HOSPICAINE
(Bupivacaine Hydrochloride)

5 mg/mL

Injection

COMPOSITION

Each ml contains:
Bupivacaine Hydrochloride 7.5mg
Dextrose Anhydrous 82.5mg

THERAPEUTIC INDICATIONS

Bupivacaine Hydrochloride solution for injection used for the production of local anesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anesthesia is required. Because sensory nerve block is more marked than motor block, bupivacaine is especially useful in the relief of pain, e.g., during labour.

Bupivacaine Hydrochloride is not recommended for intravenous regional anesthesia (Bier Block)

Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of Bupivacaine Hydrochloride.

DOSAGE AND ADMINISTRATION

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. Dosages of Bupivacaine Hydrochloride should be reduced for elderly and/or debilitated patients and patients with cardiac and/or liver disease. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.
For specific techniques and procedures, refer to standard textbooks.
There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. Bupivacaine Hydrochloride is not approved for this use.
Bupivacaine Hydrochloride produces complete sensory block, but the effect on motor function differs among the concentrations
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.
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 anesthesia should be used. Individual variations in onset and duration occur.
Table 1 Dosage recommendations for adults

	Conc mg/ml	Volume ml
SURGICAL ANAESTHESIA		
Lumbar Epidural Administration for surgery [1)]	5.0	15-30
Lumbar Epidural Administration for Caesarean Section [1)]	5.0	15-30
Thoracic Epidural Administration for surgery [1)]	5.0	5-10
Caudal Epidural Block [1)]	5.0	20-30
Major Nerve Block (e.g. brachial plexus, femoral, sciatic) [2)]	5.0	10-35
Field block	5.0	≤30

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.
3) Bupivacaine without adrenaline.
In general, surgical anesthesia (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 anesthesia.
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 recognized 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.
Experience to date indicates that 400 mg administered over 24 hours is well tolerated in the average adult.

Special precautions for disposal and other handling
For single use only.
Use immediately after opening. Discard any unused solution.
This product should be inspected visually for particulate matter and discoloration prior to administration. Solutions which are discolored or which contain particulate matter should not be administered

CONTRAINDICATIONS

Bupivacaine hydrochloride solutions for injection are contraindicated in patients with hypersensitivity to the bupivacaine hydrochloride or to local anaesthetic agents of the amide type or to any of the excipients
Bupivacaine hydrochloride is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.
Solutions of bupivacaine hydrochloride are contra-indicated for intravenous regional anesthesia (Bier's-block)
Epidural anesthesia, 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 and spinal tumours; tuberculosis of the spine; pyogenic infection of the skin at or adjacent to the site of lumbar puncture; cardiogenic or hypovolemic shock; coagulation disorders or ongoing anticoagulation treatment.
SPECIAL WARNINGS AND PRECAUTIONS FOR USE
LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH
There have been reports of cardiac arrest during the use of bupivacaine for epidural anesthesia 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 utilized 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 anesthesia is administered. The clinician responsible should take the necessary precautions to avoid intravascular injection.
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.
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 anesthesia 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 anesthesia 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 hypovolemia due to any cause can develop sudden and severe hypotension during epidural anesthesia. Epidural anesthesia should therefore be avoided or used with caution in patients with untreated hypovolemia or significantly impaired venous return.
• Retrobulbar injections may very rarely reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnea, 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.
• Paracervical block may have a greater adverse effect on the fetus than other nerve blocks used in obstetrics. Due to the systemic toxicity of bupivacaine special care should be taken when using bupivacaine for paracervical block.
• 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.
Epidural anesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include pre-loading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10-15mg intravenously. Severe hypotension may result from hypovolemia due to haemorrhage or dehydration, or aorto-caval occlusion in patients with massive ascites, large abdominal tumour or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation.
Patients with hypovolemia due to any cause can develop sudden and severe hypotension during epidural anesthesia.
Epidural anesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicemia 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.
Pediatric Use: Until further experience is gained in pediatric patients younger than 12 years, administration of bupivacaine in this age group is not recommended. Continuous infusions of bupivacaine in children have been reported to result in high systemic levels of bupivacaine and seizures; high plasma levels may also be associated with cardiovascular abnormalities.
Geriatric Use: Patients over 65 years, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing anesthesia with bupivacaine. Elderly patients may require lower doses of bupivacaine. In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. This product is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

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.

FERTILITY, PREGNANCY AND LACTATION

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 anesthesia. Such effects may be due to high concentrations of anaesthetic reaching the fetus.
Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer bupivacaine, taking into account the importance of the drug to the mother. Bupivacaine enters the mother's milk, but in such small quantities that there is no risk of affecting the child at therapeutic dose levels.
Effects on 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.

ADVERSE DRUG REACTIONS

Accidental sub-arachnoid injection can lead to very high spinal anesthesia possibly with apnea and severe hypotension.
The adverse reaction profile for Bupivacaine solution for injection 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 recognized consequence of regional and particularly epidural and spinal anesthesia. 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 localized areas of paraesthesia or anesthesia, motor weakness, loss of sphincter control and paraplegia. Occasionally these are permanent.
The adverse reactions considered at least possibly related to treatment with Bupivacaine solution for injection 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) including isolated reports, or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Table 2 Table of Adverse Drug Reactions (ADR)

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic reaction/shock
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
	Rare	Cardiac arrest, cardiac arrhythmias
Vascular disorders	Very Common	Hypotension
	Common	Hypertension
Respiratory disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Renal and Urinary	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.

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 vascularized areas. 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 generalized convulsions. These signs must not be mistaken for neurotic behavior. 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 apnea may occur. Acidosis, hyperkalemia 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.

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 anesthesia 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 authorization 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 at pv@searlecompany.com

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.

Management of Local Anesthetic Emergencies

The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control the convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory, and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, successful outcome may require prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD50 in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

PHARMACOLOGICAL PROPERTIES

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 anesthesia, 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 fibers by preventing the inward movement of sodium ions through the cell membrane of the nerve fibers. 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 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.

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 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 fetus is less than in the mother, which results in lower total plasma concentrations in the fetus.
Bupivacaine is extensively metabolized 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.

PRECLINICAL SAFETY DATA
Bupivacaine hydrochloride is a well-established active ingredient.

PRESENTATION

Hospicaine 5mg/ml Injection is available in a pack of 5 Ampoules x 10ml.

REGISTRATION NUMBER

Hospicaine 5mg/ml Injection: 103035
Manufacturing license Number: 000016

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Store below 30°C.
- Protect from sunlight and heat.
- Keep all medicines out of sight and reach of children.
- Do not freeze.
- Injection should not be used if container is leaking, solution is cloudy or it contains un-dissolved particle(s).

(Bupivacaine Hydrochloride)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:
The Searle Company Limited,
F-319, S.I.T.E., Karachi-Pakistan.

Marketed by:
IBL HealthCare Limited,
One IBL Centre, 2nd Floor, Plot # 1,
Block 7 & 8, D.M.C.H.S, Tipu Sultan Road,
Off Shahra-e-Faisal, Karachi - Pakistan.

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