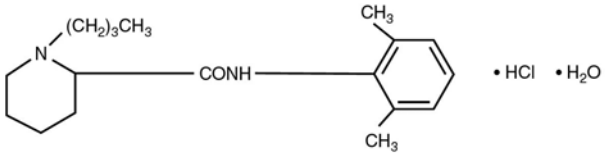
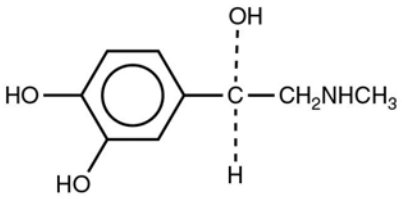
Marcaine™
Bupivacaine Hydrochloride Injection, USP

Marcaine™
With Epinephrine 1:200,000 (as bitartrate)
Bupivacaine Hydrochloride and Epinephrine Injection, USP Rx only

DESCRIPTION
Bupivacaine hydrochloride is 2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Epinephrine is (-)-3,4-Dihydroxy-α-[(methylamino)methyl] benzyl alcohol. It has the following structural formula:



MARCAINE is available in sterile isotonic solutions with and without epinephrine (as bitartrate) 1:200,000 for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solutions of MARCAINE may be autoclaved if they do not contain epinephrine. Solutions are clear and colorless.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

MARCAINE – Sterile isotonic solutions containing sodium chloride. In multiple-dose vials, each mL also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to between 4 and 6.5 with sodium hydroxide or hydrochloric acid.

MARCAINE with epinephrine 1:200,000 (as bitartrate)—Sterile isotonic solutions containing sodium chloride. Each mL contains bupivacaine hydrochloride and 0.0091 mg epinephrine bitartrate, with 0.5 mg sodium metabisulfite, 0.001 mL monothioglycerol, and 2 mg ascorbic acid as antioxidants, 0.0017 mL 60% sodium lactate buffer, and 0.1 mg edetate calcium disodium as stabilizer. In multiple-dose vials, each mL also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to between 3.4 and 4.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE 0.5% with epinephrine 1:200,000 (as bitartrate) at 25°C is 1.008 and at 37°C is 1.008.

CLINICAL PHARMACOLOGY
Local anesthetics 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.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. 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 onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine for dental use, in many patients up to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Local anesthetics appear to cross the placenta by passive diffusion. 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. 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. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profile of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the

highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of MARCAINE for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of MARCAINE in adults is 2.7 hours and in neonates 8.1 hours.

In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.

Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of MARCAINE.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

INDICATIONS AND USAGE

MARCAINE is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. (See **WARNINGS**.)

Experience with nonobstetrical surgical procedures in pregnant patients is not sufficient to recommend use of 0.75% concentration of MARCAINE in these patients.

MARCAINE is not recommended for intravenous regional anesthesia (Bier Block). See **WARNINGS**.

The routes of administration and indicated MARCAINE concentrations are:

• local infiltration	0.25%
• peripheral nerve block	0.25% and 0.5%
• retrobulbar block	0.75%
• sympathetic block	0.25%
• lumbar epidural	0.25%, 0.5%, and 0.75% (0.75% not for obstetrical anesthesia)
• caudal	0.25% and 0.5%
• epidural test dose	0.5% with epinephrine 1:200,000
• dental blocks	0.5% with epinephrine 1:200,000

(See **DOSAGE AND ADMINISTRATION** for additional information.)

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

CONTRAINDICATIONS

MARCAINE is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.

MARCAINE is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of MARCAINE solutions.

WARNINGS

THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

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 INSURING 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. (See also **ADVERSE REACTIONS**, **PRECAUTIONS**, 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.

Local anesthetic solutions containing antimicrobial preservatives, i.e., those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because safety has not been established with regard to intrathecal injection, either intentionally or unintentionally, of such preservatives.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or

subarachnoid injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of MARCAINE containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamineoxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in pediatric patients younger than 12 years, administration of MARCAINE in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE cannot be recommended because of insufficient data on the clinical use of such mixtures.

There have been reports of cardiac arrest and death during the use of MARCAINE for intravenous regional anesthesia (Bier Block). Information on safe dosages and techniques of administration of MARCAINE in this procedure is lacking. Therefore, MARCAINE is not recommended for use in this technique.

MARCAINE with epinephrine 1:200,000 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 nonasthmatic people. Single-dose ampuls and single-dose vials of *MARCAINE* without epinephrine do not contain sodium metabisulfite.

PRECAUTIONS

General: The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See **WARNINGS**, **ADVERSE REACTIONS**, and **OVERDOSAGE**.) During major regional nerve blocks, the patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

Epidural Anesthesia: During epidural administration of MARCAINE, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Injections should be made slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative.

During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When using a “continuous” catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. When clinical conditions permit, the test dose should contain epinephrine (10 mcg to 15 mcg has been suggested) to serve as a warning of unintended intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient “epinephrine response” within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated

patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart rate should be monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a transient rise in systolic blood pressure. The test dose should also contain 10 mg to 15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect an unintended intrathecal administration. This will be evidenced within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). The Test Dose formulation of MARCAINE contains 15 mg of bupivacaine and 15 mcg of epinephrine in a volume of 3 mL. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status. Local anesthetics should also be used with caution in patients with hypotension or heartblock.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic 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.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, or penis. Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.

Because amide-local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also 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 AV conduction produced by these drugs.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation anesthetics. In deciding whether to use these products concurrently in the same patient, 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.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and prompt institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)

Use in Head and Neck Area: 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 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 have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded. (See **DOSAGE AND ADMINISTRATION**.)

Use in Ophthalmic Surgery: Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anesthetic injection. Prior to retrobulbar block, as with all other regional procedures, the immediate availability of equipment, drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be assured (see also **WARNINGS** and *Use In Head and Neck Area*, above). As with other anesthetic procedures, patients should be constantly monitored following ophthalmic blocks for signs of these adverse reactions, which may occur following relatively low total doses.

A concentration of 0.75% bupivacaine is indicated for retrobulbar block; however, this concentration is not indicated for any other peripheral nerve block, including the facial nerve, and not indicated for local infiltration, including the conjunctiva (see **INDICATIONS AND USAGE** and **PRECAUTIONS**, **General**). Mixing MARCAINE with other local anesthetics is not recommended because of insufficient data on the clinical use of such mixtures.

When MARCAINE 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Use in Dentistry: Because of the long duration of anesthesia, when MARCAINE 0.5% with epinephrine is used for dental injections, patients should be cautioned about the possibility of inadvertent trauma to tongue, lips, and buccal mucosa and advised not to chew solid foods or test the anesthetized area by biting or probing.

Information for Patients: When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of caudal or epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the package insert of MARCAINE.

Patients receiving dental injections of MARCAINE should be cautioned not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

Clinically Significant Drug Interactions: The administration of local anesthetic 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, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted. The mutagenic potential and the effect on fertility of bupivacaine hydrochloride have not been determined.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. MARCAINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of MARCAINE at term for obstetrical anesthesia or analgesia. (See **Labor and Delivery**)

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are comparable to the daily maximum recommended human dose (MRHD) of 400 mg/day on a mg/m^2 body surface area (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level representing approximately 1/5th the MRHD on a BSA basis.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, & 40 mg/kg mg/kg/day, decreased pup survival was observed at the high dose. The high dose is comparable to the daily MRHD of 400 mg/day on a BSA basis.

Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRICAL USE OF 0.75% MARCAINE.

MARCAINE is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics**.) The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

Epidural, caudal, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and gravid uterus displaced to the left.

Nursing Mothers: 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.

Pediatric Use: Until further experience is gained in pediatric patients younger than 12 years, administration of MARCAINE 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. (See **WARNINGS**, **PRECAUTIONS**, and **OVERDOSAGE**.)

Geriatric Use: Patients over 65 years, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing anesthesia with MARCAINE. (See **ADVERSE REACTIONS**.)

Elderly patients may require lower doses of MARCAINE. (See **PRECAUTIONS**, **Epidural Anesthesia** and **DOSAGE AND ADMINISTRATION**.)

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. (See **CLINICAL PHARMACOLOGY**.)

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. (See **CLINICAL PHARMACOLOGY**.)

ADVERSE REACTIONS

Reactions to MARCAINE are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

The most commonly encountered acute adverse experiences which demand immediate counter-measures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea (“Total or High Spinal”). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Patients over 65 years, particularly those with hypertension, may be at increased risk for experiencing the hypotensive effects of MARCAINE. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System Reactions: These are characterized by excitation and/or depression. 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, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of local anesthetic administrations.

Cardiovascular System Reactions: High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See **WARNINGS**, **PRECAUTIONS**, and **OVERDOSAGE**.)

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and the physiological and physical effects of a dural puncture. A high spinal is characterized by paralysis of the legs, loss of consciousness, respiratory paralysis, and bradycardia.

Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

Neurologic effects following other procedures or routes of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution. (See **ADVERSE REACTIONS**, **WARNINGS**, and **PRECAUTIONS**.)

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 LD_{50} in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

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 MARCAINE 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. MARCAINE is not approved for this use (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

In recommended doses, MARCAINE produces complete sensory block, but the effect on motor function differs among the three concentrations.

0.25%—when used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% or 0.75% solutions.

0.5%— provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

0.75%—produces complete motor block. Most useful for epidural block in abdominal operations requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.

The duration of anesthesia with MARCAINE is such that for most indications, a single dose is sufficient.

Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of MARCAINE 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.

These doses may be repeated up to once every three hours. In clinical studies to date, total daily doses have been up to 400 mg. Until further experience is gained, this dose should not be exceeded in 24 hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine.

The dosages in Table 1 have generally proved satisfactory and are recommended as a guide for use in the average adult. These dosages should be reduced for elderly or debilitated patients. Until further experience is gained, MARCAINE is not recommended for pediatric patients younger than 12 years. MARCAINE is contraindicated for obstetrical paracervical blocks, and is not recommended for intravenous regional anesthesia (Bier Block).

Use in Epidural Anesthesia: During epidural administration of MARCAINE, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In obstetrics, only the 0.5% and 0.25% concentrations should be used; incremental doses of 3 mL to 5 mL of the 0.5% solution not exceeding 50 mg to 100 mg at any dosing interval are recommended. Repeat doses should be preceded by a test dose containing epinephrine if not contraindicated. Use only the single-dose ampuls and single-dose vials for caudal or epidural anesthesia; the multiple-dose vials contain a preservative and therefore should not be used for these procedures.

Test Dose for Caudal and Lumbar Epidural Blocks: The Test Dose of MARCAINE (0.5% bupivacaine with 1:200,000 epinephrine in a 3 mL ampul) is recommended for use as a test dose when clinical conditions permit prior to caudal and lumbar epidural blocks. This may serve as a warning of unintended intravascular or subarachnoid injection. (See **PRECAUTIONS**.) The pulse rate and other signs should be monitored carefully immediately following each test dose administration to detect possible intravascular injection, and adequate time for onset of spinal block should be allotted to detect possible intrathecal injection. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or cardiovascular effects from the epinephrine. (See **WARNINGS** and **OVERDOSAGE**.)

Use in Dentistry: The 0.5% concentration with epinephrine is recommended for infiltration and block injection in the maxillary and mandibular area when a longer duration of local anesthetic action is desired, such as for oral surgical procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (9 mg) per injection site will usually suffice; an occasional second dose of 1.8 mL (9 mg) may be used if necessary to produce adequate anesthesia after making allowance for 2 to 10 minutes onset time. (See **CLINICAL PHARMACOLOGY**.) The lowest effective dose should be employed and time

should be allowed between injections; it is recommended that the total dose for all injection sites, spread out over a single dental sitting, should not ordinarily exceed 90 mg for a healthy adult patient (ten 1.8 mL injections of 0.5% MARCAINE with epinephrine). Injections should be made slowly and with frequent aspirations. Until further experience is gained, MARCAINE in dentistry is not recommended for pediatric patients younger than 12 years.

Unused portions of solution not containing preservatives, i.e., those supplied in single-dose ampuls and single-dose vials, should be discarded following initial use.

This product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

Table 1. Recommended Concentrations and Doses of MARCAINE

Type of Block	Conc.	Each Dose (mL)	Each Dose (mg)	Motor Block[1]
Local infiltration	0.25%[4]	up to max.	up to max.	—
Epidural	0.75%[2,4]	10-20	75-150	complete
	0.5%[4]	10-20	50-100	moderate to complete
	0.25%[4]	10-20	25-50	partial to moderate
Caudal	0.5%[4]	15-30	75-150	moderate to complete
	0.25%[4]	15-30	37.5-75	moderate
Peripheral nerves	0.5%[4]	5 to max.	25 to max.	moderate to complete
	0.25%[4]	5 to max.	12.5 to max.	moderate to complete
Retrobulbar[3]	0.75%[4]	2-4	15-30	complete
Sympathetic	0.25%	20-50	50-125	—
Dental[3]	0.5% w/epi	1.8-3.6 per site	9-18 per site	—
Epidural[3] Test Dose	0.5% w/epi	2-3	10-15 (10-15 micrograms epinephrine)	—

[1]With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intra-abdominal surgery.
[2]For single-dose use, not for intermittent epidural technique. Not for obstetrical anesthesia.
[3]See **PRECAUTIONS**.
[4]Solutions with or without epinephrine.

HOW SUPPLIED

These solutions are not for spinal anesthesia.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

MARCAINE —Solutions of MARCAINE that do not contain epinephrine may be autoclaved. Autoclave at 15-pound pressure, 121°C (250°F) for 15 minutes.

NDC No.	Container	Fill	Quantity
	0.25%—Contains 2.5 mg bupivacaine hydrochloride per mL.		
0409-1559-10	Single-dose vials	10 mL	box of 10
0409-1559-30	Single-dose vials	30 mL	box of 10
0409-1587-50	Multiple-dose vials	50 mL	box of 1
	0.5%—Contains 5 mg bupivacaine hydrochloride per mL.		
0409-1560-10	Single-dose vials	10 mL	box of 10
0409-1560-29	Single-dose vials	30 mL	box of 10
0409-1610-50	Multiple-dose vials	50 mL	box of 1
	0.75%—Contains 7.5 mg bupivacaine hydrochloride per mL.		
0409-1582-10	Single-dose vials	10 mL	box of 10
0409-1582-29	Single-dose vials	30 mL	box of 10

MARCAINE with epinephrine 1:200,000 (as bitartrate)—Solutions of MARCAINE that contain epinephrine should not be autoclaved and should be protected from light. Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

NDC No.	Container	Fill	Quantity
	0.25% with epinephrine 1:200,000—Contains 2.5 mg bupivacaine hydrochloride per mL.		
0409-1746-10	Single-dose vials	10 mL	box of 10
0409-1746-30	Single-dose vials	30 mL	box of 10
0409-1752-50	Multiple-dose vials	50 mL	box of 1
	0.5% with epinephrine 1:200,000—Contains 5 mg bupivacaine hydrochloride per mL.		
0409-1749-03	Single-dose ampuls	3 mL	box of 10
0409-1749-10	Single-dose vials	10 mL	box of 10
0409-1749-29	Single-dose vials	30 mL	box of 10
0409-1755-50	Multiple-dose vials	50 mL	box of 1

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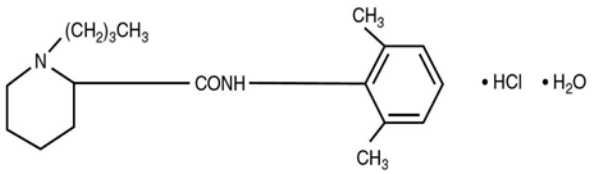
Marcaine™
Spinal
bupivacaine hydrochloride in dextrose injection, USP
STERILE HYPERBARIC SOLUTION
FOR SPINAL ANESTHESIA

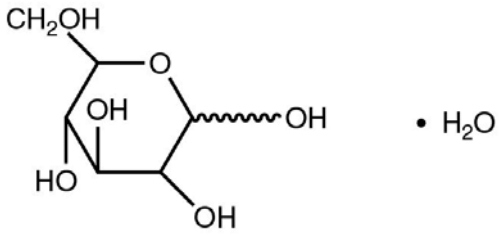
Rx only

DESCRIPTION

Bupivacaine hydrochloride is 2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Dextrose is D-glucopyranose monohydrate and has the following structural formula:



MARCAINE™ Spinal is available in sterile hyperbaric solution for subarachnoid injection (spinal block).

Bupivacaine hydrochloride is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Each mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride (anhydrous) and 82.5 mg dextrose (anhydrous). The pH of this solution is adjusted to between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid.

The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C and 1.03 at 37°C.

MARCAINE Spinal does not contain any preservatives.

CLINICAL PHARMACOLOGY

Local anesthetics 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.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal.

However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended direct intravascular injection of bupivacaine. Therefore, when epidural anesthesia with bupivacaine is considered, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. 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 onset of sensory blockade following spinal block with MARCAINE Spinal is very rapid (within one minute); maximum motor blockade and maximum dermatome level are achieved within 15 minutes in most cases. Duration of sensory blockade (time to return of complete sensation in the operative site or regression of two dermatomes) following a 12 mg dose averages 2 hours with or without 0.2 mg epinephrine. The time to return of complete motor ability with 12 mg MARCAINE Spinal averages 3 1/2 hours without the addition of epinephrine and 4 1/2 hours if 0.2 mg epinephrine is added. When compared to equal milligram doses of hyperbaric tetracaine, the duration of sensory blockade was the same but the time to complete motor recovery was significantly longer for tetracaine. Addition of 0.2 mg epinephrine significantly prolongs the motor blockade and time to first postoperative narcotic with MARCAINE Spinal.

Local anesthetics appear to cross the placenta by passive diffusion. 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. 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. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profiles of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment

represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of MARCAINE in adults is 2.7 hours and in neonates 8.1 hours. In clinical studies, elderly patients exhibited a greater spread and higher maximal level of analgesia than younger patients. Elderly patients also reached the maximal level of analgesia more rapidly than younger patients, and exhibited a faster onset of motor blockade. The total plasma clearance was decreased and the terminal half-life was lengthened in these patients.

Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecolylxylidine is the major metabolite of MARCAINE.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

INDICATIONS AND USAGE

MARCAINE Spinal is indicated for the production of subarachnoid block (spinal anesthesia).

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

CONTRAINDICATIONS

MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type.

The following conditions preclude the use of spinal anesthesia:

1. Severe hemorrhage, severe hypotension or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output.
2. Local infection at the site of proposed lumbar puncture.
3. Septicemia.

WARNINGS

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 INSURING 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. (See also **ADVERSE REACTIONS** and **PRECAUTIONS**.) 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.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such

infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid during the performance of spinal anesthesia is indicative of entry into the subarachnoid space. However, aspiration should be performed before the anesthetic solution is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of MARCAINE containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in patients younger than 18 years, administration of MARCAINE in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE cannot be recommended because of insufficient data on the clinical use of such mixtures.

PRECAUTIONS

General: The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See **WARNINGS** and **ADVERSE REACTIONS**.) The patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

There should be careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness after local anesthetic injection. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used with caution in patients with severe disturbances of cardiac rhythm, shock, or heart block.

Sympathetic blockade occurring during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Patients over 65 years, particularly those with hypertension, may be at increased risk for experiencing the hypotensive effects of MARCAINE Spinal. Blood pressure should, therefore, be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the

severity of hypotension and response of treatment. The level of anesthesia should be carefully monitored because it is not always controllable in spinal techniques.

Because amide-type local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also 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 AV conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than dosage recommendations for other major blocks and most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, 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.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures, and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending upon the physician's evaluation of the situation and ability to deal with the complications or complaints which may occur:

- Pre-existing diseases of the central nervous system, such as those attributable to pernicious anemia, poliomyelitis, syphilis, or tumor.
- Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage.
- Chronic backache and preoperative headache.
- Hypotension and hypertension.
- Technical problems (persistent paresthesias, persistent bloody tap).
- Arthritis or spinal deformity.
- Extremes of age.
- Psychosis or other causes of poor cooperation by the patient.

Information for Patients: When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

Clinically Significant Drug Interactions: The administration of local anesthetic 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, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted. The mutagenic potential and the effect on fertility of bupivacaine hydrochloride have not been determined.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. MARCAINE Spinal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia or analgesia. (See **Labor and Delivery**.)

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are approximately 30-times the daily maximum recommended human dose (MRHD) of 12 mg/day on a mg dose/m^2 body surface area (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level being approximately 8-times the MRHD on a BSA basis.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, & 40 mg/kg mg/kg/day, decreased pup survival was observed at the high dose. The high dose is approximately 30-times the daily MRHD of 12 mg/day on a BSA basis.

Labor and Delivery: Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient’s legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

There have been reports of cardiac arrest during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The package insert for MARCAINE hydrochloride for epidural, nerve block, etc., has a more complete discussion of preparation for, and management of, this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of

bupivacaine hydrochloride 0.75% recommended for spinal anesthesia in obstetrics. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine hydrochloride in dextrose injection) is recommended for spinal anesthesia in obstetrics.

Nursing Mothers: 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.

Pediatric Use: Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

Geriatric Use: Patients over 65 years, particularly those with hypertension, may be at increased risk for developing hypotension while undergoing spinal anesthesia with MARCAINE Spinal. (See **PRECAUTIONS**, **General** and **ADVERSE REACTIONS**, *Cardiovascular System*.)

Elderly patients may require lower doses of MARCAINE Spinal. (See **PRECAUTIONS**, **General** and **DOSAGE AND ADMINISTRATION**.)

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. (See **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**.)

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. (See **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**.)

ADVERSE REACTIONS

Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics.

The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Respiratory System: Respiratory paralysis or underventilation may be noted as a result of upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation, may contribute to underventilation. This will usually be noted within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, differing intercurrent drug usage and differing surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

Cardiovascular System: Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in elderly patients, particularly those with hypertension, and patients with shrunken blood volume, shrunken interstitial fluid volume, cephalad spread of the local anesthetic, and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart

block, ventricular arrhythmias, and, possibly, cardiac arrest. (See **WARNINGS**, **PRECAUTIONS**, and **OVERDOSAGE** sections.)

Central Nervous System: Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see *Respiratory System*) and hypotension for the same reason (see *Cardiovascular System*) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses or inadvertent intravascular injection may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. 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.

Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities, and loss of sphincter control all of which may have slow, incomplete, or no recovery; hypotension, high or total spinal block; urinary retention; headache; backache; septic meningitis, meningismus; arachnoiditis; slowing of labor; increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; and fecal and urinary incontinence.

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Other: Nausea and vomiting may occur during spinal anesthesia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone, and sometimes, contributory mechanical obstruction of venous return.

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 a high or total spinal, 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).

Hypotension due to sympathetic relaxation may be managed by giving intravenous fluids (such as isotonic saline or lactated Ringer's solution), in an attempt to relieve mechanical obstruction of venous return, or by using vasopressors (such as ephedrine which increases the force of myocardial contractions) and, if indicated, by giving plasma expanders or whole blood.

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 a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after 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 LD_{50} in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

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 MARCAINE Spinal should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease.

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. MARCAINE Spinal is not approved for this use (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

The extent and degree of spinal anesthesia depend upon several factors including dosage, specific gravity of the anesthetic solution, volume of solution used, force of injection, level of puncture, and position of the patient during and immediately after injection.

Seven and one-half mg (7.5 mg or 1 mL) MARCAINE Spinal has generally proven satisfactory for spinal anesthesia for lower extremity and perineal procedures including TURP and vaginal hysterectomy. Twelve mg (12 mg or 1.6 mL) has been used for lower abdominal procedures such as abdominal hysterectomy, tubal ligation, and appendectomy. These doses are recommended as a guide for use in the average adult and may be reduced for the elderly or debilitated patients. Because experience with MARCAINE Spinal is limited in patients below the age of 18 years, dosage recommendations in this age group cannot be made.

Obstetrical Use: Doses as low as 6 mg bupivacaine hydrochloride have been used for vaginal delivery under spinal anesthesia. The dose range of 7.5 mg to 10.5 mg (1 mL to 1.4 mL) bupivacaine hydrochloride has been used for Cesarean section under spinal anesthesia.

In recommended doses, MARCAINE Spinal produces complete motor and sensory block.

Unused portions of solutions should be discarded following initial use.

MARCAINE Spinal should be inspected visually for discoloration and particulate matter prior to administration; solutions which are discolored or which contain particulate matter should not be administered.

HOW SUPPLIED

Single-dose ampuls of 2 mL (15 mg bupivacaine hydrochloride with 165 mg dextrose), is supplied as follows:

NDC No.	Container	Fill	Quantity
0409-1761-02	Uni-Amp™	2 mL	package of 10
0409-1761-62	Uni-Amp™	2 mL	bulk package of 800

Store at 20 to 25ºC (68 to 77ºF). [See USP Controlled Room Temperature.]

MARCAINE Spinal solution may be autoclaved once at 15 pound pressure, 121°C (250°F) for 15 minutes. Do not administer any solution which is discolored or contains particulate matter.

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EN-2919

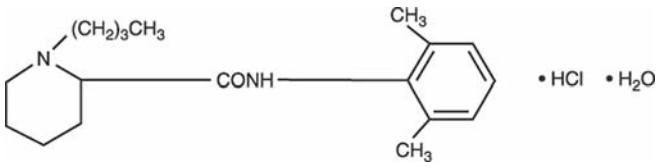
Hospira, Inc., Lake Forest, IL 60045 USA

Bupivacaine HCl
0.5% with epinephrine
1:200,000 (as bitartrate)
(bupivacaine hydrochloride and epinephrine injection, USP)

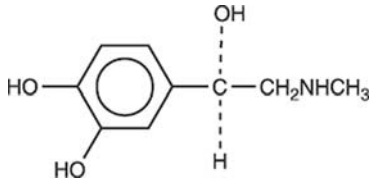
THIS SOLUTION IS INTENDED FOR DENTAL USE. Rx only

DESCRIPTION

Bupivacaine hydrochloride is (±) -1-Butyl-2′,6′-pipecoloxylidide monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Epinephrine is (-)-3,4-Dihydroxy-α-[(methylamino)methyl] benzyl alcohol. It has the following structural formula:



BUPIVACAINE HCl is available in a sterile isotonic solution with epinephrine (as bitartrate) 1:200,000. Solutions of BUPIVACAINE HCl containing epinephrine may not be autoclaved.

BUPIVACAINE HCl is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine.

All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

CLINICAL PHARMACOLOGY

BUPIVACAINE HCl stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting local anesthesia.

The onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine for dental use, in many patients up to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

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 analgesic is reduced.

After injection of BUPIVACAINE HCl for caudal, epidural or peripheral nerve block in man, peak levels of BUPIVACAINE HCl in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. Because of its amide structure, BUPIVACAINE HCl is not detoxified by plasma esterases but is detoxified, via conjugation with glucuronic acid, in the

liver. When administered in recommended doses and concentrations, BUPIVACAINE HCl does not ordinarily produce irritation or tissue damage, and does not cause methemoglobinemia.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

INDICATIONS AND USAGE

BUPIVACAINE HCl is indicated for the production of local anesthesia for dental procedures by infiltration injection or nerve block in adults.

BUPIVACAINE HCl is not recommended for children.

CONTRAINDICATIONS

BUPIVACAINE HCl is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of BUPIVACAINE HCl solutions.

WARNINGS

LOCAL ANESTHETICS SHOULD BE EMPLOYED ONLY 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 INSURING 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. (See also **ADVERSE REACTIONS** and **PRECAUTIONS**.) 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.

Small doses of local anesthetics injected into the head and neck area, as small as nine to eighteen milligrams, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression, and/or respiratory arrest, cardiovascular stimulation or depression and cardiac arrest have been reported. Reactions resulting in fatalities have occurred on rare occasions. In a few cases, resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed.

Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular injection. However, a negative aspiration does not ensure against an intravascular injection.

Reactions resulting in fatality have occurred on rare occasions with the use of local anesthetics, even in the absence of a history of hypersensitivity.

This solution, which contains a vasoconstrictor, should be used with extreme caution for patients whose medical history and physical evaluation suggest the existence of hypertension, arteriosclerotic heart disease, cerebral vascular insufficiency, heart block, thyrotoxicosis and diabetes, etc., as well as patients receiving drugs likely to produce alterations in blood pressure.

BUPIVACAINE HCl with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of BUPIVACAINE HCl containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in children younger than 12 years, administration of BUPIVACAINE HCl in this age group is not recommended.

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 nonasthmatic people.

PRECAUTIONS

The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of BUPIVACAINE HCl may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Because of the long duration of anesthesia, when BUPIVACAINE HCl 0.5% with epinephrine is used for dental injections, patients should be cautioned about the possibility of inadvertent trauma to tongue, lips, and buccal mucosa and advised not to chew solid foods or test the anesthetized area by biting or probing.

Changes in sensorium, such as excitation, disorientation, drowsiness, may be early indications of a high blood level of the drug and may occur following inadvertent intravascular administration or rapid absorption of BUPIVACAINE HCl.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Caution is advised in administration of repeat doses of BUPIVACAINE HCl to patients with severe liver disease.

Local anesthetic procedures should be used with caution when there is inflammation and/or sepsis in the region of the proposed injection.

Drug Interactions: See **WARNINGS** concerning solutions containing a vasoconstrictor.

If sedatives are employed to reduce patient apprehension, use reduced doses, since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

BUPIVACAINE HCl should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, 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.

Information for Patients: When appropriate, the dentist should discuss information including adverse reactions in the package insert for BUPIVACAINE HCl.

Clinically Significant Drug Interactions: The administration of local anesthetic 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, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted. The mutagenic potential and the effect on fertility of bupivacaine hydrochloride have not been determined.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. BUPIVACAINE HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of BUPIVACAINE HCl at term for obstetrical anesthesia or analgesia.

Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are approximately 4-times the daily maximum recommended human dose (MRHD) of 90 mg/day on a mg dose/m^2 body surface area (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level being a comparable dose to the MRHD on a BSA basis.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, & 40 mg/kg mg/kg/day, decreased pup survival was observed at the high dose. The high dose is approximately 4-times the daily MRHD of 90 mg/day on a BSA basis.

Nursing Mothers: It is not known whether local anesthetic drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when local anesthetics are administered to a nursing woman.

Pediatric Use: Until further experience is gained in children younger than 12 years, administration of BUPIVACAINE HCl in this age group is not recommended.

ADVERSE REACTIONS

Reactions to BUPIVACAINE HCl are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. *Allergic reactions,* which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Transient facial swelling and puffiness may occur near the injection site.

Treatment of Reactions: Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The dentist should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultra-short-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

DOSAGE AND ADMINISTRATION

As with all local anesthetics, the dosage varies and depends upon the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance, and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. For specific techniques and procedures, refer to standard textbooks.

The 0.5% concentration with epinephrine is recommended for infiltration and block injection in the maxillary and mandibular area when a longer duration of local anesthetic action is desired, such as for oral surgical procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (9 mg) per injection site will usually suffice; an occasional second dose of 1.8 mL (9 mg) may be used if necessary to produce adequate anesthesia after making allowance for 2 to 10 minutes onset time (see **CLINICAL PHARMACOLOGY**). The lowest effective dose should be employed and time should be allowed between injections; it is recommended that the total dose for all injection sites, *spread out* over a single dental sitting, should not ordinarily exceed 90 mg for a healthy adult patient (ten 1.8 mL

injections of 0.5% BUPIVACAINE HCl with epinephrine). Injections should be made slowly and with frequent aspirations. Until further experience is gained, BUPIVACAINE HCl in dentistry is not recommended for children younger than 12 years.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from light.

0.5% Bupivacaine hydrochloride with epinephrine 1:200,000 (as bitartrate) – Sterile isotonic solutions containing sodium chloride. Each 1 mL contains 5 mg bupivacaine hydrochloride and 0.0091 mg epinephrine bitartrate, with 0.5 mg sodium metabisulfite, 0.001 mL monothioglycerol, and 2 mg ascorbic acid as antioxidants, 0.0017 mL 60% sodium lactate buffer, and 0.1 mg edetate calcium disodium as stabilizer. The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Solutions of BUPIVACAINE HCl that contain epinephrine should not be autoclaved and should be protected from light. Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate. This product is latex-free.

NDC 0409-7600-01 1.8 mL cartridges, containers of 50, to fit the Carpule™ aspirator.

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Hospira, Inc., Lake Forest, IL 60045 USA