SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Hydrochloride 2.5 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2.5 mg of bupivacaine hydrochloride

Each ampoule with 10ml solution contains 25 mg of bupivacaine hydrochloride.

Excipient with known effect: Each ml of 2.5 mg/ml solution for injection contains approximately 3.38 mg (0.15 mmol) of Sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless, aqueous, sterile solution.

pH of the solution is between 4.0 and 6.5 and osmolality is 270-330 mOsmol/Kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine Hydrochloride 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 situations where prolonged anaesthesia is required. Because sensory nerve block is more marked than motor block, Bupivacaine Hydrochloride is especially useful in the relief of pain, e.g. during labour.

Bupivacaine Hydrochloride is indicated for

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

The suggested dose and strength of solution appropriate for each indication are provided in Section 4.2.

4.2. Posology and method of administration

Posology

Adults and children above 12 years of age

The dosage varies and depends upon 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. The lowest dosage needed to provide effective anaesthesia should be administered. 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 150 mg bupivacaine hydrochloride monohydrate. Doses of up to 50 mg 2-hourly may subsequently be used. A maximum dose of 2 mg/kg should not be exceeded in any four-hour period.

The following table is a guide to dosage for the more commonly used techniques in the average adult. The figures reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

N.B. When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing a local neural injury must be considered.

The clinician's experience and knowledge of the patient's physical status is important in calculating the required dose. The lowest dose required for adequate anaesthesia should be used. Individual variations in onset and duration occur.

Table 1 Dosage recommendations for adults

	Conc (mg/ml)	**Volume (ml)**	**Dose (mg)**	**Onset (min)**	**Duration of effect (hours)[7]**
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration [(1)]					
Surgery	5.0	15-30	75-150	15-30	2-3

Caesarean Section	5.0	15-30	75-150	15-30	2-3
Thoracic Epidural Administration (1)					
Surgery	2.5	5-15	12.5-37.5	10-15	1.5-2
	5.0	5-10	25-50	10-15	2-3
Caudal Epidural Block (1)					
	2.5	20-30	50-75	20-30	1-2
	5.0	20-30	100-150	15-30	2-3
Major Nerve Block (2) (e.g. brachial plexus, femoral, sciatic)	5.0	10-35	50-175	15-30	4-8
Field block (e.g. minor nerve blocks and infiltration)	2.5	<60	<150	1-3	3-4
	5.0	□30	□150	1-10	3-8
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Intermittent injections (3) *(e.g. post-operative pain relief)*	2.5	6-15; minimum interval 30	15-37.5; minimum interval	2-5	1-2
		minutes	30 minutes		
Continuous infusion (4)	1.25	10-15/h	12.5-18.8/h	-	-
	2.5	5-7.5/h	12.5-18.8/h	-	-
Continuous infusion, labour pain relief (4)	1.25	5-10/h	6.25-12.5/h	-	-
Thoracic Epidural Administration					
Continuous infusion(4)	1.25	5-10/h	6.3-12.5/h	-	-
	2.5	4-7.5/h	10-18.8/h	-	-
Intra-Articular Block (6) (eg, single injection following knee arthroscopy)	2.5	≤40	≤100[5]	5-10	2-4 h after wash out
Field Block *(eg, minor nerve blocks and infiltration)*	2.5	≤60	≤150	1-3	3-4

Notes:

1) Dose includes test dose.
2) The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, see also section 4.4.

3) In total ≤500 mg/24 h.
4) This solution is often used for epidural administration in combination with a suitable opioid for pain management. In total ≤400 mg/24 h.
5) If additional bupivacaine is used by any other techniques in the same patient, an overall dose limit of 150 mg should not be exceeded.
6) There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. Bupivacaine solution for injection is not approved for this indication (see section 4.4).
7) Bupivacaine without adrenaline.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When a less intense block is required (e.g. in the relief of labour pain), the use of a lower concentration is indicated. The volume of drug used will affect the extent of spread of anaesthesia.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3-5 ml bupivacaine containing adrenaline (epinephrine) is recommended.

An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately (see section 4.8.1).

Experience to date indicates that 400 mg administered over 24 hours is well tolerated in the average adult.

Paediatric population 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.

Table 2 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 (pre- and postoperative**)**					
Caudal Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Lumbar Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Thoracic Epidural Administration **a)**	2.5	0.6-0.8	1.5-2	20-30	2-6
Field Block (eg, minor nerve blocks and infiltration)	2.5 5.0		0.5-2.0 0.5-2.0		
Peripheral Nerve Blocks (e.g ilioinguinal – iliohypogastric)	2.5 5.0		0.5-2.0 0.5-2.0	a) a)	

a) Thoracic epidural blocks need to be given by incremental dosage until the desired level of anaesthesia is achieved.
b) The onset and duration of peripheral nerve blocks depend on the type of block and the dose administered.

In children the dosage should be calculated on a weight basis up to 2 mg/kg.

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.

Peritonsillar infiltration has been performed in children above 2 years of age with bupivacaine 2.5 mg/ml at a dose of 7.5-12.5mg per tonsil.

Ilioinguinal-iliohypogastric blocks have been performed in children aged 1 year or older with bupivacaine 2.5 mg/ml at a dose of 0.1-0.5 ml/kg equivalent to 0.25-1.25 mg/kg. Children aged 5 years or older have received bupivacaine 5 mg/ml at a dose of 1.25-2 mg/kg.

For penile blocks bupivacaine 5 mg/ml has been used at total doses of 0.2-0.5 ml/kg equivalent to 1-2.5 mg/kg.

The safety and efficacy of bupivacaine with and without adrenaline in children aged < 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
The medicinal product is for epidural use, intraarticular use, subcutaneous use or perineural use only.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Bupivacaine hydrochloride solutions are contra-indicated in patients with hypersensitivity to local anaesthetic agents of the amide type.

Solutions of bupivacaine hydrochloride are contra-indicated for injection into inflamed or infected areas and for intravenous regional anaesthesia (Bier's-block) and obstetrical paracervical block.

Epidural anaesthesia, regardless of the local anaesthetic used, has its own contra- indications which include:

Active diseases of the central nervous system such as meningitis, poliomyelitis and intracranial haemorrhage, sub-acute combined degeneration of the cord due to pernicious anaemia and cerebral and 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 anticoagulation treatment.

4.4. Special warnings and precautions for use

There have been reports of cardiac arrest or death during the use of bupivacaine for epidural anaesthesia or peripheral nerve blockade where resuscitative efforts have been difficult, and were required to be prolonged before the patient responded. However, in some instances resuscitation has proven difficult or impossible despite apparently adequate preparation and appropriate management.

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.

Adequate resuscitation equipment should be available whenever local or general anaesthesia is administered. Overdosage or accidental intravenous injection may give rise to toxic reactions with marked restlessness, twitching or convulsions followed by coma with apnoea and cardiovascular collapse.

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. 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 intravascular injection (see section 4.2) and be appropriately trained and familiar with the diagnosis and treatment of side effects, systematic toxicity and other complications (see section 4.9).

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.

Overdosage or accidental 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.

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 the late stages of pregnancy.
- 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.

Patients allergic to ester-type local anaesthetic drugs (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide type such as bupivacaine.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used.

- Local anaesthetics should be used with caution for epidural anaesthesia in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.
- The physiological effects generated by a central neural blockade are more pronounced in the presence of hypotension. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia. Epidural anaesthesia should therefore be avoided or used with caution in patients with untreated hypovolaemia or significantly impaired venous return.
- Retrobulbar injections may very rarely reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions, etc. These must be diagnosed and treated promptly.
- 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.
- 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.
- Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.

There have been post-marketing reports of chondrolysis in patients receiving post- operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for bupivacaine solution for injection.

Hypotension and bradycardia may occur as normal physiological phenomena following sympathetic block with

central neural blocks. Epidural anaesthesia and subarachnoid block may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

The lowest dose that produces effective anaesthesia should be used. 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. The maximum recommended dose should not be exceeded.

The continuous or repeated administration of this product may give rise to cumulative toxicity and tachyphylaxis. Bupivacaine hydrochloride should be used with caution in patients with epilepsy, impaired cardiac conduction or in those with hepatic or renal damage.

Bupivacaine hydrochloride solutions should be used with caution in persons with known drug sensitivities. Patients allergic to ester-type local anaesthetic drugs (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide type such as Bupivacaine Hydrochloride.

Since Bupivacaine hydrochloride is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow (e.g. in severe shock).

Epidural anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. The risk of such effects can be reduced, e.g. by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration, or aorto-caval occlusion in patients with massive ascites, large abdominal tumours or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation.

Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia.

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.

Children should be given doses commensurate with their age and weight.

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.

Hepatic dysfunction, with reversible increases of alanine aminotransferase (ALT), alkaline phosphates (AlkP) and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. Association between bupivacaine use and the development of drug-induced liver injury (DILI) has been reported in a small number of literature reports especially with prolonged use. While the pathophysiology of this reaction remains unclear, immediate withdrawal of bupivacaine has shown rapid clinical improvement. If signs of hepatic dysfunction are observed during administration with bupivacaine, the medicinal product should be discontinued.

Paediatric population:

The safety and efficacy of Bupivacaine hydrochloride in children < 1 year of age have not been established. Only limited data are available.

The use of bupivacaine for intra-articular block in children 1 to 12 years of age has not been documented.

The use of bupivacaine for major nerve block in children 1 to 12 years of age has not been documented.

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.

Information on sodium content

Each ml of Bupivacaine 2.5 mg/ml solution for injection contains approximately 0.15 mmol (3.38 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet.

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 Section 4.4).

4.6. Fertility, Pregnancy and lactation

Pregnancy

It is reasonable to assume that a large number of pregnant women and women of childbearing age have been given bupivacaine hydrochloride.

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 section 4.4)

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 human data on the effect of bupivacaine on fertility are available.

4.7 Effects on ability to drive and use machines

Bupivacaine has minor influence on the ability to drive and use machines. Besides the direct anaesthetic effect, 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

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 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 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.

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

The adverse reaction profile for Bupivacaine 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. In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock).

Tabulated list of adverse reactions

The adverse reactions considered at least possibly related to treatment with Bupivacaine 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 to <1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (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, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Renal and urinary	Common	Urinary retention
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.

1.1.1 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. Signs of toxicity in the central nervous system generally precede cardiovascular toxic effects, unless the patient is receiving a general anaesthetic or is heavily sedated with medicinal products such as benzodiazepine or barbiturate.

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, hypocalcaemia 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.

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 general anaesthesia.

1.1.2 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 cardiovascular depression occurs (hypotension, bradycardia) appropriate treatment with intravenous fluids, vasopressor, inotropic agents and/or lipid emulsion should be considered. Children should be given doses commensurate with age and weight.

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.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 the slower increase in local anaesthetic blood concentration (See sections 4.8.1 & 4.8.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B51

Bupivacaine hydrochloride is a long acting local anaesthetic of the amide type with both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia) with less pronounced motor block.

Onset and duration of the local anaesthetic effect of bupivacaine depends on the dose and site of administration.

Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. The sodium channels of the nerve membrane are considered a receptor for local anaesthetic molecules.

Local anaesthetics may have similar effects on other excitable membranes e.g. in the brain and myocardium. If excessive amounts of drug reach the systemic circulation, symptoms and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems.

Central nervous system toxicity (See section 4.8.1) usually precedes the cardiovascular effects as central nervous system toxicity occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration depending on the extent of the concomitant sympathetic block.

5.2. Pharmacokinetic properties

Bupivacaine has a pKa of 8.2 and a partition coefficient of 346 (25°C n-octanol/ phosphate buffer pH 7.4). The metabolites have a pharmacological activity that is less than that of bupivacaine.

The plasma concentration of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site.

Bupivacaine shows complete and biphasic absorption from the epidural space with half-lives in the order of 7 min and 6 h respectively. The slow absorption is rate- limiting in the elimination of bupivacaine, which explains why the apparent half-life after epidural administration is longer than that after intravenous administration.

Bupivacaine has a total plasma clearance of 0.58 l/min, a volume of distribution at steady state of 73 l, a terminal half-life of 2.7 h and an intermediate hepatic extraction ratio of 0.38 after IV administration. It is mainly bound to alpha-l-acid glycoprotein

with plasma binding of 96%. Clearance of bupivacaine is almost entirely due to liver metabolism and more sensitive to changes in intrinsic hepatic enzyme function that to liver perfusion.

In adults, the terminal half-life of bupivacaine is 3.5 hours. The maximum blood concentration varies with the site of injection and is highest after intercostal nerve blockade.

Total dose, rather than concentration, is an important determinant of peak blood levels.

Bupivacaine is biodegraded in the liver and only 6% is excreted unchanged in the urine.

Paediatric population

In children the pharmacokinetics are similar to that in adults.

An increase in total plasma concentration has been observed during continuous epidural infusion. This is related to a postoperative increase in alpha 1-acid glycoprotein. The unbound, i.e. pharmacologically active, concentration is similar before and after surgery.

Bupivacaine readily crosses the placenta and equilibrium with regard to the unbound concentration is rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

Bupivacaine is extensively metabolised in the liver, predominately by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to PPX, both mediated by cytochrome P4503A4. About 1% of bupivacaine is excreted in the urine as unchanged drug in 24 h and approximately 5% as PPX. The plasma concentrations of PPX and 4-hydroxy-bupivacaine during and after continuous administration of bupivacaine are low as compared to the parent drug.

5.3 Preclinical safety data

Bupivacaine hydrochloride is a well established active ingredient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride (tonicity contributor)

Sodium Hydroxide (pH adjustment)

Hydrochloric acid (pH adjustment) Water for Injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

10 ml type I clear glass ampoules. .

Each carton contains 1, 5, 10, 20 and 100 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.

Only clear solutions practically free from particles should be used. Any unused solution should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eugia (UK) Ltd
Ares Block,
Odyssey Business Park,
West End Road,
Ruislip, HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 56284/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/12/2024

10 DATE OF REVISION OF THE TEXT

27/07/2025