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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-971**

Final Printed Labeling

Septocaine™

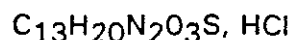
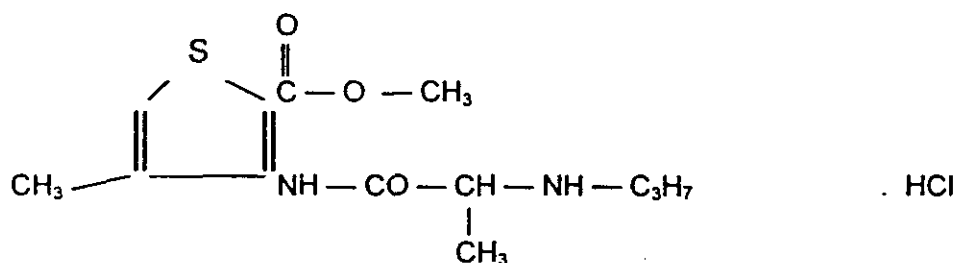
(articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 injection)

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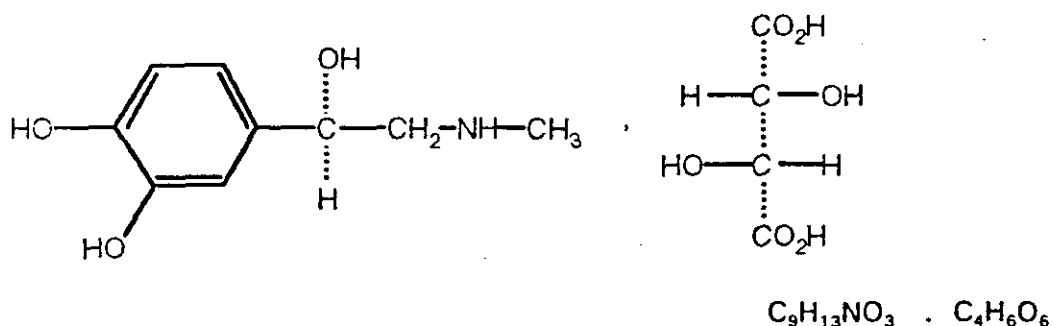
For Infiltration and Nerve Block Anesthesia

DESCRIPTION

Septocaine™ injection is a sterile, aqueous solution that contains articaine HCl 4% (40 mg/mL) with epinephrine bitartrate in a 1:100,000 strength. Articaine HCl is a local anesthetic, which is 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 molecular and structural formulae are displayed below :



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 1:100,000 as the free base. It has a molecular weight of 333.3. The molecular and structural formulae are displayed below:



Septocaine™ contains articaine HCl (40mg/mL), epinephrine as bitartrate (1:100,000), 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 to 5.0 with sodium hydroxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption : Following dental injection by the submucosal route of an articaine solution containing 1:200,000 epinephrine, articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after the second. Pharmacokinetics of articaine are similar to those of lidocaine.

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

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

Excretion : The elimination half-life of articaine is about 1.8 hours and that of articainic acid is about 1.5 hours. 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

Effect of Age : No studies have been performed to evaluate the pharmacokinetics of Septocaine™ injection in geriatric or pediatric subjects.

Race : There is insufficient information to determine whether the pharmacokinetics of Septocaine™ injection differs by race.

Renal and Hepatic Insufficiency : No studies have been performed with Septocaine™ injection in patients with renal or hepatic dysfunction.

Pharmacodynamics

Mechanism of action : Articaine HCl is a member of the amino amide class of local anesthetics. 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. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone. Epinephrine is a vasoconstrictor added to articaine HCl to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration.

The onset of anesthesia following administration of Septocaine™ has been shown to be within 1 to 6 minutes of injection. Complete anesthesia lasts approximately 1 hour.

Administration of articaine HCl with epinephrine 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).

CLINICAL TRIALS

Three randomized, double-blind, active-controlled studies were designed to evaluate effectiveness of Septocaine™ as a dental anesthetic. A total of 882 patients received Septocaine™. Of these, 7% were between 4 and 16 years old, 87% were between 17 and 65 years old, and 6% were at least 65 years old. In addition, 53% of patients were female and 47% were male, with a racial/ethnic distribution of 73% white, 11% Hispanic, 8% black, 5% Asian, and 3% "other" races/ethnicities. These patients underwent simple dental procedures such as single uncomplicated extractions, routine operative procedures, single apical resections, and single crown procedures, and complex dental procedures such as multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, mucogingival operations, and other surgical procedures on the bone. Septocaine™ 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. These values are summarized in Table 1.

Table 1. Summary of VAS Pain Scores

| | SEPTOCAINE™ (articaine HCl 4% with epinephrine 1:100,000) | |
|-------------------------|---|-----------------------|
| | Simple Procedures | Complex Procedures |
| Number of patients | 674 | 207 |
| Investigator score (cm) | | |
| Mean | 0.3 | 0.5 |
| Median | 0.0 | 0.2 |
| Range | 0 - 9.0 | 0 - 7.3 |
| Patient score (cm) | | |
| Mean | 0.4 | 0.6 |
| Median | 0.0 | 0.2 |
| Range | 0 - 8.0 | 0 - 8.7 |

INDICATIONS AND USAGE

Septocaine™ is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

CONTRAINDICATIONS

Septocaine™ is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type, or in patients with known hypersensitivity to sodium metabisulfite.

WARNINGS

ACCIDENTAL INTRAVASCULAR INJECTION MAY BE ASSOCIATED WITH CONVULSIONS, FOLLOWED BY CENTRAL NERVOUS SYSTEM OR CARDIORESPIRATORY DEPRESSION AND COMA, PROGRESSING ULTIMATELY TO RESPIRATORY ARREST. DENTAL PRACTITIONERS AND/OR CLINICIANS WHO EMPLOY LOCAL ANESTHETIC AGENTS 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.

Intravascular injections should be avoided. To avoid intravascular injection, aspiration should be performed before Septocaine™ 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.

Septocaine™ contains epinephrine that can cause local tissue necrosis or systemic toxicity. Usual precautions for epinephrine administration should be observed.

Septocaine™ 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.

PRECAUTIONS

General : Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use (See WARNINGS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of Septocaine™ may cause significant increases in blood levels with each repeated dose because of possible accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients and pediatric patients should be given reduced doses commensurate with their age and physical condition. Septocaine™ should also be used with caution in patients with heart block.

Local anesthetic solutions, such as Septocaine™, containing a vasoconstrictor should be used cautiously. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Septocaine™ 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.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with 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.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

In vitro studies show that about 5% to 10% of articaine is metabolized by the human liver microsomal P450 isoenzyme system. However, because no studies have been performed in patients with liver dysfunction, caution should be used in patients with severe hepatic disease. Septocaine™ should also be used with caution in patients 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.

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 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 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)

Information for Patients : The patient should be informed in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections.

Clinically Significant Drug Interactions : The administration of local anesthetic solutions containing epinephrine to patients receiving monoamine oxidase inhibitors 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 generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

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 micronucleous tests (one with Septocaine™ and one with articaine HCl alone) showed no mutagenic effects. No effects on male or female fertility were observed in rats for Septocaine™ administered subcutaneously in doses up to 80 mg/kg/day (approximately two times the maximum male and female recommended human dose on a mg/m² basis).

Pregnancy : Teratogenic Effects-Pregnancy Category C.

In developmental studies, no embryofetal toxicities were observed when Trade Narne® was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the maximum recommended human dose on a mg/m² basis). In rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m² basis) did cause fetal death and increase fetal skeletal variations, but these effects may be attributable to the severe maternal toxicity, including seizures, observed at this dose.

When articaine hydrochloride was administered subcutaneously to rats throughout gestation and lactation, 80 mg/kg (approximately 2 times the maximum recommended human dose on a mg/m² basis) 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 maximum recommended human dose on a mg/m² basis) did not produce these effects. A similar study using Septocaine™ (articaine hydrochloride and epinephrine 1:100,000) rather than articaine hydrochloride alone produce maternal toxicity, but no effects of offspring.

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. Septocaine™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Pediatric Use : In clinical trials, 61 pediatric patients between the ages of 4 and 16 years received Septocaine™. Among these pediatric patients, doses from 0.76 mg/kg to 5.65 mg/kg (0.9 to 5.1 mL) were administered safely to 51 patients for simple procedures and doses between 0.37 mg/kg and 7.48 mg/kg (0.7 to 3.9 mL) were administered safely to 10 patients for complex procedures. However, there was insufficient exposure to Septocaine™ at doses greater than 7.00 mg/kg in order to assess its safety in pediatric patients. No unusual adverse events were noted in these patients. Approximately 13% of these pediatric patients required additional injections of anesthetic for complete anesthesia. Safety and effectiveness in pediatric patients below the age of 4 years have not been established. Dosages in pediatric patients should be reduced, commensurate with age, body weight, and physical condition. See DOSAGE AND ADMINISTRATION.

Geriatric Use : In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Septocaine™. 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 safely 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 safely 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 safely 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. 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. 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.

ADVERSE REACTIONS

Reactions to Septocaine™ 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.

The reported adverse events are derived from clinical trials in the US and UK. Of the 1325 patients treated in the primary clinical trials, 882 were exposed to Septocaine™.

Table 2

Adverse Events in controlled trials with an incidence of 1% or greater in patients administered Septocaine™ (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 Injection)

| Body system | Septocaine™ N (%) |
|--------------------|----------------------|
| Number of Patients | 882 (100%) |
| 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%) |

The following list includes adverse and intercurrent events that were recorded in 1 or more patients, but occurred at an overall rate of less than one percent, and were considered clinically relevant.

Body as a Whole - abdominal pain, accidental injury, asthenia, back pain, injection site pain, malaise, neck pain.

Cardiovascular System - hemorrhage, migraine, syncope, tachycardia.

Digestive System - constipation, diarrhea, 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 - dizziness, dry mouth, facial paralysis, hyperesthesia, increased salivation, nervousness, neuropathy, paresthesia, somnolence.

Respiratory System - pharyngitis, rhinitis.

Skin and Appendages - pruritus, skin disorders

Urogenital System - dysmenorrhea.

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, PRECAUTIONS, General, and ADVERSE REACTIONS**).

Management of Local Anesthetic Emergencies : The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as hypoventilation, 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, prior to the use of local anesthetics, with the use of anticonvulsant drugs. 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 cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

DOSAGE AND ADMINISTRATION

Table 3 (Recommended Dosages) summarizes the recommended volumes and concentrations of Septocaine™ for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults, administered by submucosal infiltration and/or nerve block.

Table 3. Recommended Dosages

| PROCEDURE | Septocaine™ Injection | |
|--------------|-----------------------|----------------------------------|
| | Vol (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 ABOVE SUGGESTED VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.

These 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. Do not exceed the

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 since the incidence of side effects may be dose-related.

MAXIMUM RECOMMENDED DOSAGES

Adults : For normal healthy adults, the maximum dose of articaine HCl administered by submucosal infiltration and/or nerve block should not exceed 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.

Pediatric Patients : Use in pediatric patients under 4 years of age is not recommended. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.

STERILIZATION, STORAGE, AND TECHNICAL PROCEDURES

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.

HOW SUPPLIED

Septocaine™ (articaine HCl 4% with epinephrine 1:100,000 injection) is available in 1.7 mL glass cartridges, in boxes of 50 cartridges. The product is formulated with a 15% overage of epinephrine.

NDC XXXXX-XXX-XX Box of 50 cartridges

Store at 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.

Manufactured in France by : Spécialités SEPTODONT, France.
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