

PRODUCT MONOGRAPH

ULTRACAINE D-S INJECTION

(4% articaine hydrochloride with epinephrine 1:200,000 as epinephrine hydrochloride)

ULTRACAINE D-S FORTE INJECTION

(4% articaine hydrochloride with epinephrine 1:100,000 as epinephrine hydrochloride)

Solutions for Injection

Local Anesthetic for Dental Use

Manufactured by:

Sanofi - Aventis Deutschland GmbH
Frankfurt am Main, Hessen, Germany

Imported by:

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ULTRACAINE D-S INJECTION and ULTRACAINE D-S FORTE INJECTION
(4% articaine hydrochloride with 1:200,000 or 1:100,000 epinephrine)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medical Ingredients
Submucosal, perivascular, palatal injection	1.7ml solution in a glass cartridge containing: Ultracaine D-S Injection: 4% articaine hydrochloride (40 mg/mL) 1:200,000 epinephrine (0.005 mg/mL epinephrine base, which corresponds to 0.006 mg/mL epinephrine hydrochloride) Ultracaine D-S Forte Injection: 4% articaine hydrochloride (40 mg/mL) 1:100,000 epinephrine (0.010 mg/mL epinephrine base, which corresponds to 0.012 mg/mL epinephrine hydrochloride)	Hydrochloric acid, Sodium chloride, Sodium metabisulphite, Distilled water

INDICATIONS AND CLINICAL USE

Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine) solutions for injection are indicated for infiltration anesthesia and nerve block anesthesia in clinical dentistry.

Geriatrics (>65 years of age)

Elderly patients should be given reduced doses commensurate with their age and physical condition.

Pediatrics (<4 years of age)

The use of Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) in children under the age of 4 years is not recommended (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) are contraindicated in patients with a known hypersensitivity to the active substances, sulphites, or to any of the other excipients.

Due to the articaine content, Ultracaine D-S and Ultracaine D-S Forte must not be used in cases of:

- hypersensitivity to other local anesthetics of the amide type,
- in the presence of inflammation and/or sepsis near the proposed injection site;

- severe cardiac impulse formation (e.g. marked bradycardia) and severe conduction disturbances (e.g. 2nd or 3rd degree AV block)
- acute decompensated heart failure (acute congestive heart failure)
- severe shock or severe hypotension
- patients with cholinesterase deficiency
- in patients with existing neurologic disease

Use Ultracaine D-S and Ultracaine D-S Forte with the caution required of any vasopressor drug. Due to the vasoconstrictor (epinephrine) content, Ultracaine D-S and Ultracaine D-S Forte must not be used in:

- anaesthesia of the extremities (such as fingers) due to the risk of ischemia,
- patients with narrow-angle glaucoma,
- patients with cardiovascular concerns such as:
 - patients with severe hypertension,
 - patients with paroxysmal tachycardia or known arrhythmias with rapid heart rate,
 - patients with recent (3 to 6 months) myocardial infarction,
 - patients with recent (3 months) coronary artery bypass surgery,
 - patients taking non-cardioselective beta-blockers (e.g. propranolol), (due to the risk of hypertensive crisis or severe bradycardia),
- patients with pheochromocytoma,
- patients with hyperthyroidism, and
- patients currently or recently receiving treatment with tricyclic antidepressants or MAO inhibitors.

Intravenous use is contraindicated.

Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) must not be used in patients with both bronchial asthma and a hypersensitivity to sulphites, as treatment may precipitate acute allergic reactions with anaphylactic symptoms, such as bronchospasm.

WARNINGS AND PRECAUTIONS

General

Local anaesthetics should only be used by clinicians trained in the diagnosis and management of dose-related toxicity and other acute emergencies which may arise from their use. Adequate facilities, resuscitative drugs and equipment, oxygen and personnel should be immediately available for proper management of toxic reactions and related emergencies (see ADVERSE REACTIONS and OVERDOSAGE).

Cardiovascular

As with other local anesthetics combined with epinephrine, excessive plasma levels can depress the myocardium, which may lead to heart block, cardiac arrhythmia, tachycardia, bradycardia, blood pressure changes (usually hypotension) and possibly fatal cardiac arrest.

Patients with impaired cardiovascular function may be less able to compensate for functional changes associated with cardiovascular effects of toxic blood concentrations of Ultracaine. The use of articaine with lower concentrations of epinephrine (1:200,000) is recommended in such patients.

Use local anesthetics containing a vasoconstrictor cautiously in areas with limited blood supply or in patients with peripheral vascular disease.

Endocrine and Metabolism

Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) should be used with extreme caution in patients whose medical history and physical evaluation suggest the existence of thyrotoxicosis or diabetes (see CONTRAINDICATIONS and DRUG INTERACTIONS). The use of articaine with lower concentrations of epinephrine (1:200,000) is recommended in these patients.

Hematologic

Methemoglobinemia

As with any local anesthetic, Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) may cause methemoglobinemia; though rare, this has been observed when an intravenous regional anesthesia technique was used. Ultracaine D-S and Ultracaine D-S Forte solutions, when used as directed in dental procedures, have not been associated with methemoglobinemia.

Methemoglobinemia values of less than 20% usually do not produce any clinical symptoms. The usual clinical signs of methemoglobinemia are cyanosis of the nail beds and lips. Although the possibility of methemoglobinemia occurring in dental patients is extremely rare, it can be rapidly reversed by the use of 1-2 mg/kg body weight of methylene blue administered intravenously over a 5 minute period.

Immune

The sodium metabisulphite component of Ultracaine D-S and Ultracaine D-S Forte can precipitate hypersensitivity reactions, particularly in patients with bronchial asthma. Such reactions may manifest as vomiting, diarrhoea, wheezing, acute asthma attacks, impaired consciousness or shock.

Neurologic

As with other local anesthetics combined with epinephrine, excessive plasma levels cause systemic reactions involving the central nervous system, characterized by excitation and/or depression. The initial manifestations may include nervousness, dizziness, headache, tremors, or temporary visual disturbances (blurred vision, blindness, double vision), followed by drowsiness, convulsions, unconsciousness and possibly life-threatening or fatal respiratory arrest. Since excitement may be transient or absent, the initial manifestations may include drowsiness, sometimes merging into unconsciousness and rarely fatal respiratory arrest (see OVERDOSAGE). Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus.

Use with caution in patients with a history of epilepsy (see ADVERSE REACTIONS).

Peri-operative Considerations

Combinations of different anaesthetics cause additive effects on the cardiovascular system and CNS (see DRUG INTERACTIONS).

Respiratory

In patients with chronic bronchitis or pulmonary emphysema the use of articaine with epinephrine 1:200,000 is recommended (Ultracaine D-S).

Special Populations

Pregnant Women: The safe use of Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) in pregnant women has not been established.

Epinephrine and articaine cross the placental barrier. Animal studies indicate that articaine with epinephrine, can have harmful effects on embryo-fetal and postnatal development, though it is not clear whether this is a direct effect or due to maternal toxicity. Animal studies have shown that

epinephrine (alone) can impair utero-placental perfusion and cause congenital malformations (see TOXICOLOGY).

Ultracaine D-S and Ultracaine D-S Forte should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: The safety for infants of milk from breastfeeding mothers recently treated with Ultracaine D-S and Ultracaine D-S Forte has not been studied. Because many drugs are excreted in human milk, caution should be exercised when Ultracaine products are administered to a nursing woman. After treatment with Ultracaine products, nursing mothers may choose to pump and discard breast milk for approximately 4 hours following an injection of Ultracaine (to minimize infant ingestion), and then resume breastfeeding.

Pediatrics (4-17 years of age): The use of Ultracaine D-S or Ultracaine D-S Forte in children under the age of 4 years is not recommended (see DOSAGE AND ADMINISTRATION).

Carers of young children should be warned of the risk of accidental soft tissue injury due to self-biting, due to prolonged soft tissue numbness (see ADVERSE REACTIONS).

Hepatic / Renal dysfunction: No clinical studies have been performed in patients with severe renal or hepatic dysfunction. Use with caution in these patients.

ADVERSE REACTIONS

General disorders and administration site conditions

Reactions to Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine) are characteristic of those associated with amide-type local anesthetics and/or vasoconstrictors. As with other local anesthetics applied to the head and neck area, there are rare reports of life-threatening or fatal shock, respiratory or cardiac arrest following treatment with articaine with epinephrine.

In isolated cases, inadvertent intravascular injection may lead to the development of ischemic zones at the injection site, sometimes progressing to tissue necrosis (see also DOSAGE AND ADMINISTRATION).

Cardiovascular:

Cardiovascular adverse events may include cardiac arrhythmia, tachycardia, bradycardia, rise in blood pressure, hypotension, cardiac failure and shock (possibly life-threatening).

Gastrointestinal: Nausea, vomiting.

Hematologic: methemoglobinemia (see WARNINGS AND PRECAUTIONS).

Immune system disorders:

Allergic or allergy-like hypersensitivity reactions may occur at the injection site (e.g. edematous swelling or inflammation) or independently of the site (e.g. urticaria, skin reddening, itching, conjunctivitis, rhinitis, and angioneurotic edema). Signs of angioneurotic edema may include swelling of the upper and/or lower lip and/or cheeks, glottal oedema with globus hystericus, difficulty in swallowing, and difficulty in breathing. Any of these reactions may progress to acute asthmatic attacks, impaired consciousness, and life-threatening or fatal anaphylactic shock.

Nervous system disorders

Dose-related central nervous system reactions may occur: agitation, nervousness, stupor sometimes progressing to loss of consciousness, coma, respiratory disorders sometimes progressing to

respiratory arrest, muscular tremor and muscular twitching sometimes progressing to generalised convulsions. These reactions are more likely after overdose or inadvertent intravascular injection.

Other nervous system disorders: dizziness, paresthesia, hypoesthesia. Headaches (frequent).

Persistent paresthesias of the lips and oral tissues have occurred after blocking the inferior alveolar nerve. Nerve lesions (e.g. facial nerve paresis) and reduced gustatory sensitivity in the orofacial region have been reported.

Convulsions have been causally associated with the use of articaine products containing epinephrine, in some patients with a history of convulsive disorder (e.g. suffering from convulsions, epilepsy, or epilepsy-related disorders).

Ophthalmologic disorders

Visual disturbances (blurred vision, double vision, mydriasis, blindness) have been reported during or shortly after injection of local anaesthetics in the area of the head, and were not always reversible.

DRUG INTERACTIONS

Ultracaine D-S and Ultracaine D-S Forte (articaine with epinephrine solutions) must not be administered to patients taking non-cardioselective beta-blockers (e.g. propranolol), due to the risk of epinephrine-induced hypertensive crisis and severe bradycardia (see CONTRAINDICATIONS).

Local anesthetics containing sympathomimetic vasoconstrictors, e.g. epinephrine, must not be used in patients who are taking MAO inhibitors or tricyclic antidepressants, due to the risk of severe, prolonged hypertension. This can occur up to 14 days after MAO inhibitor treatment has ended (see CONTRAINDICATIONS).

Epinephrine may attenuate the effect of oral antidiabetic drugs, by inhibiting the release of insulin from the pancreas (see WARNINGS AND PRECAUTIONS).

Treatment with enflurane, halothane, or other inhaled halogenated anesthetics may increase myocardial sensitivity to catecholamines such as epinephrine. Dose-related cardiac arrhythmias may occur if patients are treated with Ultracaine D-S or Ultracaine D-S Forte during or immediately following the administration of a halogenated anesthetic.

DOSAGE AND ADMINISTRATION

As with all local anesthetics, the appropriate dose depends upon the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be used.

To prevent the serious systemic adverse reactions associated with high plasma concentrations of local anesthetics or epinephrine, procedures to avoid intravascular injection should be used.

Injections should be made slowly or in incremental doses, with frequent aspirations before and during the injection to avoid intravascular injection. After each injection, the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs, and state of consciousness should be

monitored. The blood levels of Ultracaine or its metabolites may accumulate significantly with repeated dosing. Tolerance to elevated blood levels varies with the status of the patient.

A practice injection of 5 or 10% of the dose is recommended to assess the risk of allergy.

As for other anesthetics, avoid excessive premedication with sedatives, tranquilizers, and anti-emetic agents, especially in children and elderly patients.

In patients receiving anticoagulation or antiplatelet treatment (e.g. heparin or acetylsalicylic acid), inadvertent vascular puncture during local anaesthesia may lead to serious bleeding.

Debilitated patients, elderly patients, acutely ill patients, and pediatric patients should be given reduced doses commensurate with their age and physical condition.

Dosage for adults, and children 4-17 years of age.

Procedure	<u>Ultracaine D-S & Ultracaine D-S Forte</u>	
	Volume (ml)	Total dose 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

Adults

It is recommended that the dosage of articaine hydrochloride, as Ultracaine D-S or Ultracaine D-S Forte, should not exceed 7 mg/kg body weight in adults.

Children (4-17 years of age)

The minimum volume necessary to achieve adequate anaesthesia should be used; the injection amount should be individually tailored to the age and weight of the child. A maximum dose of 7 mg articaine hydrochloride per kg of body weight (0.175 ml/kg) should not be exceeded.

The use of Ultracaine D-S or Ultracaine D-S Forte in children under 4 years of age is not recommended.

Geriatrics (>65 years of age)

Elderly patients should be given reduced doses commensurate with their age and physical condition.

OVERDOSAGE

The type of toxic reaction is unpredictable and depends on factors such as dosage, the rate of absorption and the clinical status of patient. These reactions call for extreme preparedness, as serious and life-threatening symptoms may develop rapidly and with little warning.

Symptoms

Reactions due to systemic absorption are primarily of two types and related to stimulation and/or depression of the CNS.

CNS stimulation may include restlessness, anxiety, confusion, hyperpnoea, nausea, vomiting, tremor, twitching, tonic-clonic seizures. Patients may experience a rise in blood pressure with facial reddening and tachycardia.

CNS depression may include dizziness impairment of hearing, loss of ability to speak, loss of consciousness, muscle atony, vasomotor paralysis (weakness, pallor) dyspnoea and death due to respiratory paralysis.

Cardiovascular depression can lead to bradycardia, arrhythmias, ventricular fibrillation, fall in blood pressure, cyanosis, cardiovascular collapse and possibly fatal cardiac arrest.

Treatment

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. 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 current information regarding the management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Ultracaine (articaine with epinephrine) has been shown to block conduction by interfering with the process fundamental to the generation of the nerve action potential, namely, the large transient increase in the permeability of the membrane to sodium ions that is produced by a slight depolarization of the membrane.

Ultracaine kinetics were determined in man by radioassay following a single intramuscular dose of 5 mg/kg and a single intravenous dose of 1 mg/kg of ³⁵S-labelled articaine hydrochloride. The maximal blood concentration was reached 45 to 60 minutes after the intramuscular injection. The elimination from the blood occurred in two phases with the following half-lives: 1.2 and 69.7 hours, and 2.0 and 31.5 hours after i.v. and i.m. injection, respectively. Ultracaine is excreted mainly via the kidneys, in three phases, with the following half-life: 2.5, 4.4 and 210 hours, and 1.6, 4.6 and 39 hours after i.v. and i.m. injection, respectively. The total excretion of radioactivity, through the kidneys, was 89% after i.v. injection and 76% after i.m. injection while 1.5% (i.v.) and 1.3% (i.m.) were excreted with the feces. After the intramuscular injection, two metabolites (M¹ and M²)

accounting for 87% and 2%, respectively, of the administered dose were found. No metabolite was detected in the blood following an i.v. injection. In the urine, only metabolites were found.

A study in male volunteers demonstrated that a single submucosal injection of 80 mg articaine 4% with epinephrine (1:200 000) resulted in a mean maximum serum concentration of 326 ± 158 ng/ml. The C_{max} was reached an average of 17.7 ± 6.6 minutes after injection. Articaine is rapidly hydrolysed to its primarily inactive principal metabolite, articaine carboxylic acid. Maximum concentrations of the metabolite were reached 46.2 ± 9.2 minutes after injection.

STORAGE AND STABILITY

Ultracaine D-S and Ultracaine D-S Forte are liquid products.

Temperature: Store at room temperature, below +25°C. Do not freeze.

Light: Protect from exposure to light.

Others: Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Handle the product with care.

Ultracaine D-S and Ultracaine D-S Forte are packaged in 1.7 mL glass cartridges.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms: Ultracaine D-S and Ultracaine D-S Forte are available as solutions for injection.

Composition: **Ultracaine D-S** contains 4% articaine hydrochloride (40 mg/mL) with 1:200,000 epinephrine (0.006 mg/mL epinephrine hydrochloride, which corresponds to 0.005 mg/mL epinephrine as a free base), sodium metabisulphite (0.50 mg/ml) as antioxidant, and water for injection.

Ultracaine D-S Forte contains 4% articaine hydrochloride (40 mg/mL) with 1:100,000 epinephrine (0.012 mg/mL epinephrine hydrochloride, which corresponds to 0.010 mg/mL epinephrine as a free base)), sodium metabisulphite (0.50 mg/ml) as antioxidant, and water for injection.

Packaging: Ultracaine D-S and Ultracaine D-S Forte solutions are available in 1.7 mL cartridges, in boxes of 100 cartridges.

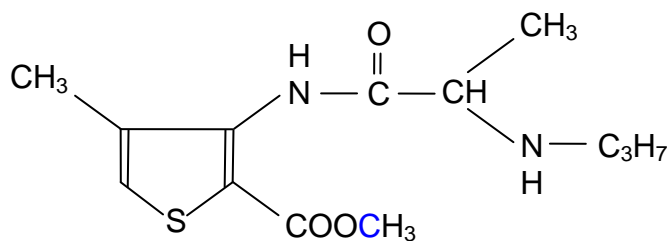
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Articaïne hydrochloride

Structural Formula:



Molecular Formula: C₁₃H₂₀N₂O₃S

Molecular Weight: 320.9

Chemical Name: 3-n-propyl-amino-propionylamino-2-carbomethoxy-4- methylthiophene hydrochloride

Physical Form: a white, fine, odourless, crystalline powder

Solubility: soluble in water and ethanol, slightly soluble in chloroform

Melting Range: 175-176°C

DETAILED PHARMACOLOGY

General:

Local anesthetics block nerve conduction when applied locally to nerve tissue in appropriate concentration. They block the action potential of the nerve by their direct interaction with the voltage sensitive Na⁺ channels. After systemic absorption local anesthetics may have a cardiodepressive effect which could lead to impairment of myocardial performance and circulatory regulation.

In the isolated perfused guinea pig heart it has been demonstrated that articaïne, procaine and lidocaine have negative inotropic effects. Articaïne and lidocaine cause less vasodilatation than procaine. Both of these effects are reversible within a few minutes.

The effects of an I.V. administration of 5 mg/kg of articaïne, lidocaine and procaine, on the arterial blood pressure of anesthetized cats, showed that the blood pressure reaction following intravenous

administration of local anesthetics is dependent on the injection rate. However, lidocaine revealed a markedly stronger hypotensive effect than procaine or articaine.

The cardiac electrophysiological effects of articaine were compared with those of bupivacaine and lidocaine. The right septal wall of the hearts of male White New Zealand rabbits (n = 42) were removed, placed in a 15 mL recording chamber and superfused with Tyrode's solution. The drugs were perfused over the tissue at three increasing concentrations (articaine: 10, 20 and 40 ug/mL; bupivacaine: 1, 3 and 5 ug/mL and lidocaine: 5, 10 and 20 ug/mL) and their effects on the action potentials of Purkinje fibers (PF) and ventricular muscle (VM) tissues were determined. The effects of bupivacaine (5 ug/mL) were generally equivalent to those of articaine (40 ug/mL) in depressing action potential overshoot, amplitude and maximal rate of depolarization (V_{max}), thereby indicating that bupivacaine was eight times more cardiodepressant. The effects of bupivacaine at this lower concentration persisted significantly (p < 0.05) longer (36.3 min) than those of articaine (21.3 min). A rate dependant decrease in steady-state (SS) V_{max} was observed with bupivacaine 5 ug/mL and lidocaine 20 ug/mL at 1, 2 and 3 Hz, however articaine 40 ug/mL increased SS V_{max} at 1 and 2 Hz and only decreased SS V_{max} at 3 Hz. Drug superfusion of a bolus exposure of the anesthetic bupivacaine (30 to 1 ug/mL) resulted in PF-VM conduction blockade of 57.7 min duration which was significantly longer (p < 0.001) than lidocaine (100 to 2.5 ug/mL; 15 min) and articaine (200 to 5 ug/mL; 21.6 min).

The toxic effects of veratrine, histamine or acetylcholine are suitable models for animal studies of shock. The circulatory collapse induced by veratrine can be partially corrected or reversed by local anesthetics. Intravenous administration of 5-10 mg/kg of articaine was found to prevent the critical drop in blood pressure induced by veratrine (25-50 ug/kg I.V.). However, articaine neither prevented nor altered the decrease in blood pressure produced by acetylcholine (0.5-1.5 ug/kg) and histamine (6-10 ug/kg).

In the isolated small intestine of the guinea pig, the spasmolytic effect of articaine on the contractions caused by barium chloride, histamine and carbachol corresponds to those of other local anesthetics.

Articaine had a vasodilative effect of the magnitude of that of lidocaine and butanilcaine when tested in the isolated, perfused rabbit ear, constricted with 2 ug/mL of norfenefrine. Procaine proved to be slightly more active under the same test conditions.

Convulsions in rats, induced by high doses of articaine, were antagonized by xanthine derivatives as well as by hypnotics.

No formation of methemoglobin was found in cats or rats after administration of articaine or lidocaine. Prilocaine induced a marked methemoglobinemia formation in cats but not in rats.

Cervical spinal anesthesia did not bring about any adverse effects on the spinal cord or the meninges following subdural injection of 5 mL of articaine solution (20 mg/mL) under sterile conditions through the foramen magnum in beagle dogs. Under identical conditions, similar results were obtained following injection of lidocaine and isotonic saline.

Special Pharmacology

The conduction anesthetic effect of articaine (0.05-0.5%) on the sciatic nerve of the decapitated frog was examined and the dose-response curves compared with those of lidocaine and procaine (0.05-0.5%). Articaine proved to be 1.5 times and 1.9 times more active than lidocaine and procaine, respectively.

The infiltration anesthetic effect of articaine (0.1-4.0%) on cutaneous wheals of guinea pigs was examined and the dose response curves compared with those of lidocaine and procaine (0.1-4.0%). Articaine showed a superior activity to lidocaine and procaine in the higher concentrations.

The topical anesthetic effect of articaine 1% on the cornea of rabbits was examined and compared with those of procaine 1%, tetracaine 0.1%, lidocaine 1% and prilocaine 1%. Articaine had a weak topical anesthetic activity which was found to be superior to prilocaine and procaine, but inferior to tetracaine and lidocaine.

Pharmacokinetics

Elimination and metabolism of articaine labelled with ³⁵S were determined in dogs, rats and dwarf pigs. Following an intramuscular injection, the radioactive substance was eliminated predominantly through the kidneys. A rapid metabolism was observed in all species; only very little or none of the original substance was detected in the excretion products. During *in vitro* experiments with rat liver slices and organs homogenates the metabolism occurred at a similar speed.

The biochemical degradation of articaine is initiated by saponification (hydrolysis) of the carboxylic acid ester group to give free carboxylic acid. From that point, the reaction can follow several pathways: cleavage of the carboxylic acid, formation of an acid amide group by internal cyclization and oxidative reactions.

Blood levels of articaine labelled with ³⁵S were determined in dwarf pigs following an intravenous or intramuscular injection of 10 mg/kg body weight. The serum elimination half-lives were 3.5 and 51 hours. Articaine is 95% protein bound. In the dwarf pigs, after 12 hours, 65% of the radioactivity administered was eliminated in the urine following intravenous injection and 59% following intramuscular injection. After 48 hours, 80 to 82% of the administered dose was eliminated in the urine and 8 to 12% in the feces following the intravenous injection. The urinary excretion occurred in two phases with half-lives of 3 and 10 hours.

TOXICOLOGY

The acute and subacute toxicity of articaine was studied in mice, rats, rabbits and dogs. Repeated parenteral administrations of the local anesthetic to rats and dogs were used to assess its tolerance whereas the local tolerance of articaine was evaluated in rabbits and dogs following intravenous, intramuscular, subcutaneous, epidural, subdural and intrathecal administration.

Acute Toxicity

The LD₅₀ values are shown in the following table:

Species	Route	LD50 (in mg/kg)	95% Confidence Limits
Mice	i.v. ¹	37.0	33.5 - 42.0
	i.v. ²	37.9	36.2 - 39.6
	i.v. ^{2,3}	3.7	3.2 - 4.3
	i.v. ^{2,4}	7.6	6.4 - 8.9
	i.v. ^{2,6}	20.2	19.6 - 20.8

Rats	p.o. ²	978.0	868 - 1102
	i.m. ²	278.0	260 - 298
	i.v. ¹	25.0	24.0 - 26.0
	i.v. ²	23.2	22.1 - 24.3
	i.v. ^{2,3}	11.4	10.4 - 12.5
Rabbits	i.v. ^{2,5}	8.2	7.3 - 9.3
	i.m. ²	189.0	154 - 233
	i.v. ²	20.6	18.6 - 22.8
	i.v. ²	19.6	18.6 - 20.7
	i.v. ^{2,3}	19.2	17.9 - 20.6
	i.v. ^{2,5}	14.1	12.1 - 16.5

- | | |
|---------------------------------|-----------------------------------|
| 1. Wilcoxon test | 2. Clarz program |
| 3. with epinephrine 1:100,000 | 4. with epinephrine 1:200,000 |
| 5. with norepinephrine 1:25,000 | 6. with norepinephrine 1:200,000. |

Muscular tremor, staggering gait, twitching, tonic-clonic convulsions, respiratory depression, pulmonary edema in rats and transitory loss of consciousness (lateral position) were the most frequently observed symptoms in lethally dosed animals.

The maximum tolerated dose of articaine administered i.m. to beagle dogs was 100 mg/kg; for i.v. dosing in beagle dogs the maximum tolerated dose was 50 mg/kg.

Subacute toxicity

Rats

Articaine was administered daily for 5 days per week over 5 weeks to 4 groups of 20 (10M, 10F) rats at intramuscular doses of 0, 25, 50 and 100 mg/kg. At doses of 25, 50 and 100 mg/kg, articaine produced morphologic changes in the muscle and connective tissue at the injection site which was characterized by localized hemorrhage primarily in the subcutaneous tissue. The 100 mg/kg dose elicited immediate signs of acute toxicity and a 30% incidence of deaths primarily due to pulmonary edema. An increase in the weight of the adrenals of males was observed. Lower doses of 25 and 50 mg/kg showed no other significant changes in the parameters studied.

Articaine was administered daily for 5 days per week over 5 weeks to 4 groups of 20 (10M, 10F) rats at intravenous doses of 0, 3, 6 and 12 mg/kg. There appears to be no physiologically significant toxic effects of articaine in doses of 3 and 6 mg/kg. At a dose of 12 mg/kg, signs of an acute toxicity consisting of excitement or restlessness, protrusion of eyeballs, and, occasionally, brief periods of tremors and clonic convulsions were noted immediately following the daily injection. A few cases of acute pulmonary collapse were reversed by artificial respiration.

Dogs

Articaine (3% solution) was administered daily for 30 days to groups of 6 beagle dogs (2M and 1F, 1M and 2F) at intramuscular doses of 25 and 50 mg/kg. Two beagle dogs (1M and 1F) were used as controls. At 50 mg/kg, symptoms such as salivation, tremor, disturbed equilibrium, and convulsions occurred soon after administration from the first day on, though not every day. These reactions persisted up to 45 minutes, but they did not affect clinical-chemical data. Vomiting occurred on three occasions. Clinical and clinical-chemical examinations, necropsy and subsequent histological examinations did not reveal any pathological changes attributable to articaine.

Articaine was administered daily for 30 days to groups of 6 beagle dogs (2M and 1F, 1M and 2F) at intravenous doses of 5 and 10 mg/kg. Two beagle dogs (1M and 1F) were used as controls. At 10 mg/kg, vomiting occurred in one male on two occasions. One female after being given 10 mg/kg at double the normal rate of injection, lay transiently on its side and had mild extensor spasms; the incident did not appear to have any after-effects. Clinical and clinical-chemical examinations, necropsy and subsequent histological examinations did not reveal any findings attributable to articaine.

Tissue tolerance

Nine groups of two rabbits each received a 6% solution of articaine without or with vasoconstrictors (2.0 mg% epinephrine or 4.8 mg % norepinephrin). Articaine was injected by the subcutaneous, intramuscular or intravenous route in volumes of 0.1 mL (sc.), 0.5 mL (i.m.) or 0.25 and 0.5 mL (i.v.). Local tolerance was evaluated two and five days later by macroscopic and microscopic examinations in all groups except in the two rabbits which received articaine intravenously without vasoconstrictor. In the latter animals, tolerance was evaluated one and two days post-injection. Articaine was well tolerated when injection by the i.v. route but poorly tolerated following i.m. administration.

Tolerance following s.c. administration occupied an intermediate position. Articaine was better tolerated in the absence of a vasoconstrictor than in the presence of epinephrine or norepinephrine. Articaine with 2.0 mg% epinephrine was generally better tolerated than articaine with 4.8 mg% norepinephrine.

The epidural tolerance was evaluated in six beagle dogs (5M and 1F) treated with a single injection of 5.0 mL of a 2.0% solution of articaine with 2 mg% of epinephrine. The animals were sacrificed by groups of two after 1, 3 and 8 days. Articaine was well tolerated epidurally.

The subdural tolerance was evaluated in six beagle dogs (4M and 2F), two treated with a single injection of 200 mg articaine dissolved in 4 to 5 mL cerebrospinal fluid, two with lidocaine in the same concentration and two with saline. The animals were sacrificed after 2 and 5 days. Articaine as well as lidocaine and saline were well tolerated by the animals.

The intrathecal tolerance (atlanto-occipital joint) was evaluated in eleven beagle dogs (5M, 6F) eight treated with a single dose of 200 mg/kg of articaine and three (1M, 2F) with the cerebrospinal fluid as control. The animals were sacrificed after 1, 2 and 8 days. Articaine produced no pathological changes of the spinal cord, the meninges or the efferent spinal nerve roots. In another study, the intrathecal tolerance (suboccipital) was evaluated in nine beagle dogs, six (2M, 4F) treated with a single dose of articaine, 200 mg per animal with epinephrine 1:200,000 and three (1M, 2F) treated with the cerebrospinal fluid as control. The animals were sacrificed after 1, 2 and 8 days. The combination of articaine with epinephrine produced no pathological changes of the spinal cord, the meninges or the efferent spinal nerve roots.

Mutagenicity

Articaine was tested in two mutagenicity screening tests, namely the Ames test and Micronucleus test, and showed no mutagenic effect in either test.

Teratology

Articaine HCl (4%) with epinephrine (1:100,000) has been shown to increase fetal deaths and skeletal variations in rabbits after repeated daily subcutaneous doses for 15 days during mid-gestation (articaine dose of 80 mg/kg/day, i.e. approximately 4 times the maximum recommended human dose, MRHD, based on body surface area). It is unclear whether these are direct or indirect effects, (e.g. due to severe maternal toxicity, including seizures). In contrast, no embryo-fetal toxicities were observed in equivalent studies at articaine doses up to 40 mg/kg/day in rabbits and

80 mg/kg/day in rats (approximately 2 times the MRHD for articaine, based on body surface area; epinephrine 1:100,000).

In pre- and postnatal developmental studies, pregnant rats were given repeated daily subcutaneous doses of 4% articaine with epinephrine 1:100,000 from day 6 of gestation through the end of lactation. A dose of 80 mg/kg/day articaine HCl (approximately 2 times the MRHD for articaine, based on body surface area) affected developmental parameters in F1 pups (e.g. delayed eye opening, adversely affected passive avoidance, a measure of learning). This dose also produced severe maternal toxicity in some animals. These effects were not observed at lower doses (20 or 40 mg/kg/day articaine HCl, with 1:100,000 epinephrine (0.012 mg/mL epinephrine HCl)).

Administration of epinephrine (alone) to rats and rabbits, was associated with reduced implantation, congenital malformations and impaired utero-placental perfusion.

Rats

Articaine (alone) was administered daily, intravenously, on days 7 through 16 of gestation to groups of 20 to 24 pregnant rats at doses of 0, 0.8, 4.0 and 20 mg/kg body weight. At 20 mg/kg, tonic-clonic convulsions were noted in the animals and four females died of this reaction. Articaine neither impaired intra-uterine development of the foetuses, nor did it cause anomalies of internal organs or the skeleton.

Rabbits

Articaine (alone) was administered daily, intravenously, on days 7 through 19 of gestation to groups of ten Silver-Yellow rabbits at doses of 0, 0.8, 3.2 and 12.5 mg/kg body weight. Articaine neither caused impairment of the general condition of the dams nor did it cause adverse effects on the intra-uterine development of the foetuses. The foetuses were normally developed and exhibited no external, organ or skeletal anomalies which might be attributed to the substance. The death rate of the foetuses in utero was not increased as compared to the norm.

REFERENCES

1. Adelman MH. Sudden death during cyclopropane-ether anaesthesia following the administration of epinephrine: Case Report. *Anesthesiol.* 1941; 2: 657-60.
2. Anderson N, Johansen SH. Incidence of catechol-amine-induced arrhythmias during Halothane anesthesia. *Anesthesiol.* 1963; 24:51-56.
3. Boakes AJ, Lawrence DR. Interactions between sympathomimetic amines and antidepressant agents in man. *Br Med J* 1973; 311-315.
4. Elad S, Admon D, Kedmi M, Naveh E, Benzki E, Ayalon S et al. The cardiovascular effect of local anesthesia with articaine plus 1:200,000 adrenalin versus lidocaine plus 1:100,000adrenalin in medically compromised cardiac patients: a prospective, randomized, double blinded stud y. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 105(6):725-730.
5. El-Qutob D, Morales C, Pelaez A. Allergic reaction caused by articaine. *Allergol Immunopathol (Madr)* 2005; 33(2):115-116.
6. Goodman LS, Gilman A. *The Pharmacological Basis of Therapeutics.* Eight Edition 1990, Pergamon Press Inc., New York, 311-31.

7. Hofer H. Report of the österr Studienges für Atomenergetic. Biol. Abtlg des Forschungszentrums Seitersdorf 1975.
8. Hofer H., Eberl R., Altmann HZ. Pharmacokinetische Untersuchungen mit 35-S markierten Carticain. Prakt. Anästh. 1974;9;157-61.
9. Lampe KF. Drug Evaluations, 6th Edition 1986, American Medical Association, Chicago, Illinois: 275-82.
10. Malamed SF. Handbook of Local Anaesthesia 3rd Edition 1990, Moseby-Year Book Inc., St. Louis, Missouri.
11. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. J Am Dent Assoc 2001. Feb; 132(2):177-85.
12. Matteo RS, Katz RL, Papper EM. The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man. Anesthesiol. 1963; 24:327-330.
13. McEvoy GK. AHFS Drug Information, American Society of Hospital Pharmacists Inc 1992:1946-49.
14. Meyers FH, Jawetz E, Goldfein A., Review of Medical Pharmacology, 7th Edition 1980, Lange Medical Publications, Los Altos, California, 217-25.
15. Moller RA, Covino BG. Cardiac Electrophysiologic Effects of Articaine Compared with Bupivacaine and Lidocaine. Anesth Analg 1993; 76:1266-73.
16. Muller WPE, Weiser P, Scholler KL. Pharmacokinetics of articaine during mandibular nerve block. Reg Anaesth 1991; 14:52-55.
17. Muschaweck R, Rippel RZ. Ein neues Lokalanaesthetikum (Carticain) aus der Thiophenreihe. Prakt. Anaesth 1974; 9:135-46.
18. Oertel R, Rahn R, Kirch W. Clinical pharmacokinetics of articaine. Clin Pharmacokinet. 1997 Dec; 33(6):417-25.
19. Rahn R, Vogt R, Hellenbrecht K, Feller K. Serum levels of articaine following intraoral local anesthesia with Ultracaine D-S or Ultracaine 2% without vasoconstrictor. Dtsch Zahnarztl Z 1992; 47:126-28.
20. Reynolds JEF. Martindale: The Extra Pharmacopoeia, 29th Edition 1989; The Pharmaceutical Press, London 1205-8 and 1453.
21. Ross NM. Epinephrine in Dental Anesthesia. JAMA 1967; 201:334.
22. Sjoqvist F. Psychotropic Drug interactions between monoamino oxidase (MAO) inhibitors and other substances. Proc Roy Soc Med 1965; 58:967-78.
23. USP DI: Drug Information for the Health Care Professional, 13th Edition 1993 U.S. Pharmacopoeial Convention Inc, Vol.1 127-34.

PART III: CONSUMER INFORMATION

Ultracaine D-S, solution for injection
(4% articaine HCl + epinephrine 1:200,000)

Ultracaine D-S Forte, solution for injection
(4% articaine HCl + epinephrine 1:100,000)

This leaflet is part III of a three-part "Product Monograph" published when Ultracaine D-S and Ultracaine D-S Forte were approved for sale in Canada. This leaflet is a summary designed specifically for Consumers. It will not tell you everything about Ultracaine D-S and Ultracaine D-S Forte. Contact your dentist or doctor if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

Ultracaine D-S and Ultracaine D-S Forte are used for the local anaesthesia (freezing) for dental treatments in adults and children 4 years of age and older.

What it does:

Ultracaine contains two active ingredients: 1) articaine (local anaesthetic) that causes loss of feeling (freezing) in the gums and surrounding tissues, and 2) epinephrine (adrenaline) that narrows the blood vessels, reduces bleeding, and helps the freezing last longer during dental treatments.

When it should not be used:

Ultracaine D-S and Ultracaine D-S Forte should not be used in patients who:

- are allergic to articaine or other similar local anaesthetics,
- are allergic to sulphites or any of the other ingredients of this medication,
- suffer from severe heart rhythm disorders,
- have a very slow pulse,
- suffer from acute heart failure,
- have very low blood pressure,
- suffer from asthma attacks, which can be triggered by hypersensitivity to the sulphites in this medicine,
- suffer from excessive pressure in your eyes (glaucoma),
- have an overactive thyroid,
- suffer from sudden heart palpitations (tachycardia),
- suffered a heart attack in the last 3 to 6 months,
- underwent coronary artery bypass surgery in the last 3 months,
- take certain heart medications, known as beta blocker medications, such as propranolol,
- suffer from an adrenaline-producing tumour in the adrenal gland,
- have uncontrolled high blood pressure,
- are currently taking certain medications for the treatment of depression and Parkinson's disease (tricyclic antidepressants, MAO inhibitors).

What the medicinal ingredients are:

- articaine HCl, epinephrine (adrenaline)

What the non-medicinal ingredients are:

- hydrochloric acid, sodium chloride, sodium metabisulphite, and distilled water

What dosage forms it comes in:

Ultracaine D-S and Ultracaine D-S Forte are available to the dentist, in single use cartridges containing 1.7 millilitres (mL) of the solution for injection by the dentist.

Ultracaine D-S solution contains 40 milligrams (mg) of articaine HCl and 0.006 mg epinephrine HCl (adrenaline HCl) in each mL. This corresponds to 0.005 mg of epinephrine base in each mL (1:200,000).

Ultracaine D-S Forte solution contains 40 mg of articaine HCl and 0.012 mg epinephrine HCl (adrenaline HCl) in each mL. This corresponds to 0.010 mg of epinephrine base in each mL (1:100,000).

WARNINGS AND PRECAUTIONS

You should talk to your dentist or doctor prior to dental treatment:

- about health problems you have now, or have had in the past,
- about other medicines you take, including medications you can buy without a prescription,
- if you have heart, liver, lung or kidney disease;
- if you have a neurological, or psychiatric disorder,
- you have a deficiency of a specific enzyme (cholinesterase deficiency),
- if you have epilepsy,
- if you are pregnant,
- if you are nursing.

If you are breastfeeding an infant or small child, you may want to pump and discard your breast milk for about 4 hours following the dental treatment involving an injection of Ultracaine D-S, or Ultracaine D-S Forte. This will help minimize the amount of this medication in the breast milk given to your infant or young child.

Recovery from local anaesthesia (freezing) after a dental treatment usually occurs gradually, within minutes to hours after treatment.

Before the freezing has worn off, avoid drinking hot liquids or chewing, because it will be difficult to know if the liquid is too hot, or if you are biting your tongue, inner cheek or lips by mistake.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your dentist or doctor if you are taking, or have recently taken any other medicines.

For example, the following medications may interact with Ultracaine D-S or Ultracaine D-S Forte:

- certain types of medications, known as "tricyclic" antidepressants or "MAO inhibitors", for the treatment of depression or Parkinson's disease,

- certain heart medications, known as beta blockers (such as propranolol),
- oral medicines (pills) for the treatment of diabetes.

PROPER USE OF THIS MEDICATION

Usual dose:

Ultracaine D-S and Ultracaine D-S Forte solutions are only for injection by dental professionals at the time of dental treatment. They are not for intravenous injection.

Your dentist will determine the dose to use. The lowest dosage needed to provide effective freezing should be used. The maximum dose is 7 milligrams of articaine per kilogram of body weight (0.175 ml/kg), for adults and children 4 years old or older.

These medications are not recommended for use in children less than 4 years old.

Overdose:

If an excessive quantity of Ultracaine is present in your body, you may experience one or more of the following side effects (likely soon after injection): restlessness, anxiety, confusion, facial reddening, drowsiness, nausea, vomiting, dizziness, difficulty speaking, hearing or seeing (for example, blurred or double vision), muscular weakness, tremor, twitching, difficulty breathing, an increase or decrease in your blood pressure, or heart rhythm disturbances.

Tell your dentist immediately if you have any of the above symptoms, as special monitoring and care may be required to prevent them from becoming more serious side effects.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects may include: headache, nausea and vomiting. You may feel temporary tingling or prickling sensations near the area that was frozen (paraesthesia).

Additional side effects in children

Compared to adults, children have an increased risk after a dental procedure of biting their numb area(s) before the freezing has worn off. This could result in injuries to their lips, inner cheeks and /or tongue.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your dentist or doctor		Seek immediate medical assistance
		Only if severe	In all cases	
Uncommon (may affect up to 1 in 100 people)	Rapid heart-beat (tachycardia)			✓
	Unknown (frequency cannot be estimated from the available data)			✓
	Numbness in the injected area or face, that does not fade away (hypoesthesia)			✓
	Disturbed sight, taste or sensation of touch in injected area, that does not fade away (paraesthesia)			✓
	Heart rhythm disturbances			✓
	Increase or decrease in blood pressure			✓
	Lowered heart rate (bradycardia),			✓
	Visual disorders, nervousness, anxiety, dizziness, difficulty hearing or seeing (for example, blurred or double vision, blindness), drowsiness, convulsions, difficulty breathing.			✓
	Wheezing, acute asthma attack (hypersensitivity / allergic reactions)			✓
	Inflammation at injection site (including redness, swelling and/or strong itching), with red eyes, runny nose, face and /or throat area swelling, difficulty breathing (hypersensitivity / allergic reactions)			✓

This is not a complete list of side effects. For any unexpected effects after a dental treatment involving Ultracaine products, contact your dentist, doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program**
 Health Canada
 Postal Locator 0701E
 Ottawa, Ontario
 K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.hansamed.net>

or by contacting the sponsor, Hansamed Ltd, at:
Tel. 1-800-363-2876

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