EXHIBIT II

Recent Product Insert for Carbocaine® Injection, 3%
(Dated July 2005)
**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 local anesthetic, is 1-methyl-2', 6'-pipidoloxylidide monohydrochloride with the following structural formula:

![Structural Formula of Carbocaine](https://example.com/structure.png)

It is a white, crystalline, odorless powder soluble in water, but very resistant to both acid and alkaline hydrolysis.

**INDICATIONS AND USAGE:**

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

**COMPOSITION:**

<table>
<thead>
<tr>
<th>Cartridge</th>
<th>Concentration</th>
<th>Levonordefrin</th>
<th>Sodium Chloride</th>
<th>Hydrochloric Acid</th>
<th>Water, for injection q.s. ad</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>20 mg</td>
<td>30 mg</td>
<td>4 mg</td>
<td>0.5 mg</td>
<td>1 mL</td>
</tr>
<tr>
<td>3%</td>
<td>20 mg</td>
<td>30 mg</td>
<td>4 mg</td>
<td>0.5 mg</td>
<td>1 mL</td>
</tr>
</tbody>
</table>

Water for injections q.s. ad pH

**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 90 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 20 hours. It has been shown that hydroxylation and N-demethylation, which are deactivation reactions, play important roles in the metabolism of the anesthetic. These 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' - pipidoloxylidide).

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

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

**WARNINGS:**

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

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

**CONTRAINDICATIONS:**

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

**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.

**ADVERSE REACTIONS:**

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 aware of the possibility of asphyxiation in persons with reduced respiratory capacity. Circulatory collapse may occur following the rapid intravenous injection of local anesthetics. The treatment of adverse reactions to local anesthetics usually involves discontinuation of the drug and institution of supportive measures, such as the administration of oxygen, artificial ventilation, intravenous fluid therapy, and cardiac and respiratory monitoring. In severe cases, the administration of vasopressor agents may be necessary. The use of adrenalincontaining local anesthetic solutions has been associated with precipitation of cardiovascular disturbances and death from cardiac arrest in susceptible patients. The patient's condition should be observed for several hours after the injection of a local anesthetic to detect the onset of adverse reactions which may occur with the administration of a local anesthetic, particularly in patients with cardiovascular disease. The effective plasma levels of local anesthetics are at least an order of magnitude below those known to cause cardiovascular collapse or death in animal species.

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, cerebrovascular disease, coronary artery disease, thyrotoxicosis and diabetes, etc. The solution which contains a vasoconstrictor (CARBOCAINE) also contains sodium bisulfite, a sulfite that may cause an allergic-type reaction 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.

**FOR INTRAVENOUS USE:**

The solution which contains a vasoconstrictor (CARBOCAINE) should be used with extreme caution in patients with a history of severe disturbances of cardiac rhythm or heart block.
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 minimum 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 products 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 Neo-Cobefrin, 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 vasopressor drugs and of ergot-type oxytocic drugs may produce severe, persistent hypertension or cerebrovascular accidents.

Phenelzine and tranylcypromine may induce 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 and 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.

Pregnancy: Teratogenic Effects: Prenatal and Neonatal: 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 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 ascribing to safe concentrations and dosages for pediatric 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 following 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 or respirator may result in progressive cerebral hypoxia and seizure or severe cardiovascular catastrophes. 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, anaphylactic 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 patent 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 lorazepam (e.g., diazepam) or phenytoin (e.g., Dilantin) intravenously.

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 LD50's in mice for Mepivacaine Hydrochloride 3% are 33 and 258 mg/kg, respectively. The acute IV and SC LD50's in mice for Mepivacaine Hydrochloride 2% with Levonordefrin 120,000 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. When 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:

Child's Weight (lbs) x Maximum Recommended Dose 150 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 child's weight or (for 2% mepivacaine) calculated maximum amount of drug:

<table>
<thead>
<tr>
<th>Maximum Allowable Dosage</th>
<th>Cartridges</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% Mepivacaine (Plain)</td>
<td>2% Mepivacaine 1:20,000 Levonordefrin</td>
</tr>
<tr>
<td>3 mg/ml (270 mg max.)</td>
<td>5 mg/ml (180 mg max.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Number of Cartridges</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>120</td>
</tr>
<tr>
<td>50</td>
<td>150</td>
</tr>
<tr>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>80</td>
<td>240</td>
</tr>
<tr>
<td>100</td>
<td>270</td>
</tr>
</tbody>
</table>


Carboxylate 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 particle matter and coloration 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 2% injection (mepivacaine hydrochloride injection, USP) is available in cartons containing 5 blisters of 10 x 1.7 ml dental cartridges, 50 per carton. CARBOCAINE 2% with NEO-COBREFFRIN 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. |
| All solutions should be stored at controlled room temperature, below 25°C (77°F). Protect from light and do not permit to freeze. For protection from light, retain in box until time of use. Once opened, the solution should be discarded after 14 days. The solution should be removed by disposable filterable cap. Cartridge warmers should not be used with CARBOCAINE products. |

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