



| Table 4: Adverse Reactions in Controlled Trials with an Incidence of Less than 1% but Considered Clinically Relevant in Patients Administered SEPTOCAINE |                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Body System                                                                                                                                              | Reactions                                                                                                                                                            |
| 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                                                                                                                                           | Dizziness; dry mouth; facial paralysis; hyperesthesia; increased salivation; nervousness; neuropathy; paresthesia; somnolence; exacerbation of Kearns-Sayre Syndrome |
| 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 SEPTOCAINE. 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 butyrophenes 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)]*.

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

| Table 5: Examples of Drugs Associated with Methemoglobinemia |                                                                                                           |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Class                                                        | Examples                                                                                                  |
| Nitrates/Nitrites                                            | nitric oxide, nitroglycerin, nitroprusside, nitrous oxide                                                 |
| Local anesthetics                                            | articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine |
| Antineoplastic agents                                        | cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase                                         |
| Antibiotics                                                  | dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides                                           |
| Antimalarials                                                | chloroquine, primaquine                                                                                   |
| Anticonvulsants                                              | phenobarbital, phenytoin, sodium valproate                                                                |
| Other drugs                                                  | acetaminophen, metoclopramide, quinine, sulfasalazine                                                     |

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 SEPTOCAINE. 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). SEPTOCAINE 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.

8.3 Nursing Mothers

It is not known whether SEPTOCAINE 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. When using SEPTOCAINE, nursing mothers may choose to pump and discard breast milk for approximately 4 hours (based on plasma half-life) following an injection of SEPTOCAINE (to minimize infant ingestion) and then resume breastfeeding.

8.4 Pediatric Use

Safety and effectiveness of SEPTOCAINE 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. The safety and effectiveness of SEPTOCAINE for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures have been established in pediatric patients ages 4 to 16 years old. 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 SEPTOCAINE 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 and Hepatic Impairment

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 impairment *[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.

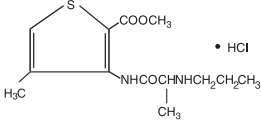
If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and/or cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

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

11 DESCRIPTION

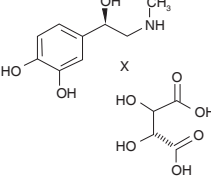
SEPTOCAINE (articaine hydrochloride and epinephrine injection), for intraoral submucosal infiltration use, is a sterile, aqueous solution that contains articaine HCl 4% (68 mg/1.7mL) (40 mg/mL) and epinephrine bitartrate in an epinephrine 1:200,000 or epinephrine 1:100,000 strength.

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/Sørensen 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 with 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:



SEPTOCAINE contains the following inactive ingredients: 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 SEPTOCAINE. Complete anesthesia lasts approximately 1 hour for infiltrations and up to approximately 2 hours for nerve block. Administration of SEPTOCAINE 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.

**Elimination**

**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.

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 SEPTOCAINE 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. SEPTOCAINE containing epinephrine 1:100,000 was administered by intraoral submucosal infiltration or nerve block for these dental procedures.

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 SEPTOCAINE containing epinephrine 1:100,000 versus SEPTOCAINE 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 SEPTOCAINE containing epinephrine 1:100,000 versus SEPTOCAINE 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 SEPTOCAINE containing epinephrine 1:100,000 versus SEPTOCAINE containing epinephrine 1:200,000 during bilateral maxillary periodontal surgeries in patients ranging from 21 to 65 years old. SEPTOCAINE 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

SEPTOCAINE (articaine hydrochloride and epinephrine) injection is a clear, colorless solution available in 1.7 mL single-dose glass cartridges, packaged in boxes of 50 cartridges in the following two strengths (less than a full cartridge or more than one cartridge may be used for an individual patient):

- Articaine HCl 4% (68 mg/1.7mL) (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL) (NDC 0362-9048-02)
- Articaine HCl 4% (68 mg/1.7mL) (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL) (NDC 0362-9049-02)

**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.

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.

**Methemoglobinemia:**

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

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