

**Articaine hydrochloride 4% and epinephrine 1:200,000
Articaine hydrochloride 4% and epinephrine 1:100,000
(articaine HCl and epinephrine) Injection; Intraoral Submucosal Injection**

BRIEF SUMMARY. [See Package Insert For Full Prescribing Information]

USE

Articaine HCl 4% and Epinephrine 1:100,000 Injection is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures. For most routine dental procedures, Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:200,000 is preferred. Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000 may be used when more pronounced hemostasis or improved visualization of the surgical field is desirable.

CONTRAINDICATIONS

Articaine HCl 4% and Epinephrine 1:100,000 Injection is contraindicated in patients with a known history of hypersensitivity to products containing sulfites.

WARNINGS AND PRECAUTIONS

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 who employ local anesthetic agents including Articaine HCl 4% and Epinephrine 1:100,000 Injection 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 Articaine HCl 4% and Epinephrine 1:100,000 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.

Dosage recommendations should not be exceeded (see **DOSAGE AND ADMINISTRATION** in package insert).

Systemic toxicity – Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses of Articaine HCl 4% and Epinephrine 1:100,000, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations 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 vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Articaine HCl 4% and Epinephrine 1:100,000 should be used with caution in patients with heart block as well as those with impaired cardiovascular function.

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of Articaine HCl 4% and Epinephrine 1:100,000 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.

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.

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. 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.

Vasoconstrictor toxicity – Articaine HCl 4% and Epinephrine 1:100,000 Injection contains epinephrine, a vasoconstrictor that can cause local tissue necrosis or systemic toxicity. Usual precautions for epinephrine administration should be observed. Articaine HCl 4% and Epinephrine 1:100,000 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. 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, EL, editor: Cardiovascular disease in dental practice, Dallas 1986, American Heart Association.)

Methemoglobinemia – Articaine, like other local anesthetics, is capable of producing methemoglobinemia. The clinical signs of methemoglobinemia include 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.

Anaphylaxis and Allergic-Type Reactions – Articaine HCl 4% and Epinephrine 1:100,000 Injection 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.

ADVERSE REACTIONS

Clinical Studies Experience

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.

The reported adverse reactions are derived from clinical trials in the US and UK. Table 1 displays the adverse events reported in clinical trials where 882 individuals were exposed to Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000 and Table 2 displays the adverse events reported in clinical trials where 182 individuals were exposed to Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000 and 179 individuals were exposed to Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:200,000.

Table 1. Adverse Reactions in controlled trials with an incidence of 1% or greater in patients administered Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000.

Body System epinephrine 1:100,000	Articaine HCl 4% and Epinephrine 1:100,000 containing
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%)

Table 2. Adverse Reactions in controlled trials with an incidence of 1% or greater in patients administered Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000 and Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:200,000.

Number of patients	Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine	Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine
Exposed to drug	1:100,000 (N=182)	1:200,000 (N=179)
Number of patients that reported any Adverse Event	35	33 (18%)
Pain	14 (7.6%)	11 (6.1%)
Headache	6 (3.2%)	9 (5%)
Positive blood aspiration into syringe	6 (3.2%)	3 (1.6%)

Swelling	5 (2.7%)	3 (1.6%)
Trismus	3 (1.6%)	1 (0.5%)
Nausea and emesis	0 (0%)	3 (1.6%)
Sleepiness	1 (0.5%)	2 (1.1%)
Numbness and tingling	2 (1%)	1 (0.5%)
Palpitation	2 (1%)	0 (0%)
Ear symptoms (earache, otitis media)	2 (1%)	1 (0.5%)
Cough, persistent cough	2 (1%)	0 (0%)

The following list includes adverse reactions observed in less than 1% of patients, but were considered clinically relevant.

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.

Postmarketing Experience

Persistent paresthesias of the lips, tongue, and oral tissues have been reported with use of articaine hydrochloride, 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.

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.

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 generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects-Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women with Articaine HCl 4% and Epinephrine 1:100,000 Injection. Articaine HCl 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). Articaine HCl 4% and Epinephrine 1:100,000 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 HCl 4% and Epinephrine 1:100,000 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Articaine HCl 4% and Epinephrine 1:100,000 is administered to a nursing woman.

Pediatric Use: Safety and effectiveness 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.

In clinical trials, 61 pediatric patients between the ages of 4 and 16 years received Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000. 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 Articaine HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000 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. Dosages in pediatric patients should be reduced, commensurate with age, body weight, and physical condition. See **DOSAGE AND ADMINISTRATION** in package insert.

Geriatric Use: In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Articaine HCl 4% and Epinephrine 1:100,000 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 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 \geq 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 safely 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.

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).

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 patient 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.

NONCLINICAL TOXICOLOGY

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 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 HCl 4% and Epinephrine 1:100,000 containing epinephrine 1:100,000 administered subcutaneously in doses up to 80 mg/kg/day (approximately two times the maximum male and female recommended human dose based on body surface area).

HOW SUPPLIED

Articaine HCl 4% and Epinephrine 1:100,000 (articaine HCL and epinephrine) Injection is available in 1.7 mL single-use glass cartridges, packaged in boxes of 50 cartridges in the following two strengths:

Articaine HCl 4% and Epinephrine 1:100,000 containing articaine HCl 4% (40 mg/mL) and epinephrine 1:200,000 (NDC 0404-6625-05)

Articaine HCl 4% and Epinephrine 1:100,000 containing articaine HCl 4% (40 mg/mL) and epinephrine 1:100,000 (NDC 0404-6620-05)

Articaine HCl 4% and Epinephrine 1:100,000 with Monoject Disposable Dental Injector (Articaine Hydrochloride and Epinephrine) Injection Solution Articaine HCl 4% and Epinephrine, 1:100,000 is available in cardboard boxes containing 30 disposable single use injectors, each containing a single 1.7 mL cartridge (NDC 0404-6620-30)

PATIENT COUNSELING INFORMATION

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.
- Patients should be instructed not to eat or drink until normal sensation returns.

Manufactured by Novocol Pharmaceutical of Canada Inc.
Cambridge, Ontario, Canada N1R 6X3