population

The safety and efficacy of Bupivacaine and Adrenaline (Epinephrine) Injection 0. 25% w/v, 1 in 200,000 in children aged < 1 year of age have not been established. Only limited data are available.

For Epidural anaesthesia children should be given incremental doses commensurate with their age and weight as especially epidural anaesthesia at a thoracic level may result in severe hypotension and respiratory impairment.

Excipients
This medicine contains sodium metabisulphites which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicine contains 200.88 mg sodium (main component of cooking/table salt) in each 150 mg of dose. This is equivalent to 0.05% of the recommended maximum daily dietary intake of sodium for an adult.

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. (see also 4.4)

Sympathomimetic agents:

Adrenaline should not be administered concomitantly with other sympathomimetic agents because of the possibility of additive effects and increased toxicity.

Alpha-adrenergic blocking agents:

Alpha-blockers such as phentolamine antagonise the vasoconstriction and hypertension effects of adrenaline. This effect may be beneficial in adrenaline overdose (See section 4.9).

Beta-adrenergic blocking agents:

Severe hypertension and reflex bradycardia may occur with non-cardioselective beta-blocking agents such as propranolol, due to alpha-mediated vasoconstriction. Beta-blockers, especially non-cardioselective agents, also antagonise the cardiac and bronchodilator effects of adrenaline.

General Anaesthetics:

Administration of Adrenaline in patients receiving halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitise the myocardium to Adrenaline may result in arrhythmias including ventricular premature contractions, tachycardia or fibrillation (See section 4.4).

Antihypertensive agents:

Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers such as guanethidine, with the risk of severe hypertension. Adrenaline increases blood pressure and may antagonise the effects of antihypertensive drugs.

Antidepressant agents:

Tricyclic antidepressants such as imipramine inhibit reuptake of directly acting sympathomimetic agents, and may potentiate the effect of adrenaline, increasing the risk of development of hypertension and cardiac arrhythmias.

Although monoamine oxidase (MAO) is one of the enzymes responsible for Adrenaline metabolism, MAO inhibitors do not markedly potentiate the effects of Adrenaline.

Phenothiazines:

Phenothiazines block alpha-adrenergic receptors (see above).

Other drugs:

Adrenaline should not be used in patients receiving high dosage of other drugs (e.g. cardiac glycosides) that can sensitise the heart to arrhythmias. Some antihistamines (e.g. diphenhydramine) and thyroid hormones may potentiate the effects of Adrenaline, especially on heart rhythm and rate.

Solutions containing adrenaline should also be used with caution in patients receiving dopaminergics such as entacapone, the respiratory stimulant doxapram and the interotropic hormone oxytocin.

Hypokalaemia:

The hypokalaemic effect of adrenaline may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, aminophylline and theophylline. Hypokalaemia may result in increased susceptibility to cardiac, arrhythmias caused by digoxin and other cardiac glycosides.

Hyperglycaemia:

Adrenaline-induced hyperglycaemia may lead to loss of blood-sugar control in diabetic patients treated with insulin or oral hypoglycaemic agents.

4.6 Fertility, Pregnancy and lactation

Pregnancy

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.

The addition of adrenaline may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels. Foetal bradycardia may occur following paracervical nerve block.

Labour may be prolonged leading to the need for caesarean section.

Breast-feeding

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

Fertility

No data available

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

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 nonsterile 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 postmarketing 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 Following epidural injection of some local anaesthetic agents including bupivacaine, high sympathetic blockade may occasionally result in ocular and other symptoms similar to those seen in Horner's syndrome. These effects are encountered more commonly in pregnant women.
	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, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Renal and	Common	Urinary retention

Urinary disorders		

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.

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

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

Paediatric population

Adverse drug reactions in children are similar to those in adults, however, in children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during sedation or general anaesthesia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 by administration of anticonvulsant drugs 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 section 4.8.1 Acute systemic toxicity and 4.8.2 Treatment of acute systemic toxicity).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics, ATC code: N01BB51

Mechanism of action

Similar mechanism of action to other local anaesthetics in nerve axons in the peripheral nervous system. 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.

Pharmacodynamic effects

Restlessness tremour proceeding to convulsions followed by depression of the C.N.S. and death. Drowsiness is a common feature.

Signs and symptoms may be due to the inadvertent absorption of adrenaline which may lead to cardiovascular collapse or sudden ventricular fibrillation.

5.2 Pharmacokinetic properties

Distribution

Redistribution of bupivacaine is dependent on its tissue partition coefficient and the mass and perfusion of the tissue. The amount of free drug is dependent on its binding to tissue and erythrocyte proteins, its non specific binding to albumin and specific binding to alpha lipoproteins in the plasma and the pH gradient.

Elimination

It is cleared from the body by metabolism and excretion.

Paediatric population

In children the pharmacokinetics is similar to that in adults.

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 Metabisulphite (E223) B.P.

Sodium Chloride B.P.

Water for Injections B.P. (in bulk)

Sodium Acetate B.P.

6.2 Incompatibilities

(i) Should not be mixed with other drugs.

(ii) 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 the injection.

6.3 Shelf life

Unopened : 2 years

After reconstitution : not applicable

If only part of an ampoule is used, the remainder should be discarded.

6.4 Special precautions for storage

Keep in outer carton.

Do not store above 25°C.

6.5 Nature and contents of container

10 ml clear One point cut (OPC) glass ampoules, glass type I PhEur, packed in cardboard cartons to contain 10 x 10ml ampoules.

10ml, clear One point cut (OPC) glass ampoules, glass type I Ph.Eur. individually sterile wrapped in an autoclave bag and packed in cardboard cartons to contain 10 x 10ml ampoules.

6.6 Special precautions for disposal

Caution : For routes of administration see Data Sheet.

Use as directed by the physician.

Keep out of reach of children.

If only part used, discard the remaining solution.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd,
Dashwood House,
69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0556

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/03/1991 / 19/09/2001

10 DATE OF REVISION OF THE TEXT

22/01/2024