Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine 2.5 mg/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 2.5 mg bupivacaine hydrochloride anhydrous.
Each 5-mL ampoule contains bupivacaine hydrochloride monohydrate equivalent to 12.5 mg bupivacaine hydrochloride anhydrous.
Each 10-mL ampoule contains bupivacaine hydrochloride monohydrate equivalent to 25 mg bupivacaine hydrochloride anhydrous.
Each 20-mL ampoule contains bupivacaine hydrochloride monohydrate equivalent to 50 mg bupivacaine hydrochloride anhydrous.

Excipient with known effect:
Each mL of Bupivacaine 2.5 mg / mL Solution contains 0.144 mmol (3.31 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.
pH: 4.0-6.5
Osmolality: 270 – 320 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine 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

Bupivacaine is used for the production of prolonged local anaesthesia by percutaneous infiltration, intra-articular block, peripheral nerve block(s) and central neural block (caudal or epidural). Bupivacaine is also used for pain relief during labour.

4.2 Posology and method of administration

Posology
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.

Experience to date indicates a single dose of up to 150 mg bupivacaine hydrochloride. 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.

Adults and children above 12 years of age
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
Lumbar Epidural Administration [1)]					
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	**Conc mg / mL**	**Volume mL**	**Dose mg**	**Onset min**	**Duration of effect hours[7)]**
Lumbar Epidural Administration					
Intermittent injections [3)] (e.g. post-operative pain relief)	2.5	6-15; minimum interval 30 minutes	15-37.5; minimum interval 30 minutes	2-5	1-2
Lumbar Epidural Administration					
Continuous infusion [4)]	1.25	10-15/h	12.5-18.8/ h	-	-
	2.5	5-7.5/h	12.5-18.8/ h	-	-
Lumbar Epidural Administration					
Continuous infusion, labour pain relief [4)]	1.25 5.0	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 7)]					
(e.g. single injection following knee arthroscopy)	2.5	≤40	≤100[5)]	5-10	2-4 h after wash out
Field Block					
(e.g. minor nerve blocks and infiltration)	2.5	≤60	≤150	1-3	3-4

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 ≤ 400 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 is not approved for this indication (see also 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. 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).

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

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.

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 (per- 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 5.	0.6-0.8	1.5-2	20-30	2-6
Field Block (e.g. minor nerve blocks and infiltration)	2.5		0.5- 2.0		
	5.0		0.5- 2.0		
Peripheral Nerve Blocks [b)] (e.g. ilioinguinal - iliohypogastric)	2.5		0.5- 2.0	[b)]	
	5.0		0.5- 2.0	[b)]	

[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 – 12.5 mg 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.

4.3 Contraindications

- hypersensitivity to the active substance, or to local anaesthetic medicinal products of the amide type or to any of the excipients listed in section 6.1
- intravenous regional anaesthesia (Bier's-block)
- obstetrical paracervical block

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

- active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, sub-acute combined degeneration of the cord due to pernicious anaemia and cerebral, blood poisoning (septicaemia), recent spinal trauma 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

Solutions of bupivacaine hydrochloride are contraindicated for injection into inflamed or infected areas.

4.4 Special warnings and precautions for use

There have been reports of cardiac arrest 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 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. The clinician responsible should take the necessary precautions to avoid intravascular injection (see section 4.2).

Before any nerve block is attempted, intravenous access for resuscitation purposes should be established. Clinicians should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see section 4.9 & 4.8).

Major peripheral nerve blocks may require the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption. This may lead to high plasma concentrations.

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
- Bupivacaine hydrochloride should be used with caution in patients with epilepsy, 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.
- 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.
- Injection of adrenaline containing bupivacaine in areas of end arteries (e.g. penile block, Oberst block) may cause ischemic tissue necrosis.
- 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.
- Epidural anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. If hypotension develops it 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.
- 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.
- 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.

Paediatric population

The safety and efficacy of Bupivacaine 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.

5 mL ampoules:
This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

10 mL and 20 mL ampoules:
This medicinal product contains 3.31 mg sodium per 1 mL, equivalent to 0.17% of the WHO recommended maximum daily intake of 2 g 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 section 4.4).

Paediatric population

Interaction studies have only been performed in adults. There are not known interactions in paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of bupivacaine in pregnant women. Animal studies have shown reproduction toxicity (see section 5.3). Bupivacaine injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, acidosis and damping of the central nervous system 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).

Breastfeeding

Bupivacaine is excreted into the mother's milk in small amount and it is poorly absorbed orally, thus adverse effects in breastfed infants are not anticipated. It is therefore possible to breastfeed after anaesthesia with bupivacaine. Based on the latest literature data mothers with normal term or older infants generally can resume breastfeeding as soon as they are awake, stable and alert. However, care should be given to premature infants and infants at risk for apnoe, hypotonia and hypotension, who could be more sensitive to small amounts of bupivacaine and therefore should be closely observed, particularly in the first 24 hours after bupivacaine application to the mother.

Fertility

There are no data on the effect of bupivacaine hydrochloride on human fertility.

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

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.

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, < 1/10), uncommon (≥1/1,000, < 1/100), rare (≥1/10,000, < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).

Table 3

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 twiching)
	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 disorders	Common	Urinary retention

Hepatic dysfunction, with reversible increases of SGOT, SGPT, alkaline phosphates and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. If signs of hepatic dysfunction are observed during treatment with bupivacaine, the drug should be discontinued.

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.

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

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.

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascularsystem. 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.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

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). If convulsions occur they must be treated promptly by intravenous injection of an anticonvulsant Prolonged convulsions may jeopardise the patient's ventilation and oxygenation. If so, injection of a muscle relaxant will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation must be considered in such situations.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required. If hypotension is present, however, a vasopressor, preferably one with inotropic activity, e.g. ephedrine, should be given intravenously.

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.

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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Phamacotherapeutic group: Anesthetics, local; Amides; ATC code: N01BB01

Mechanism of action and Pharmacodynamic effects

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

Absorption
The absorption rate of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Intercostal block gives the highest plasma concentration (4 mg/l following a dose of 400 mg) depending on a rapid absorption whilst subcutaneous injection in abdomen gives the lowest concentrations in plasma. In children a rapid absorption is seen resulting in a high plasma concentration in caudal block (1-1.5 mg/l following a dose of 3 mg/kg).

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.

Distribution and Elimination
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 0.40. Half life during elimination in newborns is up to 8 hours longer than in adults. The half life in children above 3 months of age corresponds to the half life in adults.

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 dependent on changes in intrinsic hepatic enzyme function that to liver perfusion.

In children the pharmacokinetics are similar to that in adults.

An increase in total plasma concentration has been observed after major surgery. 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. This explains why plasma concentrations above toxic levels may be well tolerated.

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.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, acute and subchronic toxicity, non-clinical data reveal no special hazard other than those already reported elsewhere in this document.

The mutagenic and carcinogenic potential of bupivacaine has not been determined.
Bupivacaine crosses the placenta. In reproduction toxicity studies, decreased survival of the offspring of rats and embryolethality was noted in rabbits at bupivacaine doses, which were five- or nine-fold the maximum recommended daily dose in humans. A study in rhesus monkeys suggested altered postnatal behaviour following exposition to bupivacaine at birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.
After first opening, the product should be used immediately.

After dilution: Chemical and physical in-use stability has been demonstrated for 7 days at 25 ± 2°C and for 24 hours at 2 –8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 **–** 8°C, unless opening / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not refrigerate or freeze.
For storage conditions after first opening / dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Polypropylene ampoules of 5 mL, 10 mL or 20 mL. Ampoules are placed in cartons.
Pack sizes of 5, 10 and 50 ampoules.

Polypropylene ampoules of 5 mL, 10 mL or 20 mL. Each ampoule is placed individually in a plastic polypropylene blister. Blisters are placed in cartons.
Pack sizes of 5, 10 and 50 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
Only clear solutions practically free from particles should be used. Any unused solution should be discarded.
Bupivacaine should not be stored in contact with metals such as needles and syringes with details of metals that can come into contact with the solution. Metal ions might precipitate and cause swelling at the injection area.

Method for preparation of 1.25 mg / mL concentration:
Bupivacaine 2.5 mg / mL Solution for injection:

- Withdraw 250 mL of diluent from 500 mL non-pvc diluent bag/bottle and inject 250 mL of Bupivacaine 2.5 mg / mL Solution for injection into 500 mL non-pvc diluent bag/bottle to get final concentration 1.25 mg / mL.
- The diluent bag/bottle should be gently shaken for the drug uniformity.

Bupivacaine 5 mg / mL Solution for injection:

- Withdraw 125 mL of diluent from 500 mL non-pvc diluent bag/bottle and inject 125 mL of Bupivacaine 5 mg / mL Solution for injection into 500 mL non-pvc diluent bag / bottle to get final concentration 1.25 mg / mL.
- The diluent bag/bottle should be gently shaken for the drug uniformity.

Method for preparation of 2.5 mg / mL concentration:
Bupivacaine 5 mg / mL Solution for injection:

- Withdraw 250 mL of diluent from 500 mL non-pvc diluent bag/bottle and inject 250 mL of Bupivacaine 5 mg / mL Solution for injection into 500 mL non-pvc diluent bag/bottle to get final concentration 2.5 mg / mL.
- The diluent bag / bottle should be gently shaken for the drug uniformity.

Bupivacaine is compatible when admixed with 0.9% w/v (9 mg / mL) sodium chloride injection and Ringer Lactate Solution. However, this medicinal product must not be mixed with other medicinal products.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT