Carestream DENTAL

COOK-WAITE

Cook-Waite dental products

Lidocaine

Lidocaine HCl 2% and Epinephrine 1:100,000 Injection (lidocaine hydrochloride and epinephrine injection, USP)

Lidocaine HCl 2% and Epinephrine 1:50,000 Injection (lidocaine hydrochloride and epinephrine injection, USP)

This versatile, widely applicable injection delivers local anesthesia of intermediate duration.

Lidocaine is now packaged in easily stackable boxes. Convenient blister packs protect ampoules from light and air.

Reactions to Lidocaine and epinephrine are characteristic of those associated with other amide-type local drugs. Please see brief description of prescribing information on the next page.

Lidocaine is part of the complete line of Cook-Waite products – the brand dental professionals have relied on for more than 60 years. And remember: all Cook-Waite products are backed by the name you trust for quality, consistency and support.

Ordering Information

Description	US REF No
Lidocaine HCl 2% and Epinephrine 1:100,000 Injection (lidocaine hydrochloride and epinephrine injection, USP)	155 9889
Lidocaine HCl 2% and Epinephrine 1:50,000 Injection (lidocaine hydrochloride and epinephrine injection, USP)	162 8262

Carbocaine® 3%

Carbocaine® 3% (mepivacaine hydrochloride injection, USP) without vasoconstrictor

Carbocaine® 2%

Carbocaine® 2% with Neo-Cobefrin® (mepivacaine hydrochloride and levonordefrin injection, USP)

Each of your patients has his or her own medical history and special dental needs. It's nice to know that Cook-Waite drugs give you a confident choice for them, too. Cook-Waite Carbocaine 3% (mepivacaine HCl injection, USP) is indicated for both children and adults.

Carbocaine 2% with Neo-Cobefrin contains a vasoconstrictor, levonordefrin, which has a pharmacologic activity similar to that of epinephrine. Carbocaine 2% with Neo-Cobefrin provides anesthetic of longer duration for more prolonged procedures.

Carbocaine is now packaged in boxes for easy storage. Convenient blister packs protect ampoules. Carbocaine is part of the complete line of Cook-Waite products – the brand dental professionals have relied on for more than 60 years.

Like all products in the Cook-Waite family, Carbocaine is backed by the name you trust for quality, consistency and support.

Ordering Information

Description	US REF No
Carbocaine® 3% (mepivacaine hydrochloride injection, USP) without vasoconstrictor	143 0735
Carbocaine® 2% with Neo-Cobefrin® (mepivacaine hydrochloride and levonordefrin injection, USP)	144 9313

Marcaine®

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

Marcaine 0.5% with epinephrine 1:200,000 injection (as bitartrate) brand of bupivacaine hydrochloride and epinephrine injection, USP, provides long-lasting, profound anesthesia. Please refer to enclosed prescribing information for reactions, precautions and dosage recommendation.[1]

Marcaine is part of the complete line of Cook-Waite products – the brand dental professionals have relied on for more than 60 years. Cook-Waite products are the name you can trust for quality, consistency and support.

[1] Reactions to Marcaine are characteristic of those associated with other amide-type local drug products. 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. Marcaine is contraindicated in patients with a known hypersensitivity to it or to any local drug product agent of the amide type or to other components of bupivacaine solutions. Marcaine 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. Please see the enclosed package insert for full prescribing information.and support.

Ordering Information

Description	US REF No
Marcaine® 0.5% with epinephrine 1:200,000 injection (as bitartrate) (bupivacaine hydrochloride and epinephrine injection, USP)	185 2557

Zorcaine

Zorcaine (articaine HCl and epinephrine) Injection, Articaine hydrochloride 4% and epinephrine 1:100,000

Articaine

With Zorcaine, our line of drug products just got more complete. Zorcaine is the newest local anesthetic product from Cook-Waite — the brand dental professionals have relied on for more than 60 years.

Like all products in the Cook-Waite family, Zorcaine is the name you can trust for quality, consistency and support.

Ordering Information

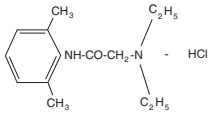
Description	US REF No
Zorcaine (articaine HCl and epinephrine) Injection, Articaine hydrochloride 4% and epinephrine 1:100,000	894 2831

Lidocaine HCl 2% and Epinephrine 1:50,000 Injection
Lidocaine HCl 2% and Epinephrine 1:100,000 Injection
(lidocaine hydrochloride and epinephrine injection, USP)

Rx only SOLUTIONS FOR LOCAL ANESTHESIA IN DENTISTRY

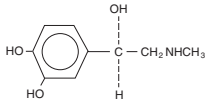
DESCRIPTION
Sterile isotonic solutions containing a local anesthetic agent, Lidocaine Hydrochloride, and a vasoconstrictor, epinephrine (as bitartrate) and are administered parenterally by injection. Both solutions are available in single dose cartridges of 1.7 mL (See INDICATIONS AND USAGE for specific uses).

Solutions contain lidocaine hydrochloride which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-monohydrochloride, and has the following structural formula:



$C_{14}H_{22}N_2O.HCl.H_2O$ M.W. 288.8

Epinephrine is (-)-3,4-Dihydroxy-a-[(Methylamino) methyl] benzyl alcohol and has the following structural formula:



$C_9H_{13}NO_3.C_4H_6O_6$ M.W. 333.3

CLINICAL PHARMACOLOGY
Mechanism of action
Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anesthetic action.

Onset and duration of anesthesia
When used for infiltration anesthesia in dental patients, the time of onset averages less than two minutes for each of the two forms of lidocaine hydrochloride and epinephrine injection, USP. Lidocaine HCl 2% and epinephrine 1:50,000 or lidocaine HCl 2% and epinephrine 1:100,000 provide an average pulp anesthesia of at least 60 minutes with an average duration of soft tissue anesthesia of approximately 2½ hours.

When used for nerve blocks in dental patients, the time of onset for both forms of lidocaine hydrochloride and epinephrine injection, USP averages 2-4 minutes. Lidocaine HCl 2% and epinephrine 1:50,000 or lidocaine HCl 2% and epinephrine 1:100,000 provide pulp anesthesia averaging at least 90 minutes with an average duration of soft tissue anesthesia of 3 to 3¼ hours.

Hemodynamics
Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. These changes may be attributable to a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine when present.

COMPOSITION OF LIDOCAINE HYDROCHLORIDE AND EPINEPHRINE INJECTION, USP

BRAND NAME	PRODUCT IDENTIFICATION		FORMULA		
			SINGLE DOSE CARTRIDGE		
	Lidocaine hydrochloride	Epinephrine (as the bitartrate)	Sodium Chloride	Potassium metabisulfite	Edetate Disodium
	Concentration %	Dilution	(mg/mL)	(mg/mL)	(mg/mL)
LIDOCAINE HCl 2% and EPINEPHRINE 1:50,000	2	1:50,000	6.5	1.2	0.25
LIDOCAINE HCl 2% and EPINEPHRINE 1:100,000	2	1:100,000	6.5	1.2	0.25

The pH of the lidocaine hydrochloride and epinephrine injection, USP solutions are adjusted to USP limits with sodium hydroxide.

Pharmacokinetics and metabolism

Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentration of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-l-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.

Studies of lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey, arterial blood levels of 18-21 mcg/mL have been shown to be the threshold for convulsive activity.

INDICATIONS AND USAGE
Lidocaine hydrochloride and epinephrine injection, USP solutions are indicated for the production of local anesthesia for dental procedures by nerve block or infiltration techniques.

Only accepted procedures for these techniques as described in standard textbooks are recommended.

CONTRAINDICATIONS
Lidocaine hydrochloride and epinephrine injection, USP is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any components of the injectable formulations.

WARNINGS
DENTAL PRACTITIONERS WHO EMPLOY LOCAL ANESTHETIC AGENTS SHOULD BE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF EMERGENCIES WHICHMAY ARISE FROM THEIR USE. RESUSCITATIVE EQUIPMENT, OXYGEN AND OTHER RESUSCITATIVE DRUGS SHOULD BE AVAILABLE FOR IMMEDIATE USE.

To minimize the likelihood of intravascular injection, aspiration should be performed before the local anesthetic solution is injected. If blood is aspirated, the needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not assure that intravascular injection will be avoided.

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

Lidocaine hydrochloride and epinephrine injection, USP solutions contain potassium 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.

Lidocaine hydrochloride and epinephrine injection, USP, along with other local anesthetics, is capable of producing methemoglobinemia. The clinical signs of methemoglobinemia are cyanosis of the nail beds and lips, fatigue and weakness. If methemoglobinemia does not respond to administration of oxygen, administration of methylene blue intravenously 1-2 mg/kg body weight over a 5 minute period is recommended.

The American Heart Association has made the following recommendation regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used." (Kaplan, EL. editor: Cardiovascular disease in dental practice, Dallas 1986, American Heart Association).

PRECAUTIONS
General
The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Consult standard textbooks for specific techniques and precautions for various regional anesthetic procedures. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (See WARNINGS AND ADVERSE REACTIONS).

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical condition.

If sedatives are employed to reduce patient apprehension, reduced doses should be used since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect. Young children should be given minimal doses of each agent.

Lidocaine should be used with caution in patients with severe shock or heart block. Lidocaine should also be used with caution in patients with impaired cardiovascular function. Local anesthetic solutions containing a vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury (such as exfoliating or ulcerating lesions) or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be monitored after each local anesthetic injection. Restlessness, anxiety tinnitus, dizziness, blurred vision, tremors, depression or drowsiness should alert the practitioner to the possibility of central nervous system toxicity. Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position: placing the patient in the recumbent position is recommended when an adverse response is noted after injection of a local anesthetic (See ADVERSE REACTIONS - Cardiovascular System.). Vasovagal reactions may elicit a range of clinical manifestations, from prodrome signs of pre-syncope (e.g., lightheadedness, pallor, nausea, sweating, visual disturbances, weakness) to brief loss of consciousness (i.e., syncope).

Lidocaine should be used with caution in patients with hepatic disease, since amide-type local anesthetics are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction, and since 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 suspected triggering agent (s) and prompt treatment, including oxygen therapy, dantrolene (consult dantrolene sodium intravenous package insert before using) and other supportive measures.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in the 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. 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. 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).

Clinically significant drug interactions
The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines may produce severe prolonged hypotension or 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 ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

As the Lidocaine HCl 2% and epinephrine 1:100,000 and the Lidocaine HCl 2% and epinephrine 1:50,000 solutions both contain a vasoconstrictor (epinephrine), concurrent use of either with a Beta-adrenergic blocking agent (propranolol, timolol, etc.) may result in dose-dependent hypertension and bradycardia with possible heart block.

Drug/Laboratory test interactions
The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination, without isoenzyme separation, as a diagnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.

Carcinogenesis, mutagenesis, impairment of fertility
Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY
Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Nursing mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric use
Dosages in pediatric population should be reduced, commensurate with age, body weight and physical condition (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide-type local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels (which may be caused by excessive dosage, rapid absorption unintended intravascular injection or slow metabolic degradation), injection technique, volume of injection, hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central Nervous System
CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular system
Cardiovascular manifestations in response to lidocaine are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest. In addition, the beta-adrenergic receptor-stimulating action of epinephrine may lead to excitatory cardiovascular responses, such as tachycardia, palpitations, and hypertension.

Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position. Less commonly, they may result from a direct effect of the drug. Failure to recognize the premonitory signs such as sweating, a feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and seizure or serious cardiovascular catastrophe. Management consists of placing the patient in the recumbent position and ventilation with oxygen. Supportive treatment of circulatory depression may require the administration of intravenous fluids and, when appropriate, a vasopressor (e.g, ephedrine) as directed by the clinical situation.

Allergic reactions
Allergic reactions are characterized by cutaneous lesions, urticaria, edema, anaphylactoid reactions, or dyspnea due to bronchoconstriction. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Neurologic reactions
The incidences of adverse reactions (e.g., persistent neurologic deficit) associated with the use of local anesthetics may be related to the technique employed, the total dose of local anesthetic administered, the particular drug used, the route of administration, and the physical condition of the patient.

Persistent paresthesias of the lips, tongue, and oral issues have been reported with the use of lidocaine, with slow, incomplete, or no recovery. These post-marketing events have been reported chiefly following nerve blocks in the mandible and have involved the trigeminal nerve and its branches.

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 respirato ry 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 convulsions consists of immediate attention to the maintenance of a patient air way and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask.

Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of clrculatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardio-pulmonary resuscitative measures should be instituted. 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.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The intravenous LD50 of lidocaine HCl in female mice is 26 (21-31) mg/kg and the subcutaneous LD50 is 264 (203-304) mg /kg.

DOSAGE AND ADMINISTRATION
The dosage of lidocaine HCl 2% and epinephrine depends on the physical status of the patient, the area of the oral cavity to be anesthetized, the vascularity of the oral tissues, and the technique of anesthesia used. The least volume of solution that results in effective local anesthesia should be administered; time should be allowed between injections to observe the patient for manifestations of an adverse reaction. For specific techniques and procedures of a local anesthesia in the oral cavity, refer to standard textbooks.

For most routine dental procedures, lidocaine HCl 2% and epinephrine 1:100,000 is preferred. However, when greater depth and a more pronounced hemostasis are required, lidocaine HCl 2% and epinephrine 1:50,000 should be used.

Dosage requirements should be determined on an individual basis. In oral infiltration and / or mandibular block, initial dosages of 1.0 - 5.0 mL (1/2 to 2 ½ cartridges) of lidocaine HCl 2% and epinephrine 1:50,000 or lidocaine HCl 2% and epinephrine 1:100,000 are usually effective.

In children under 10 years of age, it is rarely necessary to administer more than one-half cartridge (0.9-1.0 mL or 18-20 mg of lidocaine) per procedure to achieve local anesthesia for a procedure involving a single tooth. In maxillary infiltration, this amount will often suffice to the treatment of two or even three teeth. In the mandibular block, however, satisfactory anesthesia achieved with this amount of drug, will allow treatment of the teeth of an entire quadrant. Aspiration is recommended since it reduces the possibility of intravascular injection, thereby keeping the incidence of side effects and anesthetic failures to a minimum. Moreover, injection should always be made slowly.

Maximum recommended dosages for lidocaine HCl 2% and epinephrine 1:50,000 or lidocaine HCl 2% and epinephrine 1:100,000.

Adult:
For normal healthy adults, the amount of lidocaine HCl administered should be kept below

500 mg, and in any case, should not exceed 7 mg/kg (3.2 mg/lb) of body weight.

Pediatric:
Pediatric patients: It is difficult to recommend a maximum dose of any drug for pediatric patients since this varies as a function of age and weight. For pediatric patients of less than ten years who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (e.g., Clark's rule). For example, in pediatric patients of five years weighing 50 lbs, the dose of lidocaine hydrochloride should not exceed 75-100mg when calculated according to Clark's rule. In any case, the maximum dose of lidocaine hydrochloride should not exceed 7 mg/kg (3.2 mg/lb) of body weight.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and / or contain particulate matter should not be used; and any unused portion of a cartridge of lidocaine hydrochloride and epinephrine injection, USP should be discarded.

HOW SUPPLIED
- Lidocaine hydrochloride 2% and Epinephrine 1:50,000 injection is available in cartons containing 5 blisters of 10 x 1.7 mL cartridges (NDC 31382-262-05).
- Lidocaine hydrochloride 2% and Epinephrine 1:100,000 injection is available in cartons containing 5 blisters of 10 x 1.7 mL cartridges (NDC 31382-898-05).

Store at controlled room temperature, below 25°C (77°F). Protect from light. Do not permit to freeze.

BOXES: For protection from light, retain in box until time of use. Once opened, the box should be reclosed by closing the end flap.

Do not use if color is pinkish or darker than slightly yellow or if it contains a precipitate.

Sterilization: Storage and technical Procedures

1. Cartridges should not be autoclaved, because the closures employed cannot withstand autoclaving temperatures and pressures.
2. If chemical disinfection of anesthetic cartridges is desired, either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of U.S.P grade, contain denaturants that are injurious to rubber and, therefore, are not to be used. It is recommended that chemical disinfection be accomplished just prior to use by wiping the cartridge cap thoroughly with a pledge of cotton that has been moistened with recommended alcohol.
3. Certain metallic ions (mercury, zinc, copper, etc.) have been related to swelling and edema after local anesthesia in dentistry. Therefore, chemical disinfectants containing or releasing these ions are not recommended. Antirust tablets usually contain sodium nitrite or some similar agents that may be capable of releasing metal ions. Because of this, aluminium sealed cartridges should not be kept in such solutions.
4. Quaternary ammonium salts, such as benzalkonium chloride, are electrolytically incompatible with aluminium. Cartridges of lidocaine hydrochloride and epinephrine injection, USP are sealed with aluminium caps and therefore should not be immersed in any solution containing these salts.
5. To avoid leakage of solutions during injection, be sure to penetrate the center of the rubber diaphragm when loading the syringe. An off-center penetration produces an oval shaped puncture that allows leakage around the needle. Other causes of leakage and breakage include badly worn syringes, aspirating syringes with bent harpoons, the use of syringes not designed to take 1.7 mL cartridges, and inadvertent freezing.
6. Cracking of glass cartridges is most often the result of an attempt to use a cartridge with an extruded plunger. An extruded plunger loses its lubrication and can be forced back into the cartridge only with difficulty. Cartridges with extruded plungers should be discarded.
7. Store at controlled room temperature, below 25°C (77°F).

Rev 06/13 (2285-5)

Cook-Waite

Manufactured for
CARESTREAM HEALTH, INC. by
Novocol Pharmaceutical of Canada. Inc.
Cambridge, Ontario, Canada N1R 6X3

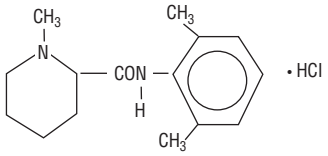
2285-5

Carbocaine® 3% injection
(mepivacaine hydrochloride injection, USP)
Carbocaine® 2%
with Neo-Cobefrin® 1:20,000 injection
(mepivacaine hydrochloride and levonordefrin injection, USP)

Rx only

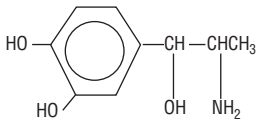
THESE SOLUTIONS ARE INTENDED FOR DENTAL USE ONLY.

DESCRIPTION: CARBOCAINE (mepivacaine hydrochloride), a tertiary amine used as a local anesthetic, is 1-methyl-2', 6' - pipecoloxylidide monohydrochloride with the following structural formula:



$C_{15}H_{22}N_2$ 0.HCl M.W. 282.81

It is a white, crystalline, odorless powder soluble in water, but very resistant to both acid and alkaline hydrolysis.
NEO-COBEFRIN, a sympathomimetic amine used as a vasoconstrictor in local anesthetic solution, is (-)- ∝ -(1-Aminoethyl)-3, 4-dihydroxybenzyl alcohol with the following structural formula:



$C_9H_{13}NO_3$ M.W. 183.21

It is a white or buff-colored crystalline solid, freely soluble in aqueous solutions or mineral acids, but practically insoluble in water.

DENTAL CARTRIDGES MAY NOT BE AUTOCLAVED.

CARBOCAINE 3% injection and CARBOCAINE 2% with NEO-COBEFRIN 1:20,000 injection are sterile solutions for injection.

COMPOSITION:	CARTRIDGE	
Each mL contains:	2%	3%
Mepivacaine hydrochloride	20 mg	30 mg
Levonordefrin	0.05 mg	-
Sodium chloride	4 mg	6 mg
Potassium metabisulfite	1.2 mg	-
Edetate disodium	0.25 mg	-
Sodium hydroxide q.s. ad pH		
Hydrochloric acid	0.5 mg	-
Water for injections qs. ad.	1 mL	1 mL

The pH of the 2% cartridge solution is adjusted between 3.3 and 5.5 with NaOH.
The pH of the 3% cartridge solution is adjusted between 4.5 and 6.8 with NaOH.

CLINICAL PHARMACOLOGY:

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

CARBOCAINE is rapidly metabolized, with only a small percentage of the anesthetic (5 to 10 percent) being excreted unchanged in the urine. CARBOCAINE because of its amide structure, is not detoxified by the circulating plasma esterases. The liver is the principal site of metabolism, with over 50 percent of the administered dose being excreted into the bile as metabolites. Most of the metabolized mepivacaine is probably resorbed in the intestine and then excreted into the urine since only a small percentage is found in the feces. The principal route of excretion is via the kidney. Most of the anesthetic and its metabolites are eliminated within 30 hours. It has been shown that hydroxylation and N-demethylation, which are detoxification reactions, play important roles in the metabolism of the anesthetic. Three metabolites of mepivacaine have been identified from adult humans: two phenols, which are excreted almost exclusively as their glucuronide conjugates, and the N-demethylated compound (2', 6' - pipecoloxylidide).

The onset of action is rapid (30 to 120 seconds in the upper jaw; 1 to 4 minutes in the lower jaw) and CARBOCAINE 3% injection will **ordinarily** provide operating anesthesia of **20 minutes** in the **upper jaw** and **40 minutes** in the **lower jaw**.

CARBOCAINE 2% with Neo-Cobefrin 1:20,000 injection provides anesthesia of longer duration for more prolonged procedures, **1 hour to 2.5 hours** in the **upper jaw** and **2.5 hours to 5.5 hours** in the **lower jaw.**

CARBOCAINE does not ordinarily produce irritation or tissue damage.

Neo-Cobefrin is a sympathomimetic amine used as a vasoconstrictor in local anesthetic solutions. It has pharmacologic activity similar to that of Epinephrine but it is more stable than Epinephrine. In equal concentrations, Neo-Cobefrin is less potent than Epinephrine in raising blood pressure, and as a vasoconstrictor.

INDICATIONS AND USAGE:

CARBOCAINE is indicated for production of local anesthesia for dental procedures by infiltration or nerve block in adults and pediatric patients.

CONTRAINDICATIONS:

CARBOCAINE is contraindicated in patients with a known hypersensitivity to amide-type local anesthetics.

WARNINGS:

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE. (See ADVERSE REACTIONS).

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

Fatalities may occur with use of local anesthetics in the head and neck region as the result of retrograde arterial flow to vital CNS areas even when maximum recommended doses are observed. The practitioner should be alert to early evidence of alteration in sensorium or vital signs.

The solution which contains a vasoconstrictor (CARBOCAINE) 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.

The solution which contains a vasoconstrictor (CARBOCAINE) also contains potassium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people. CARBOCAINE is SULFITE FREE.

CARBOCAINE, along with other local anesthetics, is capable of producing methemoglobinemia. The clinical signs of methemoglobinemia are cyanosis of the nail beds and lips, fatigue and weakness. If methemoglobinemia does not respond to administration of oxygen, administration of methylene blue intravenously 1-2 mg/kg body weight over a 5 minute period is recommended.

The American Heart Association has made the following recommendations regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used." (Kaplan, EL. editor: Cardiovascular disease in dental practice, Dallas 1986, American Heart Association).

PRECAUTIONS:

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

The lowest dose that results in effective anesthesia should be used to avoid high plasma levels and possible adverse effects. Injection of repeated doses of Mepivacaine may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites, or due to slower metabolic degradation than normal.

Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their weight and physical status.

Mepivacaine should be used with caution in patients with a history of severe disturbances of cardiac rhythm or heart block.

INJECTIONS SHOULD ALWAYS BE MADE SLOWLY WITH ASPIRATION TO AVOID INTRAVASCULAR INJECTION AND THEREFORE SYSTEMIC REACTION TO BOTH LOCAL ANESTHETIC AND 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. Young children should be given minimal doses of each agent.

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

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

Information for Patients: The patient should be cautioned against loss of sensation and possibility of biting trauma should the patient attempt to eat or chew gum prior to return of sensation.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing vasopressors, such as Neo-Cobefrin, Epinephrine or Norepinephrine, to patients receiving tricyclic antidepressants or monoamine oxidase inhibitors may produce severe, prolonged hypertension. Concurrent use of these agents shou ld 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.

Solutions containing a vasoconstrictor should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of potent inhalation anesthetics.

MEPIVACAINE SHOULD BE USED WITH CAUTION IN PATIENTS WITH KNOWN DRUG ALLERGIES AND SENSITIVITIES. A thorough history of the patient's prior experience with Mepivacaine or other local anesthetics as well as concomitant or recent drug use should be taken (see CONTRAINDICATIONS). Patients allergic to methylparaben or para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide type such as Mepivacaine. Since Mepivacaine is metabolized in the liver and excreted by the kidneys, it should be used cautiously in patients with liver and renal disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of Mepivacaine HCl in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnacy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with this solution. It is also not known whether this solution can cause fetal harm when administered to a pregnant woman or can effect reproductive capacity. This solution should be given to a pregnant woman only if clearly needed.

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

Pediatric Use: Great care must be exercised in adhering to safe concentrations and dosages for pedodontic administration (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS:

Reactions to CARBOCAINE are characteristic of those associated with other amide-type local anesthetics. Systemic adverse reactions involving the central nervous system and the cardiovascular system usually result from high plasma levels (which may be due to excessive dosage, rapid absorption, inadvertent intravascular injection, or slow metabolic degradation), injection technique, or volume of injection.

A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance to normal dosage on the part of the patient.

Persistent paresthesias of the lips, tongue, and oral tissues have been reported with the use of mepivacaine, with slow, incomplete, or no recovery. These post-markeing events have been reported chiefly following nerve blocks in the mandible and have involved the trigeminal nerve and its branches.

Reactions involving the *central nervous system* are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision, or tremors may occur followed by drowsiness, convulsions, unconsciousness, and possible respiratory arrest. Since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular reactions are depressant. They may be the result of direct drug effect or more commonly in dental practice, the result of vasovagal reaction, particularly if the patient is in the sitting position. Failure to recognize premonitory signs such as sweating, feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and seizure or serious cardiovascular catastrophe. Management consists of placing the patient in the recumbent position and administration of oxygen. Vasoactive drugs such as Ephedrine or Methoxamine may be administered intravenously.

Allergic reactions are rare and may occur as a result of sensitivity to the local anesthetic and are characterized by cutaneous lesions of delayed onset or urticaria, edema and other manifestations of allergy. The detection of sensitivity by skin testing is of limited value. As with other local anesthetics, anaphylactoid reactions to Mepivacaine have occurred rarely. The reaction may be abrupt and severe and is not usually dose related. Localized puffiness and swelling may occur.

OVERDOSAGE:

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patient airway and supporting ventilat ion (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilatory therapy, small increments of anticonvulsive agents may be given intravenously, such as benzodiazephine (e.g., diazepam) or ultrashort-acting barbiturates (e.g., thiopental or thiamylal) or short-acting barbiturates (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressor (e.g., Ephedrine) as dictated by the clinical situation. Allergic reactions should be managed by conventional means.

IV and SC LD_{50}'s in mice for Mepivacaine Hydrochloride 3% are 33 and 258 mg/kg, respectively. The acute IV and SC LD_{50}'s in mice for Mepivacaine Hydrochloride 2% with Levonordefrin 1:20,000 are 30 and 184 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

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

For infiltration and block injections in the upper or lower jaw, the average dose of 1 cartridge will usually suffice.

Each cartridge contains 1.7 mL (34 mg of 2% or 51 mg of 3%).

5.3 cartridges (180 mg of the 2% solution or 270 mg of the 3% solution) are usually adequate to effect anesthesia of the entire oral cavity. Whenever a larger dose seems to be necessary for an extensive procedure, the maximum dose should be calculated according to the patient's weight. A dose of up to 3 mg per pound of body weight may be administered. At any single dental sitting the total dose for all injected sites should not exceed 400 mg in adults.

The maximum pediatric dose should be *carefully calculated*.

Maximum dose for pediatric population =

$$\frac{\text{Child's Weight (lbs.)}}{150} \times \text{Maximum Recommended Dose for Adults (400 mg)}$$

The following table, approximating these calculations, may also be used as a guide. This table is based upon a recommended maximum for larger pediatric population of 5.3 cartridges (the maximum recommended adult dose) during any single dental sitting, regardless of the pediatric patient's weight or (for 2% mepivacaine) calculated maximum amount of drug:

	Maximum Allowable Dosage*			
	3% Mepivacaine (Plain)		2% Mepivacaine 1:20,000 Levonordefrin	
	3 mg/lb (270 mg max.)		3mg/lb (180 mg max.)	
Weight (lb.)	mg	Number of Cartridges	mg	Number of Cartridges
20	60	1.2	60	1.8
30	90	1.8	90	2.6
40	120	2.3	120	3.5
50	150	2.9	150	4.4
60	180	3.5	180	5.3
80	240	4.7	180	5.3
100	270	5.3	180	5.3
120	270	5.3	180	5.3

*Adapted from Malamed, Stanley F: Handbook of medical emergencies in the dental office, ed. 2, St. Louis, 1982. The C.V. Mosby Co.

When using CARBOCAINE for infiltration or regional block anesthesia, injection should always be made slowly and with frequent aspiration.

Any unused portion of a cartridge should be discarded.

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

DISINFECTION OF CARTRIDGES:

As in the case of any cartridge, the diaphragm should be disinfected before needle puncture. The diaphragm should be thoroughly swabbed with either pure 91% isopropyl alcohol or 70% ethyl alcohol, USP, just prior to use. Many commercially available alcohol solutions contain ingredients which are injurious to container components, and therefore, should not be used. Cartridges should not be immersed in any solution.

HOW SUPPLIED:

CARBOCAINE 3% injection (mepivacaine hydrocholoride injection, USP) is available in cartons containing 5 blisters of 10 x 1.7 mL dental cartridges, 50 per carton.

CARBOCAINE 2% with NEO-COBEFRIN 1:20,000 injection, USP (mepivacaine hydrochloride and levonordefrin injection, USP) is available in cartons containing 5 blisters of 10 x 1.7 mL dental cartridges, 50 per carton (NDC 31382-931).

Both solutions should be stored at controlled room temperature, below 25° C (77° F). **Protect from light.** Do not permit to freeze. For protection from light, retain in box until time of use. Once opened, the box should be reclosed by closing the flap. The mepivacaine 2% solution should not be used if its color is pinkish or darker th an slightly yellow or it contains a precipitate. Cartridge warmers should not be used with CARBOCAINE products.

Cook-Waite

Rev 06/13 (2271-4)

Manufactured for
CARESTREAM HEALTH, INC. by
Novocol Pharmaceutical of Canada, Inc.
Cambridge, Ontario, Canada N1R 6X3

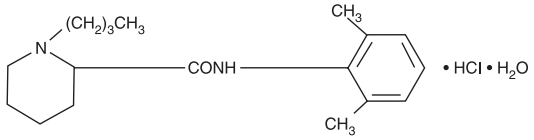
2271-4

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

Rx only THIS SOLUTION IS INTENDED FOR DENTAL USE

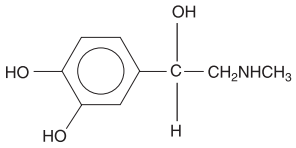
DESCRIPTION

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:



Molecular Weight - 342.90
$C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$

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



Molecular Weight - 183.20
$C_9H_{13}NO_3$

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

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.

CLINICAL PHARMACOLOGY

Bupivacaine 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 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. Because of its amide structure, bupivacaine 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 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

Marcaine® 0.5% with epinephrine 1:200,000 injection is indicated for the production of local anesthesia for dental procedures by infiltration injection or nerve block in adults.

Marcaine® 0.5% with epinephrine 1:200,000 injection is not recommended for children.

CONTRAINDICATIONS

Marcaine® 0.5% with epinephrine 1:200,000 injection, 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 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.

Marcaine® 0.5% with epinephrine 1:200,000 injection or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of bupivacaine 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 in this age group in 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 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 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.

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 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.

Marcaine® 0.5% with epinephrine 1:200,000 injection 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 Marcaine® 0.5% with epinephrine 1:200,000 injection.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving mono-amine 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 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced development toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of bupivacaine 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/m2 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-time 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 in this age group is not recommended.

ADVERSE REACTIONS

Reactions to Marcaine® 0.5% with epinephrine 1:200,000 injection 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 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 bupivacaine with epinephrine). Injections should be made slowly and with frequent aspirations. Until further experience is gained, bupivacaine in dentistry is not recommended for children younger than 12 years.

Parental 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. Do not permit to freeze.

Marcaine® 0.5% with epinephrine 1:200,000 injection, (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, 7 mg sodium chloride, 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 that contain epinephrine should not be autoclaved and should be protected from light. Do not use the solution if its colour is pinkish or darker than slightly yellow or if it contains a precipitate.

Marcaine® 0.5% with epinephrine 1:200,000 injection (NDC 31382-557-05) is available in cartons containing 5 blisters of 10 X 1.8 mL dental cartridges.

Rev 06/13 (2361-4)

Cook-Waite

Manufactured for
CARESTREAM HEALTH, INC. by
Novocol Pharmaceutical of Canada. Inc.
Cambridge, Ontario, Canada N1R 6X3

2361-4

Zorcaine™ (articaine HCl and epinephrine) Injection; Intraoral Submucosal Injection

Articaine hydrochloride 4% and epinephrine 1:100,000

Articaine hydrochloride 4% and epinephrine 1:200,000

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zorcaine™ safely and effectively. See full prescribing information for Zorcaine™.

Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Zorcaine™, an amide local anesthetic containing a vasoconstrictor, is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

DOSAGE AND ADMINISTRATION

For dental injection by submucosal infiltration or nerve block. (2.1)

- For infiltration: 0.5-2.5 mL (20-100 mg articaine HCl) (2.1)
- For nerve block: 0.5-3.4 mL (20-136 mg articaine HCl) (2.1)
- For oral surgery: 1.0-5.1 mL (40-204 mg articaine HCl) (2.1)
- For most routine dental procedures, articaine hydrochloride 4% containing epinephrine 1:200,000 is preferred. However, when more pronounced hemostasis or improved visualization of the surgical field are required, Zorcaine™ containing epinephrine 1:100,000 may be used. (2.1)
- Dosages should be reduced in pediatric patients, elderly patients, and patients with cardiac or liver disease. (2.1)

Maximum recommended dosages (2.2):

- Adults: 7 mg/kg (0.175 mL/kg)
- Children 4-16 years: 7 mg/kg (0.175 mL/kg), depending on the age, weight and magnitude of the operation.

DOSAGE FORMS AND STRENGTHS

Injection (clear colorless solution), containing:

- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL) (3)
- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL) (3)

CONTRAINDICATIONS

Known hypersensitivity to sulfite. (4)

WARNINGS AND PRECAUTIONS

- **Accidental Intravascular Injection:** May be associated with convulsions followed by coma and respiratory arrest. Resuscitative equipment, oxygen and other resuscitative drugs should be available. (5.1)
- **Systemic Toxicity** (5.2)
- **Vasoconstrictor Toxicity:** Local anesthetic solutions like Zorcaine™ that contain a vasoconstrictor should be used cautiously, especially in patients with impaired cardiovascular function or vascular disease. (5.3)
- **Methemoglobinemia** (5.4)
- **Anaphylaxis and Allergic-Type Reactions** (5.5)

ADVERSE REACTIONS

The most common adverse reactions (incidence >2%) are headache and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Septodont at 1-800-872-8305 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Monoamine oxidase inhibitors, nonselective beta adrenergic antagonists, or tricyclic antidepressants may produce severe, prolonged hypertension (7)
- Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine (7)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal studies, may cause fetal harm. (8.1)
- **Nursing Mothers:** Exercise caution when administering to a nursing woman. (8.3)
- **Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 4 years have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zorcaine™, an amide local anesthetic containing a vasoconstrictor, is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Table 1 (below) summarizes the recommended volumes and concentrations of Zorcaine™ for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults, administered by submucosal infiltration or nerve block.

Table 1: Recommended Dosages for Both Strengths

Procedure	Zorcaine™ Injection	
	Volume (mL)	Total dose of articaine HCl (mg)
Infiltration	0.5 – 2.5	20 – 100
Nerve block	0.5 – 3.4	20 – 136
Oral surgery	1.0 – 5.1	40 – 204

The recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia, degree of muscular relaxation, and condition of the patient. In all cases, the smallest dose that will produce the desired result should be given.

The onset of anesthesia and the duration of anesthesia are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Caution should be exercised when employing large volumes because the incidence of side effects may be dose-related.

For most routine dental procedures, articaine hydrochloride 4% containing epinephrine 1:200,000 is preferred. However, when more pronounced hemostasis or improved visualization of the surgical field are required, Zorcaine™ containing epinephrine 1:100,000 may be used.

2.2 Maximum Recommended Dosages

- Adults: For normal healthy adults, the maximum dose of articaine HCl administered by submucosal infiltration or nerve block should not exceed 7 mg/kg (0.175 mL/kg).
- Pediatric Patients Ages 4 to 16 Years: The quantity of articaine HCl in children ages 4 to 16 years of age to be injected should be determined by the age and weight of the child and the magnitude of the operation. The maximum dose of articaine HCl 4% should not exceed 7 mg/kg (0.175 mL/kg [see Use in Specific Populations (8.4)].
- Safety and effectiveness of Zorcaine™ in pediatric patients below the age of 4 years have not been established.

2.3 Dosing in Special Populations

Dose reduction may be required in debilitated patients, acutely ill patients, elderly patients, and pediatric patients commensurate with their age and physical condition. No studies have been performed in patients with renal or liver dysfunction. Caution should be used in patients with severe liver disease. [see Warnings and Precautions (5.2), Use in Specific Populations (8.4, 8.5, and 8.6)]

3 DOSAGE FORMS AND STRENGTHS

Injection (clear colorless solution), containing:

- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL)
- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL)

4 CONTRAINDICATIONS

Zorcaine is contraindicated in patients who are hypersensitive to products containing sulfites. Products containing sulfites may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people [see Warnings and Precautions (5.5)].

5 WARNINGS AND PRECAUTIONS

5.1 Accidental Intravascular Injection

Accidental intravascular injection of Zorcaine™ may be associated with convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Dental practitioners who employ local anesthetic agents including Zorcaine™ should be well versed in diagnosis and management of emergencies that may arise from their use. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. To avoid intravascular injection, aspiration should be performed before Zorcaine™ is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Small doses of local anesthetics injected in dental blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression 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. Patients receiving these blocks should be observed constantly. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded [see Dosage and Administration (2.1)].

5.2 Systemic Toxicity

This includes toxicity arising from accidental intravascular injection of Zorcaine™ discussed in Section 5.1, as well as that related to higher systemic concentrations of local anesthetics or epinephrine [see Warnings and Precautions (5.3)]. Systemic absorption of local anesthetics including Zorcaine™ can produce effects on the central nervous and cardiovascular systems.

At blood concentrations achieved with therapeutic doses of Zorcaine™, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations of Zorcaine™ can depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, possibly resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilatation occurs, leading to decreased cardiac output and arterial blood pressure. Zorcaine™ should also be used with caution in patients with heart block as well as those with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

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 of Zorcaine™. Repeated doses of Zorcaine™ may cause significant increases in blood levels because of possible accumulation of the drug or its metabolites. The lowest dosage that results in effective anesthesia should be used to decrease the risk of high plasma levels and serious adverse effects. Tolerance to elevated blood levels varies with the status of the patient. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. Precautions for epinephrine administration, discussed in Section 5.3, should be observed.

Debilitated patients, elderly patients, acutely ill patients, and pediatric patients should be given reduced doses commensurate with their age and physical condition [see Dosage and Administration (2.1, 2.3)]. No studies have been performed in patients with liver dysfunction, and caution should be used in patients with severe hepatic disease.

5.3 Vasoconstrictor Toxicity

Zorcaine™ contains epinephrine, a vasoconstrictor that can cause local or systemic toxicity and should be used cautiously. Local toxicity may include ischemic injury or necrosis, which may be related to vascular spasm. Zorcaine™ should be used with caution in patients during and following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response.

The American Heart Association has made the following recommendation regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used." (Kaplan, 1986).

It is essential to aspirate before any injection to avoid administration of the drug into the blood stream.

5.4 Methemoglobinemia

Articaine, like other local anesthetics, can cause methemoglobinemia, particularly in conjunction with methemoglobin-inducing agents. Zorcaine™ should not be used in patients with congenital or idiopathic methemoglobinemia, or in patients who are receiving treatment with methemoglobin-inducing agents since they are more susceptible to drug-induced methemoglobinemia.

Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia include slate grey cyanosis seen in buccal mucous membranes, lips, and nail beds. In severe cases, symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrythmia, and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if methemoglobin-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level of at least 10% is present. The development of methemoglobinemia is dose-related.

Management of methemoglobinemia: If methemoglobinemia does not respond to administration of oxygen, clinically significant symptoms of methemoglobinemia should be treated with administration of a slow intravenous injection (over 5 minutes) of methylene blue at a dosage of 1-2 mg/kg body weight.

5.5 Anaphylaxis and Allergic-Type Reactions

Zorcaine™ 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. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

6 ADVERSE REACTIONS

Reactions to articaine are characteristic of those associated with other amide-type local anesthetics. Adverse reactions to this group of drugs may also result from excessive plasma levels (which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation), injection technique, volume of injection, or hypersensitivity or they may be idiosyncratic.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The reported adverse reactions are derived from clinical trials in the United States and the United Kingdom. Table 2 displays the adverse reactions reported in clinical trials where 882 individuals were exposed to Zorcaine™ containing epinephrine 1:100,000. Table 3 displays the adverse reactions reported in clinical trials where 182 individuals were exposed to Zorcaine™ containing epinephrine 1:100,000 and 179 individuals were exposed to articaine hydrochloride 4% containing epinephrine 1:200,000.

Adverse reactions observed in at least 1% of patients:

Table 2:
Adverse Reactions in Controlled Trials with an Incidence of 1% or Greater in Patients Administered Zorcaine™ containing 1:100,000 Epinephrine

Body System/Event	Zorcaine™ containing 1:100,000 epinephrine (N=882) Incidence
Body as a whole	
Face Edema	13 (1%)
Headache	31 (4%)
Infection	10 (1%)
Pain	114 (13%)
Digestive system	
Gingivitis	13 (1%)
Nervous system	
Paresthesia	11 (1%)

Table 3:
Adverse Reactions in Controlled Trials with an Incidence of 1% or Greater in Patients Administered articaine hydrochloride 4% containing 1:200,000 Epinephrine and Zorcaine™ containing 1:100,000 Epinephrine

Event	Articaine hydrochloride 4% with epinephrine 1:200,000 (N=179)Incidence	Zorcaine™ with epinephrine 1:100,000 (N=182)Incidence
Any adverse event	33 (18%)	35 (19%)
Pain	11 (6.1%)	14 (7.6%)
Headache	9 (5.%)	6 (3.2%)
Positive blood aspiration into syringe	3 (1.6%)	6 (3.2%)
Swelling	3 (1.6%)	5 (2.7%)
Trismus	1 (0.5%)	3 (1.6%)
Nausea and emesis	3 (1.6%)	0 (0%)
Sleepiness	2 (1.1%)	1 (0.5%)
Numbness and tingling	1 (0.5%)	2 (1.%)
Palpitation	0 (0%)	2 (1.%)
Ear symptoms (earache, otitis media)	1 (0.5%)	2 (1.%)
Cough, persistent cough	0 (0%)	2 (1.%)

Table 4:
Adverse Reactions in Controlled Trials with an Incidence of Less than 1% but Considered Clinically Relevant in Patients Administered Zorcaine

Body System	Events
Body as a Whole	Asthenia; back pain; injection site pain; burning sensation above injection site; malaise; neck pain
Cardiovascular System	Hemorrhage; migraine; syncope; tachycardia; elevated blood pressure
Digestive System	Dyspepsia; glossitis; gum hemorrhage; mouth ulceration; nausea; stomatitis; tongue edemas; tooth disorder; vomiting
Hemic and Lymphatic System	Ecchymosis; lymphadenopathy
Metabolic and Nutritional System	Edema; thirst
Musculoskeletal System	Arthralgia; myalgia; osteomyelitis
Nervous System exacerbation of Kearns-Sayre Syndrome	Dizziness; dry mouth; facial paralysis; hyperesthesia; increased salivation; nervousness; neuropathy; paresthesia; somnolence;
Respiratory System	Pharyngitis; rhinitis; sinus pain; sinus congestion
Skin and Appendages	Pruritus; skin disorder
Special Senses	Ear pain; taste perversion

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Zorcaine™. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.

Persistent paresthesias of the lips, tongue, and oral tissues have been reported with use of articaine hydrochloride, with slow, incomplete, or no recovery. These postmarketing events have been reported chiefly following nerve blocks in the mandible and have involved the trigeminal nerve and its branches.

Hypoesthesia has been reported with use of articaine, especially in pediatric age groups, which is usually reversible. Prolonged numbness can result in soft tissue injuries such as that of the lips and tongue in these age groups.

Ischemic injury and necrosis have been described following use of articaine with epinephrine and have been postulated to be due to vascular spasm of terminal arterial branches.

Paralysis of ocular muscles has been reported, especially after posterior, superior alveolar injections of articaine during dental anesthesia. Symptoms include diplopia, mydriasis, ptosis, and difficulty in abduction of the affected eye. These symptoms have been described as developing immediately after injection of the anesthetic solution and persisting one minute to several hours, with generally complete recovery.

7 DRUG INTERACTIONS

The administration of local anesthetic solutions containing epinephrine to patients receiving monoamine oxidase inhibitors, nonselective beta-adrenergic antagonists, or tricyclic antidepressants may produce severe, prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should be avoided; however, in situations when concurrent therapy is necessary, careful patient monitoring is essential [see Warnings and Precautions (5.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women with Zorcaine™. Articaine hydrochloride and epinephrine (1:100,000) has been shown to increase fetal deaths and skeletal variations in rabbits when given in doses approximately 4 times the maximum recommended human dose (MRHD). Zorcaine™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryo-fetal toxicity studies in rabbits, 80 mg/kg, subcutaneously (approximately 4 times the MRHD based on body surface area) caused fetal death and increased fetal skeletal variations, but these effects may be attributable to severe maternal toxicity, including seizures, observed at this dose. In contrast, no embryo-fetal toxicities were observed when articaine and epinephrine (1:100,000) was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the MRHD based on body surface area).

In pre- and postnatal developmental studies subcutaneous administration of articaine hydrochloride to pregnant rats throughout gestation and lactation, at a dose of 80 mg/kg (approximately 2 times the MRHD based on body surface area) increased the number of stillbirths and adversely affected passive avoidance, a measure of learning, in pups. This dose also produced severe maternal toxicity in some animals. A dose of 40 mg/kg (approximately equal to the MRHD on a mg/m2 basis) did not produce these effects. A similar study using articaine and epinephrine (1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects on offspring.z

8.3 Nursing Mothers

It is not known whether Zorcaine™ is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zorcaine™ is administered to a nursing woman. When using Zorcaine™, nursing mothers may choose to pump and discard breast milk for approximately 4 hours (based on plasma half life) following an injection of Zorcaine™ (to minimize infant ingestion) and then resume breastfeeding.

8.4 Pediatric Use

Safety and effectiveness of Zorcaine™ in pediatric patients below the age of 4 years have not been established. Safety of doses greater than 7 mg/kg (0.175 mL/kg) in pediatric patients has not been established. Safety and effectiveness was established in clinical trials with 61 pediatric patients between the ages of 4 and 16 years administered articaine hydrochloride 4% and epinephrine 1:100,000 injections. Fifty-one of these patients received doses from 0.76 mg/kg to 5.65 mg/kg (0.9 to 5.1 mL) for simple dental procedures and 10 patients received doses between 0.37 mg/kg and 7.48 mg/kg (0.7 to 3.9 mL) for complex dental procedures. Approximately 13% of these pediatric patients required additional injections of anesthetic for complete anesthesia. Dosages in pediatric patients should be reduced, commensurate with age, body weight, and physical condition [see Dosage and Administration (2.2)].

8.5 Geriatric Use

In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Zorcaine™ containing epinephrine 1:100,000. Among all patients between 65 and 75 years, doses from 0.43 mg/kg to 4.76 mg/kg (0.9 to 11.9 mL) were administered to 35 patients for simple procedures and doses from 1.05 mg/kg to 4.27 mg/kg (1.3 to 6.8 mL) were administered to 19 patients for complex procedures. Among the 11 patients ≥ 75 years old, doses from 0.78 mg/kg to 4.76 mg/kg (1.3 to 11.9 mL) were administered to 7 patients for simple procedures and doses of 1.12 mg/kg to 2.17 mg/kg (1.3 to 5.1 mL) were administered to 4 patients for complex procedures.

Approximately 6% of patients between the ages of 65 and 75 years and none of the 11 patients 75 years of age or older required additional injections of anesthetic for complete anesthesia compared with 11% of patients between 17 and 65 years old who required additional injections.

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal/Hepatic Insufficiency

No studies have been performed with articaine hydrochloride 4% and epinephrine 1:200,000 injection or articaine hydrochloride 4% and epinephrine 1:100,000 injection in patients with renal or hepatic dysfunction [see Warnings and Precautions (5.2)].

10 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 Warnings and Precautions (5.1, 5.2)].

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 convulsions, as well as hypo-ventilation, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation as needed. The adequacy of the circulation should be assessed. Should convulsions persist despite adequate respiratory support, treatment with appropriate anticonvulsant therapy is indicated. The practitioner should be familiar with the use of anticonvulsant drugs, prior to the use of local anesthetics. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor.

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and/or cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

For additional information about overdose treatment, call a poison control center **(1-800-222-1222).**

11 DESCRIPTION

Zorcaine™ injection is a sterile, aqueous solution that contains articaine HCl 4% (40 mg/mL) and epinephrine bitartrate in an epinephrine 1:200,000 or epinephrine 1:100,000 strength. Articaine HCl is an amino amide local anesthetic, chemically designated as 4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride and is a racemic mixture. Articaine HCl has a molecular weight of 320.84 and the following structural formula:

Articaine HCl has a partition coefficient in n-octanol/Soerensen buffer (pH 7.35) of 17 and a pKa of 7.8.

Epinephrine bitartrate, (-)-1-(3,4-Dihydroxyphenyl)-2-methylamino-ethanol (+) tartrate (1:1) salt, is a vasoconstrictor that is added to articaine HCl in a concentration of 1:200,000 or 1:100,000 (expressed as free base). It has a molecular weight of 333.3 and the following structural formula:

Zorcaine™ contains articaine HCl (40 mg/mL), epinephrine 1:100,000 (as epinephrine bitartrate), sodium chloride (1.6 mg/mL), and sodium metabisulfite (0.5 mg/mL). The product is formulated with a 15% overage of epinephrine. The pH is adjusted with sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Articaine HCl is an amide local anesthetic. Local anesthetics block the generation and 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 the affected nerve fibers. Epinephrine is a vasoconstrictor added to articaine HCl to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration.

12.2 Pharmacodynamics

Clinically, the order of loss of nerve function is as follows: (1) pain; (2) temperature; (3) touch; (4) proprioception; and (5) skeletal muscle tone.

The onset of anesthesia has been shown to be within 1 to 9 minutes of injection of Zorcaine™. Complete anesthesia lasts approximately 1 hour for infiltrations and up to approximately 2 hours for nerve block.

Administration of Zorcaine™ results in a 3- to 5-fold increase in plasma epinephrine concentrations compared to baseline; however, in healthy adults it does not appear to be associated with marked increases in blood pressure or heart rate, except in the case of accidental intravascular injection [see Warnings and Precautions (5.1)].

12.3 Pharmacokinetics

Absorption: Following dental injection by the submucosal route of an articaine solution containing epinephrine 1:200,000, articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 and 204 mg doses are 385 and 900 ng/mL, respectively. Following intraoral administration of a near maximum dose of 476 mg, articaine reaches peak blood concentrations of 2037 and 2145 ng/mL for articaine solution containing epinephrine 1:100,000 and 1:200,000, respectively, approximately 22 minutes post-dose.

Distribution: Approximately 60 to 80% of articaine HCl is bound to human serum albumin and y-globulins at 37°C in vitro.

Metabolism: Articaine HCl is metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is inactive. In vitro studies show that the human liver microsome P450 isoenzyme system metabolizes approximately 5% to 10% of available articaine with nearly quantitative conversion to articainic acid.

Excretion: At the dose of 476 mg of articaine, the elimination half-life was 43.8 minutes and 44.4 minutes for articaine solution containing epinephrine 1:100,000 and 1:200,000, respectively. Articaine is excreted primarily through urine with 53-57% of the administered dose eliminated in the first 24 hours following submucosal administration. Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide, is also excreted in urine. Articaine constitutes only 2% of the total dose excreted in urine.

Special Populations: No studies have been performed to evaluate the pharmacokinetics of Zorcaine™ injection in pediatric subjects. There is insufficient information to determine whether the pharmacokinetics of Zorcaine™ injection differs by race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to evaluate the carcinogenic potential of articaine HCl in animals have not been conducted. Five standard mutagenicity tests, including three in vitro tests (the nonmammalian Ames test, the mammalian Chinese hamster ovary chromosomal aberration test, and a mammalian gene mutation test with articaine HCl) and two in vivo mouse micronucleus tests (one with articaine and epinephrine 1:100,000 and one with articaine HCl alone) showed no mutagenic effects.

No effects on male or female fertility were observed in rats for articaine and epinephrine 1:100,000 administered subcutaneously in doses up to 80 mg/kg/day (approximately 2 times the MRHD based on body surface area).

14 CLINICAL STUDIES

Three randomized, double-blind, active-controlled studies were designed to evaluate effectiveness of Zorcaine™ containing epinephrine 1:100,000 as a dental anesthetic. Patients ranging in age from 4 years to over 65 years old underwent simple dental procedures such as single uncomplicated extractions, routine operative procedures, single apical resections, and single crown procedures, or complex dental procedures such as multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures on the bone. Zorcaine™ containing epinephrine 1:100,000 was administered as submucosal infiltration and/or nerve block. Efficacy was measured immediately following the procedure by having the patient and investigator rate the patient's procedural pain using a 10 cm visual analog scale (VAS), in which a score of zero represented no pain and a score of 10 represented the worst pain imaginable. Mean patient and investigator VAS pain scores were 0.3-0.4 cm for simple procedures and 0.5-0.6 cm for complex procedures.

Four randomized, double-blind, active-controlled studies were performed comparing Zorcaine™ containing epinephrine 1:100,000 versus articaine hydrochloride 4% containing epinephrine 1:200,000. The first two studies used electric pulp testers (EPT) to evaluate the success rate (maximum EPT value within 10 minutes), onset, and duration of Zorcaine™ containing epinephrine 1:100,000 versus articaine hydrochloride 4% containing epinephrine 1:200,000 and articaine solution without epinephrine in healthy adults between 18 and 65 years old. Results indicated that the anesthetic characteristics of the 1:100,000 and 1:200,000 formulations are not significantly different.

A third study compared the difference in visualization of the surgical field after administration of Zorcaine™ containing epinephrine 1:100,000 versus articaine hydrochloride 4% containing epinephrine 1:200,000 during bilateral maxillary periodontal surgeries in patients ranging from 21 to 65 years old. Zorcaine™ containing epinephrine 1:100,000 provided better visualization of the surgical field and less blood loss during the procedures. In a fourth study, designed to assess and compare cardiovascular safety, when the maximum dose of each formulation was administered, no clinically relevant differences in blood pressure or heart rate between formulations were observed.

15 REFERENCES

Kaplan, EL, editor. Cardiovascular disease in dental practice. Dallas; American Heart Association; 1986.

16 HOW SUPPLIED/STORAGE AND HANDLING

Zorcaine™ (articaine HCl and epinephrine) Injection is available in 1.7 mL single use glass cartridges, packaged in boxes of 50 cartridges in the following in the following strength:

- Zorcaine™ containing articaine HCl 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL) (NDC 31382-830-50)

Storage and Handling

Store at controlled room temperature 25°C (77°F) with brief excursions permitted between 15° and 30°C (59°F-86°F) [see USP Controlled Room Temperature]. Protect from light. Do Not Freeze.

For chemical disinfection of the carpule, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. Many commercially available brands of isopropyl (rubbing) alcohol, as well as solutions of ethyl alcohol not of U.S.P. grade, contain denaturants that are injurious to rubber and therefore are not to be used.

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

17 PATIENT COUNSELING INFORMATION

Loss of Sensation and Muscle Function:

- Inform patients in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections [see Adverse Reactions (6.2)].
- Instruct patients not to eat or drink until normal sensation returns.

Cook-Waite

Manufactured for
CARESTREAM HEALTH, INC. by
Novocol Pharmaceutical of Canada. Inc.
Cambridge, Ontario, Canada N1R 6X3

Rev 06/13 (2560-6)

2560-6

Ordering Information

Product Name	REF No
Lidocaine HCl 2% and Epinephrine 1:100,000 Injection (lidocaine hydrochloride and epinephrine injection, USP)	**155 9889**
Lidocaine HCl 2% and Epinephrine 1:50,000 Injection (lidocaine hydrochloride and epinephrine injection, USP)	**162 8262**
Carbocaine® 3% (mepivacaine hydrochloride injection, USP) without vasoconstrictor	**143 0735**
Carbocaine® 2% with Neo-Cobefrin® (mepivacaine hydrochloride and levonordefrin injection, USP)	**144 9313**
Marcaine® 0.5% with epinephrine 1:200,000 injection (as bitartrate) (bupivacaine hydrochloride and epinephrine injection, USP)	**185 2557**
Zorcaine (articaine HCl and epinephrine) Injection, Articaine hydrochloride 4% and epinephrine 1:100,000	**894 2831**

Would you like to know more?

For more information, call **800.933.8031** or visit **www.carestreamdental.com.**