PRODUCT MONOGRAPH

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection
(Bupivacaine Hydrochloride and Epinephrine Injection USP)

Local Anaesthetic for Dental Use

Sponsor/Manufacturer:
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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Non-medicinal Ingredients
Parenteral	Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection (Bupivacaine Hydrochloride with Epinephrine Sterile Solution 0.5% with epinephrine 1:200,000 (as bitartrate)	Sodium chloride, sodium hydroxide and/or hydrochloric acid, monothiogylcerol, ascorbic acid, sodium lactate 60% solution, edetate calcium disodium, sodium metabisulfite and water for injection.

INDICATIONS AND CLINICAL USE

Adults (>18 years of age):

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is indicated for the production of local or regional anesthesia and analgesia with the following procedures:

- Local infiltration procedures
- Peripheral nerve blocks.

Standard procedures for local infiltration, minor and major nerve blocks, should be observed.

Geriatrics (> 65 years of age):

Elderly patients should be given reduced doses commensurate with their age and physical condition.

Pediatrics (< 2 years of age):

Until further experience is gained in children younger than two years, administration of any presentation of bupivacaine injection in this age group is not recommended.

CONTRAINDICATIONS

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is contraindicated:

- In patients with a hypersensitivity to bupivacaine or to any local anesthetic agent of the amide type or to other components of bupivacaine injections.

- For intravenous regional anaesthesia (Bier Block) since unintentional leakage of bupivacaine over the tourniquet may cause systemic toxic reactions. Cardiac arrest and death have occurred (see DOSAGE AND ADMINSTRATION).

- In severe shock and in heart block and when there is inflammation and/or sepsis near the site of the proposed injection.

- Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is contraindicated in patients with a hypersensitivity to sodium metabisulfite (see **DOSAGE FORMS, COMPOSITION AND PACKAGING).**

WARNINGS AND PRECAUTIONS

General

LOCAL ANAESTHETICS SHOULD ONLY BE USED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MAY ARISE FROM THE BLOCK TO BE PERFORMED, AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, RESUSCITATIVE DRUGS, INCLUDING OXYGEN, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (see ADVERSE REACTIONS AND OVERDOSAGE). 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.

THE LOWEST DOSAGE OF LOCAL ANESTHETICS THAT RESULTS IN EFFECTIVE ANEASTHESIA OR ANALGESIA SHOULD BE USED TO AVOID HIGH PLASMA LEVELS AND SERIOUS ADVERSE REACTIONS. INJECTIONS SHOULD BE MADE SLOWLY OR IN INCREMENTAL DOSES, WITH FREQUENT ASPIRATIONS BEFORE AND DURING THE INJECTION TO AVOID INTRAVASCULAR INJECTION.

The following precautions apply to all local anesthetics: Select needles of proper length and bevel for the technique employed. Inject slowly with frequent aspirations and if blood is aspirated, relocate the needle. Inadvertent intravascular injection may cause serious complications. Absorption is more rapid when injections are made into highly vascular tissues. However, a negative aspiration is not 100% reliable.

Injection of repeated doses of bupivacaine may cause a significant increase in blood levels due to accumulation of the drug or its metabolites or slow metabolic degradation. Tolerance to

elevated blood levels varies with the physical condition of the patient.

Major peripheral nerve blocks may imply 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 rapid systemic absorption which can lead to high plasma concentrations.

Epinephrine containing solutions should not be injected into tissues supplied by end arteries, for example, fingers and toes, ears, the nose, and the penis.

Local anaesthetic procedures should be carried out sufficiently away from an inflamed region. Injections should not be performed through inflamed tissue or when there is a sepsis at or near the injection site.

Cardiovascular

The decision to use a local anesthetic containing a vasoconstrictor in patients with peripheral vascular disease will depend on the physician's appraisal of the relative advantages and risks. There have been reports of cardiac arrest or death during use of bupivacaine for peripheral nerve blockage. In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and management.

Ventricular arrhythmia ventricular fibrillation, sudden cardiovascular collapse and death have been reported when bupivacaine was utilized for local anaesthetic procedures that may have resulted in high systemic concentrations of bupivacaine.

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection should be used with caution in patients who may have severe or untreated hypertension, ischemic heart disease, cerebral vascular insufficiency, heart block, peripheral vascular disorder and any other pathological condition that might be aggravated by the effects of epinephrine.

Local anaesthetics should be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by amide-type local anaesthetics.

Patients with partial or complete heart block require special attention since local anaesthetics may depress myocardial conduction. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient’s condition before major blocks are performed. Dosage should be adjusted accordingly.

Endocrine

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection should be used with caution in patients whose medical history and physical evaluation suggest the existence of poorly controlled hyperthyroidism or advanced diabetes.

Injection in Head and Neck Area

Relatively small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care.

Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression leading to cardiac arrest have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Patients receiving these blocks should remain under constant observation and monitoring for their cardiac and pulmonary functions. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Hepatic

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anaesthetics normally, are at a greater risk of developing toxic plasma concentrations.

The safety and effectiveness of local anaesthetics depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area.

Resuscitative equipment and resuscitative drugs, including oxygen, should be available for immediate use (see **WARNINGS AND PRECAUTIONS**, and **ADVERSE REACTIONS** and **OVERDOSAGE**). During major regional nerve blocks, the patients should be in an optimal condition and have i.v. fluids running via an indwelling catheter to assure a functioning intravenous pathway. The clinician responsible should have adequate and appropriate training in the procedure to be performed, should take the necessary precautions to avoid intravascular injection (see **DOSAGE AND ADMINISTRATION**), and should be familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see **ADVERSE REACTIONS** and **OVERDOSAGE**).

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anaesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Renal

Local anaesthetics should be used with caution in patients in poor general condition due to severe renal dysfunction although regional anaesthesia is frequently indicated in these patients.

Hyper-Sensitivity

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non asthmatic people.

Special Populations

Debilitated and acutely ill patients should be given reduced doses commensurate with their age

and physical condition.

Pregnant Women Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered to these species in doses comparable, respectively, to 9 and 5 times the maximal recommended daily human dose (400 mg).

There are no adequate and well controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. Bupivacaine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: Bupivacaine is excreted in the breast milk, but in such small quantities that there is generally no risk of affecting the infant at therapeutic doses. It is not known whether epinephrine enters breast milk or not, but it is unlikely to affect the breast-fed infant.

Pediatrics: Until further experience is gained in children younger than two years, administration of any presentation of bupivacaine injection in this age group is not recommended.

Geriatrics: Elderly patients should be given reduced doses commensurate with their age and physical condition.

ADVERSE REACTIONS

Reactions to bupivacaine are characteristic of those associated with other local acting anaesthetics of the amide type.

Adverse reactions to local anaesthetics are very rare in the absence of overdose or inadvertent intravascular injection.

The most commonly encountered acute adverse experiences that demand immediate management are related to the Central Nervous System (CNS) and the cardiovascular system. These adverse reactions are generally dose-related and due to high plasma levels which may result from overdosage (see **OVERDOSAGE**),, rapid absorption from the injection site, diminished tolerance or from inadvertent intravascular injection. Factors influencing plasma protein binding, e.g., diseases which alter protein synthesis or competition of other drugs for protein binding, may diminish individual tolerances.

Central Nervous System: Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors, may occur possibly proceeding to, convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, paraesthesia, numbness of the tongue, hyperacousis, lightheadedness, dysarthria and constriction of the pupils.

Cardiovascular system: High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, hypertension, ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. Reactions due to systemic absorption may be either slow or rapid in onset. Cardiovascular collapse and arrest can occur rapidly (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **OVERDOSAGE** sections).

Allergic: Allergic type reactions are rare (<0.1%) and may occur as a result of sensitivity to local anaesthetics of the amide type. These reactions are characterized by signs such as urticaria, pruritis, erythema, angioneurotic oedema(including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and in the most severe instances, anaphylactic shock.

Neurologic: The incidence of adverse neurologic reactions may be related to the total dose of local anaesthetic administered but is also dependent upon the particular drug used, the route of the administration and the physical condition of the patient. Neurological effects may be related to local anaesthetic techniques, with or without a contribution from the drug.

DRUG INTERACTIONS

Drug-Drug Interactions

See **WARNINGS AND PRECAUTIONS** concerning solutions containing a vasoconstrictor.

Bupivacaine should be used cautiously in persons with known drug allergies or sensitivities.

Local anaesthetics

Mixing or the prior or intercurrent use of any other local anaesthetic with bupivacaine is not recommended because of insufficient data regarding the interaction and safety of such mixtures. Bupivacaine should be used with caution in patients receiving other amide-type local anaesthetics such as lidocaine, ropivacaine, mepivacaine and prilocaine since the toxic effects are additive.

Antiarrhythmic Drugs

Bupivacaine should also be used with caution with structurally related agents such as the antiarrhythmics, procainamide, disopyramide, tocainide, mexiletine and flecainide.

Class III antiarrhythmic drugs

Specific interaction studies with bupivacaine and class III anti-arrhythmic drugs (e.g.amiodarone) have not been performed, but caution is advised. Patients being treated with class III anti-arrymthmic drugs should be under close surveillance and ECG monitoring since cardiac affects may be additive.

Ergot-Containing Drugs

Bupivacaine with epinephrine or other vasopressors or vasoconstrictors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur and cerebrovascular and cardiac accidents are possible.

Monoamine Oxidase (MAO) Inhibitors

The administration of local anaesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, extreme caution and careful patient monitoring is essential.

Tricyclic Antidepressants (triptyline, imipramine)
The administration of local anaesthetic solutions containing epinephrine or norepinephrine to patients receiving tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, extreme caution and careful patient monitoring is essential.

Neuroleptics (phenothiazines, butyrophenones)
Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine resulting in hypotensive responses and tachycardia.

Sedatives
If sedatives are used to reduce patient apprehension, they should be used in reduced doses, since local anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

General Anaesthetics- Inhalation agents (halothane, cyclopropane, trichloroethylene, enflurane and related agents)
Dose related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or immediately following the administration of general anaesthesia with inhalational agents such as halothane, cyclopropane, trichloroethylene, enflurane or other related agents. In deciding whether to use these products concurrently in the same patients, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account. Use of chloroprocaine or other local anaesthetics, prior to general anaesthesia, may interfere with subsequent use of bupivacaine. Because of this, and because safety of intercurrent use with bupivacaine and other local anaesthetics has not been established, such use is not recommended.

H_2-antagonists
The H_2-antagonists cimetidine and ranitidine have been shown to reduce the clearance of bupivacaine; ranitidine to a lesser degree than cimetidine. Concomitant administration may increase likelihood of toxicity of bupivacaine.

Non –selective beta-blockers
Non –selective beta-blockers such as propranolol enhance the pressor effects of epinephrine, which may lead to severe hypertension and bradycardia.

Drug-Food Interactions
Interactions of bupivacaine with food have not been established.

Drug-Herb Interactions
Interactions of bupivacaine with herbal products have not been established.

Drug-Laboratory Interactions
Interactions of bupivacaine with laboratory tests have not been established.

Drug-Lifestyle Interactions
Interactions of bupivacaine with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General

As with all local anesthesias, the dosage varies and depends upon 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, individual tolerance, the technique of anesthesia, and the physical condition of the patient. The lowest dosage and concentration needed to provide effective anesthesia should be administered.

In recommended doses, bupivacaine produces complete sensory block, but the effect on motor functions differs among concentrations.

- 0.50% provides nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

Special Populations

Local anaesthetics should be used with caution in patients in poor general condition due to aging or other compromising factors such as advanced liver disease or severe renal dysfunction although regional anaesthetics is frequently indicated in these patients.

Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical condition.

Recommended Dose and Dosage Adjustment

The duration of anesthesia with bupivacaine is such that, for most procedures, a single dose is sufficient. Maximum dosage limit must be individualized in each case after evaluating the patient's size and physical status and the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of bupivacaine, up to 225 mg with epinephrine 1:200 000 and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case. The maximum doses of bupivacaine are considered to apply to a healthy, 70 kg young male, however, it is not recommended that they be exceeded in heavier persons.
At present there is insufficient clinical evidence with multiple dosage or intermittent dose techniques to permit precise recommendations for such procedures to be given. However, limited clinical experience in this area of use indicates that bupivacaine may be repeated in 3 to 6 hours; total daily doses have been up to 400 mg. The duration of anesthetic effect may be prolonged by the addition of a vasoconstricting substance, e.g. epinephrine.

When prolonged blocks are used, the risk of reaching a toxic plasma concentration or inducing a local neural injury must be considered. The maximum dosage limit must be determined by evaluating the size and physical condition of the patient and considering the usual rate of systemic absorption from a specific injection site. Experience to date indicates that 400 mg administered over 24 hours is well tolerated in average adults. Until further experience is gained, this dose should not be exceeded in 24 hours.

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.

Children

Until further experience is gained, bupivacaine is not recommended for children younger than two years of age.

Table 1 Dosage recommendation in children (over two years of age) for bupivacaine with epinephrine

Type of block	Conc (%)	Each dose	
		mL/Kg	Mg/Kg
Local Infiltration	0.5	Up to 0.4	Up to 2

Note: the use of bupivacaine with epinephrine for anaesthesia and/or analgesia may be supplementary to light general anaesthesia.

OVERDOSAGE

Acute systemic toxicity from local anesthetics is generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid or intravascular injection exceptionally rapid absorption from highly vascularized areas or overdosage and originates mainly in the central nervous and the cardiovascular systems (see **ADVERSE REACTIONS** and **WARNINGS AND PRECAUTIONS**). Central nervous system reactions are similar for all amide local anesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Symptoms

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.

Central nervous system toxicity is graded response with symptoms and signs of escalating severity. The first symptoms are usually circumoral paresthesia, numbness of the tongue, lightheadedness, hyperacousis, 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 a 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 normal respiration and loss of the airway. In severe cases apnea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution and subsequent metabolism and excretion of the local

anaesthetic drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system.

Cardiovascular toxic reactions are usually related to depression of the conduction system of the heart and myocardium, leading to decreased cardiac output, hypotension, heart block, bradycardia and sometimes ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation and cardiac arrest.

Treatment

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. If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.

THE FIRST STEP IN THE MANAGEMENT OF SYSTEMIC TOXIC REACTIONS, AS WELL AS UNDERVENTILATION OR APNEA, CONSISTS OF THE IMMEDIATE ESTABLISHMENT AND MAINTENANCE OF A PATENT AIRWAY AND ASSISTED OR CONTROLLED VENTILATION WITH 100% OXYGEN AND A DELIVERY SYSTEM CAPABLE OF PERMITTING IMMEDIATE POSITIVE AIRWAY PRESSURE BY MASK OR ENDOTRACHEAL INTUBATION. This may prevent convulsions if they have not already occurred.

Supportive treatment of the cardiovascular system includes intravenous (i.v.) fluids and, when appropriate, vasopressors (such as epinephrine or ephedrine which enhance myocardial contractility).

If necessary, use drugs to control convulsions. A bolus i.v. injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg bw) will paralyze the patient without depressing the CNS or cardiovascular system and facilitate endotracheal intubation, controlled ventilation and secure optimal oxygenation. An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 seconds. A bolus i.v. dose of diazepam (0.1 mg/kg) or thiopental (1-3 mg/kg) will permit ventilation and counteract central nervous system stimulation, but these drugs also depress CNS, respiratory, and cardiac function, add to possible depression, and may result in apnea. Thiopental will control convulsions rapidly, while the action of diazepam will be slower. Prolonged convulsions may jeopardize the patient’s ventilation and oxygenation. I.V. barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. For specific techniques and procedures, refer to standard textbooks.

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 cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg i.v. should be given and may be repeated, if necessary , after 2-3 minutes. Children should be given

ephedrine doses commensurate with their age and weight.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance, since hypoxia and acidosis will increase the systemic toxicity of local anaesthetics. Epinephrine (0.1 -0.2 mg intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary. A successful resuscitation may require prolonged 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 should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of non pregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitative efforts.

If cardiac arrest should occur, a successful outcome may require prolonged resuscitative efforts.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Bupivacaine is a long-acting, amide-type local anaesthetic 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.

Mechanism of Action

Bupivacaine stabilizes the neuronal membrane and prevents both the generation and the conduction of nerve impulses, thereby exerting a local anesthetic action. As with other local anaesthetics, bupivacaine causes a reversible blockage of impulse propagation along nerve fibers by preventing the inward movement of sodium ions through the cell membrane of the nerve fibers. The sodium channel of the nerve membrane is considered a receptor for local anaesthetic molecules.

Onset and Duration of Action

The onset of action is rapid, and anesthesia is long lasting. The duration of action of a local anaesthetic is dependent on a number of factors including site of injection, route of administration, concentration and volume (see **DOSAGE AND ADMINISTRATION**). It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced. The presence of epinephrine may prolong the duration of action for infiltration and peripheral nerve blocks.

Bupivacaine 0.5% has a long duration of action of up to 12 hours after peripheral nerve blocks. The onset of blockage is slower than with lidocaine, especially when anaesthetizing large nerves.

Hemodynamics

Bupivacaine, like other local anaesthetics, may also have effects on other excitable membranes e.g. in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity (see **OVERDOSAGE**) 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.

Pharmacokinetics

Absorption: The plasma concentration of local anaesthetics is dependent upon the dose, the route of administration, the patient's hemodynamic/circulatory condition, and the vascularity of the injection site. The addition of epinephrine to bupivacaine may decrease the peak plasma concentration, whereas the time to peak plasma concentration usually is little affected. The effect varies with the type of block, dose and concentration.

Following injection of bupivacaine for peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a gradual decline to insignificant levels during the next 3 to 6 hours.

Distribution: Local anesthetics are bound to plasma proteins in varying degrees. The highly lipophilic agents, such as bupivacaine, are far more highly protein-bound than the more hydrophilic compounds. Bupivacaine is approximately 95% protein-bound in normal adults. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma proteins. If plasma protein concentrations are decreased, more of the free drug will be available to exert activity. Bupivacaine is mainly bound to alpha-1-acid glycoprotein.

Bupivacaine readily crosses the placenta and equilibrium in regard to the unbound concentration is rapidly reached. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization and (3) the degree of lipid solubility. 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 than in the mother. The free concentration, however, is the same in both mother and fetus.

Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4).

Bupivacaine has a total plasma clearance of 0.58 L/min a volume of distribution at steady state of
73 L.

Metabolism: Because of its amine structure, bupivacaine is extensively metabolized in the liver predominantly by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to 2,6-pipecoloxylidine (PPX), both mediated by cytochrome P450 3A4. The major metabolite of bupivacaine is pipecoloxylidine, a dealkylated derivative. Patients with hepatic disease may be

more susceptible to the potential toxicities of the amide-type local anaesthetics.

Excretion: The plasma elimination half-life of bupivacaine in adults is 2.7 hours (range 1.2 to 4.6 hours). In infants the half-life ranges from 6 to 22 hours, thus it is significantly longer than in adults. Half-life is also prolonged in the elderly. Bupivacaine has an intermediate hepatic extraction ratio of 0.38 after i.v. administration. In children between 1 to 7 years the pharmacokinetics are similar to those in adults.

The kidney is the main excretory organ for most local anaesthetics and their metabolites. Urinary excretion is affected by renal perfusion and factors affecting urinary pH.

Clearance of bupivacaine is almost entirely due to liver metabolism and more sensitive to changes in intrinsic hepatic enzyme function than to liver perfusion.

STORAGE AND STABILITY

Store Bupivacaine HCl 0.5% and Epinephrine 1:200, between 15ºC and 25ºC (59ºF and 79ºF). Do not freeze. Protect Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection from light. Do not use if solution is coloured or contains a precipitate.

SPECIAL HANDLING INSTRUCTIONS

Due to the heat sensitivity of epinephrine, solutions of Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection must not be autoclaved and should be protected from light. Do not use if solution is pinkish or darker than slightly yellow or contains a precipitate.

Adequate precautions should be taken to avoid prolonged contact between local anaesthetic solutions containing epinephrine (low pH) and metal surfaces (e.g. needles or metal parts of syringes), since dissolved metal ions, particularly copper ions, may cause severe local irritation (swelling, edema) at the site of injection and accelerate the degradation of epinephrine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

The solubility of bupivacaine is limited at pH >6.5. This must be taken into consideration when alkaline solutions, i.e. carbonates, are added since precipitation might occur. In the case of epinephrine containing solutions, mixing with alkaline solutions may cause rapid degradation of epinephrine.

Composition and Packaging

Bupivacaine HCl 0.5% with epinephrine 1:200 000: Contains 5 mg bupivacaine hydrochloride per mL.
Single dose cartridges of 1.8 mL; boxes of 50.

These solutions are made isotonic with NaCl and the pH is adjusted with NaOH or HCl. The pH range for solutions with epinephrine is 3.8 to 4.2. Each mL of solution contains epinephrine bitartrate 0.0091 mg and, as non medicinal ingredients, sodium metabisulfite, monothioglycerol

and ascorbic acid as antioxidants, sodium lactate buffer, edetate calcium disodium as stabilizer and water for injection.

PART II: SCIENTIFIC INFORMATION

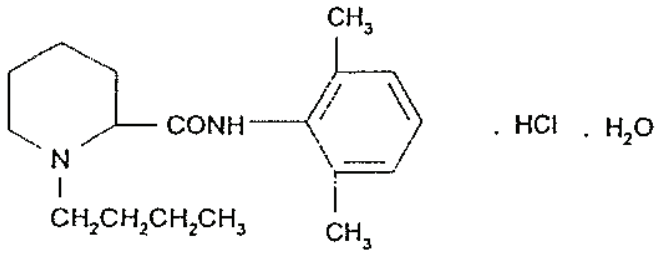
PHARMACEUTICAL INFORMATION

Bupivacaine Hydrochloride

Proper Name: Bupivacaine hydrochloride

Chemical Name: 1-Butyl-N-(2, 6-dimethylphenyl)-2-piperidinecarboxamide
1-Butyl-2', 6'-pipecoloxylidide
1-n-Butyl-2', 6'-dimethyl-2-piperidinecarboxynilide

Structural Formula:



Molecular Formula: $C_{18}H_{28}N_2O.HCl.H_2O$

Molecular mass: 342.90 g/mol

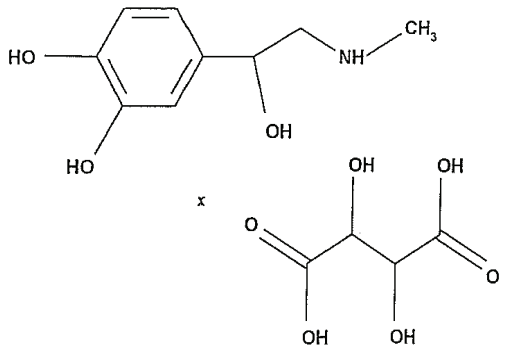
Physicochemical properties: It is a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone.

Epinephrine

Proper Name: Epinephrine Bitartrate

Chemical Name: 1) (-)-3,4-Dihydroxy-α-[methylamino)methyl] benzylalcohol (+)tartrate (1:1) salt
2) 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-(R)-[R-(R* , R*)]-2,3-dihydroxybutane dionate (1:1) salt
3) (-)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)-ethanol hydrgentartrate

Structural Formula:



Molecular Formula: $C_9H_{13}NO_3$ x $C_4H_6O_6$

Molecular Mass: 333.30 g/mol

Physicochemical properties:: white or greyish white or light brownish grey, odourless crystalline powder, which slowly darkens on exposure to light. Freely soluble in water. Slightly soluble in alcohol. Practically insoluble in chloroform and in ether. Solutions are acidic, with pH approximately 3.5.

DETAILED PHARMACOLOGY

Local anaesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

After injection of bupivacaine for peripheral nerve block in man, peak blood levels were reached in 30 to 45 minutes, followed by a decline to insignificant levels in the next 3 to 6 hours.

In metabolic studies in the rat, subcutaneous doses of C^{14} –labelled bupivacaine were rapidly absorbed. The gastrointestinal tract, liver, spleen and kidney showed relatively high concentrations. Radioactivity in adipose tissue was high immediately after drug administration but decreased rapidly and was not detected at 24 hours.

The principal route of biotransformation in the rat is by conjugation with glucuronic acid. Because of its amide structure, bupivacaine is not detoxified by plasma esterases.

As for the local anaesthetics, bupivacaine is metabolized in the liver predominantly by aromatic hydroxylation to 4-hydroxy-bupivacaine and N-dealkylation to 2,6-pipecoloxylidine (PPX), both mediated by cytochrome P450 3A4. The metabolites have a pharmacological activity that is less than that of bupivacaine. Bupivacaine and the metabolites are excreted mainly via the kidneys.

TOXICOLOGY

Acute LD_{50} determinations in the mouse and rat were as follows:

	Route of Administration	Species	Acute LD_{50} ± s.e. mg/kg at 24 hours
Bupivacaine HCl 0.5% with Epinephrine 1:200,000	I.V	Mouse	6.5 ± 0.4
	I.V.	Rat	5.4 ± 0.4
	S.C.	Mouse	66 ±8
	S.C.	Rat	51 ± 8

At high intravenous doses in mice and rats, symptoms of toxicity included CNS stimulation followed by convulsions. Central stimulation is followed by depression and death is usually due to respiratory depression. Dogs tolerated single intramuscular doses of up to 10 mg/kg, with and without epinephrine.

Bupivacaine produced seizures in rhesus monkeys when serum levels reached the 4.5 to 5.5 µg/mL range.

No significant pathologic changes were observed following sub-lethal doses of bupivacaine in the rat, rabbit, dog and monkey, except for dose-related inflammatory reactions in the muscle tissue at the injection sites. In irritation studies in the rabbit, healing of the intramuscular lesions was well

advanced or complete within seven days after the injection.

Libelius and other reported denervation-like changes in the skeletal muscle of rats following repeated intramuscular injection into the same site. They commented, however, that the conditions under which these changes occurred are not likely to be encountered in the clinical use of the drug.

No immediate or delayed allergic responses were observed in the guinea pig after sensitivity testing. No evidence of drug-induced teratogenic effects was observed in rats and rabbits given subcutaneous injections of bupivacaine.

Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered to these species in doses comparable to nine and five times, respectively the maximal recommended daily human dose (400 mg).

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PART III: CONSUMER INFORMATION

Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection
(Bupivacaine Hydrochloride and Epinephrine Injection USP)

This leaflet is part III of a three-part "Product Monograph: published when Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is used to anaesthetize the mouth for surgical operations and also for pain relief, and can be used:

- to anaesthetize the area of the mouth where surgery is to be performed.

What it does:
Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection acts by temporarily preventing the nerves in the injected area from transmitting sensations of pain, heat or cold. However, you may still experience sensations such as pressure and touch. In this way the nerve(s) is anaesthetized/numbed in the part of the mouth, which will be subjected to surgery. In many cases this means that the nerves to the muscles in the area will also be blocked, causing temporary weakness or paralysis.

When it should not be used:
Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection should not be used in patients who are allergic to:

- bupivacaine hydrochloride
- any other "-caine" type anaesthetics
- any of the non-medicinal ingredients in the product) see WHAT THE NON-MEDICINAL INGREDIENT ARE below)
- sodium metabisulfite

What the medicinal ingredients are:
Bupivacaine hydrochloride with epinephrine.

What the non-medicinal ingredients are:
Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection contains sodium chloride, sodium hydroxide and/or hydrochloric acid, monothioglycerol, ascorbic acid, sodium lactate 60% solution, edetate calcium disodium, sodium metabisulfite and water for injection.

What dosage forms it comes in:
Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is available in single –dose glass cartridges as 0.5% (5 mg/mL) with epinephrine (as bitartrate) (1:200,000).

WARNINGS AND PRECAUTIONS

You should talk to your doctor prior to surgery:

- about health problems you have now or have had in the past.
- about other medicines you take, including ones you can buy without prescription.
- if you are taking other medicines such as drugs used to treat irregular heart activity (anti-arrhythmics);
- if you have ever had a bad, unusual allergic reaction to bupivacaine or any other medicines ending with "-caine",
- if you are allergic to methylparaben, other parabens or PABA.
- if you think you may be allergic or sensitive to any ingredients in Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection . Sodium metabisulfite might cause allergic reactions (e.g. itching, hives, facial swelling and breathing difficulties) in susceptible people, especially those with a history of asthma or allergy;
- if you have heart, liver or kidney disease;
- if you are pregnant, plan to become pregnant or are breastfeeding;
- if you are planning to drive or operate any tools or machinery on the day of surgery, because Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection may temporarily interfere with your reactions and muscular coordination.

INTERACTIONS WITH THIS MEDICATION

Many drugs interact with Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection
Tell your doctor about all prescription, over the counter and natural health products that you are using (See WARNINGS AND PRECAUTIONS above).

Usage of such medicines at the same time as Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection may increase the risk of serious side effects.

PROPER USE OF THIS MEDICATION

Usual dose:
Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection should be administered by a doctor. The dose given is decided by the doctor based on the clinical need and your physical condition.

Overdose:

Serious adverse effects resulting from an overdose are extremely rare and need special treatment. The doctor is trained and equipped to handle such situations.

The first signs that too much Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injectionhas been given usually take the form of lightheadedness, numbness of the lips and round the mouth, numbness of the tongue, hearing disturbances, tingling in the ears, and visual disturbances. Tell your doctor immediately if you notice any of these symptoms. Speech symptoms, muscular twitching or tremors are more serious.

In the event of serious overdose or a misplaced injection, trembling, seizures or unconsciousness may occur.

If the administration of Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is stopped as soon as early signs of overdose appears, the risk of serious adverse effects rapidly decreases.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection may cause side effects in some people.

Medicines affect different people in different ways. Just because side effects have occurred in some patients, does not mean that you will get them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Sudden life-threatening allergic reactions (such as anaphylaxis) are rare, affecting less than 1 in 1,000 people. Possible symptoms include sudden onset of rash, itching or lumpy rash (hives); swelling of the face, lips, tongue or other parts of the body; and shortness of breath, wheezing or difficulty breathing.
If you think that Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection is causing an allergic reaction, tell your doctor immediately.

There are other possible side effects that have been reported for Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection. Tell your doctor or anesthesia professional if you experience any of the following side effects:

Frequency	Symptoms/Effect
Very Common	Low blood pressure (hypertension). This might make you feel dizzy or light headed.
	Feeling sick (nausea).
Common	Pins and needles
	Feeling dizzy
	Headache
	Slow or fast heart beat (bradycardia, tachycardia)
	High blood pressure (hypertension)
	Being sick (vomiting)
	Difficulty in passing urine.
	High temperature (fever) or stiffness (rigor)
	Back pain
Uncommon	Anxiety
	Decreased sensitivity or feeling in the skin
	Fainting
	Difficulty breathing
	Low body temperature (hypothermia)
	Some symptoms can happen if the injection was given into a blood vessel by mistake, or if you have been given too much Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection (see also OVERDOSE section above). These inlcude fits (seizures), feeling dizzy or light-headed, numbness of the lips and around the mouth, numbness of the tongue, hearing problems, problems with your sight (vision), problems with your speech, stiff muscles, and trembling.
Rare	Heart attack (cardiac arrest)
	Uneven heart beat (arrhythmias).

Other possible side effects include:
Numbness, due to nerve irritation caused by the needle or the injection. This does not usually last for long.
Possible side effects with other local anaesthetics which might also be caused by Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection

include:

Damaged nerves. Rarely (affecting less than 1 in 1,000 people), this may cause permanent problems.

This is not a complete list of side effects. For any unexpected effects while taking Bupivacaine HCl 0.5% and Epinephrine 1:200,000 Injection, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by of the following 3 ways:

Report Online at www.healthcanada.gc.ca/medeffect
Call toll free telephone: 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  OTTAWA ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Septodont, Inc. at 1-800-647-0643

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