



EXHIBIT I

**Original Product Insert for Carbocaine[®] Injection, 3%
(Dated November 2004)**



Cook-Waite

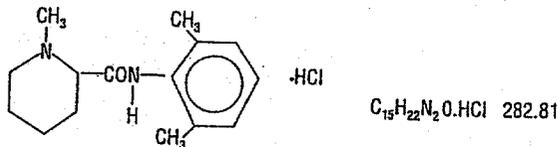
Carbocaine® 3% injection
(mepivacaine hydrochloride injection, USP)

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

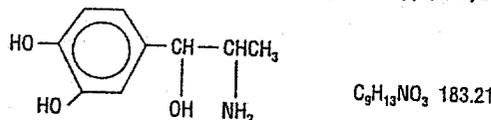
"Rx only"

THESE SOLUTIONS ARE INTENDED FOR DENTAL USE ONLY.

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



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 (-)-3-(1-Aminoethyl)-3, 4-dihydroxybenzyl alcohol with the following structural formula:



It is a white or buff-colored crystalline solid, freely soluble in aqueous solutions of 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

Each mL contains:

Mepivacaine Hydrochloride
Levonordefrin (as the base)
Sodium Chloride
Sodium Bisulfite
Water for Injection, qs. ad.

CARTRIDGE		
	2%	3%
	20 mg	30 mg
	0.05 mg	-
	4 mg	3 mg
	1 mg	-
	1 mL	1 mL

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

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. Mepivacaine because of its amide structure, is not 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 detoxication 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' - pipercoloxylidide).

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% without vasoconstrictor 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 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 hyper-sensitivity. 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 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.

CARBOCAINE 2% with NEO-COBEFRIN 1:20,000 Injection (mepivacaine hydrochloride and levonordefrin injection, USP) contains sodium 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 3% injection (mepivacaine hydrochloride injection, USP) is SULFITE FREE.

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 pediatric patients 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 pediatric patients 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 drug 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 vasoconstrictors, such as Levonordefrin, Epinephrine or Norepinephrine, to patients receiving tricyclic antidepressants or monoamine oxidase inhibitors 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 vasoconstrictor 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 in animals to evaluate the carcinogenic and mutagenic potential or the effect of fertility have not been conducted.

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 affect reproductive capacity. This 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:

Systemic adverse reactions involving the central nervous system and the cardiovascular system usually result from high plasma levels due to excessive dosage, rapid absorption, or inadvertent intravascular injection.

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

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 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 ventilation (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 benzodiazepine (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 vasoconstrictor (e.g., Ephedrine) as dictated by the clinical situation. Allergic reactions should be managed by conventional means.

IV and SC LD₅₀'s in mice for CARBOCAINE 3% are 33 and 258 mg/kg respectively. The acute IV and SC LD₅₀'s in mice for CARBOCAINE 2% with NEO-COBEFRIN 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 1.8 mL (36 mg of 2% or 54 mg of 3%). Five 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 Patient =

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

The following table, approximating these calculations, may also be used as a guide.

Weight (lb.)	Mg	Maximum Allowable Dosage		
		3% Mepivacaine (Plain) 3 mg/lb (270 mg max.)	2% Mepivacaine 1:20,000 Levonordefrin 3 mg/lb (180 mg max.)	
		Number of Cartridges	Mg	Number of Cartridges
20	60	1.1	60	1.6
30	90	1.7	90	2.5
40	120	2.2	120	3.3
50	150	2.8	150	4.2
60	180	3.3	180	5.0
80	240	4.4	180	5.0
100	270	5.0	180	5.0
120	270	5.0	180	5.0

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 hydrochloride injection, USP) 1.8 mL dental cartridges, 50 per carton. CARBOCAINE 2% with NEO-COBEFRIN 1:20,000 injection; (mepivacaine hydrochloride and Levonordefrin injection, USP) 1.8 mL dental cartridges, 50 per carton. Both solutions should be stored at controlled room temperature, between 15°C and 25°C (59°F and 77°F). Protect from light. The 2% solution should not be used if its color is pinkish or darker than slightly yellow or it contains a precipitate.



Manufactured for
EASTMAN KODAK COMPANY by
Novocel Pharmaceutical of Canada, Inc.
Cambridge, Ontario, Canada N1R 6X3

Rev. 11/04(2960-1)

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