

## AUSTRALIAN PRODUCT INFORMATION

### 4% ARTICADENT® DENTAL WITH ADRENALINE (EPINEPHRINE) 1:100,000

(Articaine hydrochloride and adrenaline (epinephrine) (as acid tartrate))

#### 1 NAME OF THE MEDICINE

Articaine hydrochloride

Adrenaline (epinephrine) (as acid tartrate)

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

**4% Articaine DENTAL with Adrenaline (epinephrine) 1:100,000** is a clear, colourless sterile aqueous solution that contains articaine hydrochloride 4% (40 mg/mL) with adrenaline (epinephrine) (as acid tartrate) in a 1:100,000 strength.

**Articaine hydrochloride:** white to almost white powder, odourless.

Articaine hydrochloride is a local anaesthetic and is a racemic mixture. Articaine hydrochloride has a partition coefficient in n-octanol/ Soerensen buffer (pH 7.35) of 17, a pKa of 7.8 and is freely soluble in water and in ethanol (96 per cent).

**Adrenaline (epinephrine) (as acid tartrate):** white or greyish-white or light brownish grey, odourless, crystalline powder, which slowly darkens on exposure to air and light. Adrenaline (epinephrine) (as acid tartrate) 1.8 mg is approximately equivalent to 1 mg of adrenaline (epinephrine). It is freely soluble in water and slightly soluble in ethanol (96 per cent).

Adrenaline (epinephrine) (as acid tartrate) is a vasoconstrictor.

4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 injection also contains the excipients with known effect, sodium metabisulfite. For the full list of excipients, see Section 6.1 List of excipients.

#### 3 PHARMACEUTICAL FORM

Articaine hydrochloride and adrenaline (epinephrine) (as acid tartrate) 2.2mL injection solution in a self-aspirating glass cartridge.

The finished product is a clear and colourless solution packed in a carton containing 50, 2.2 mL Type I glass cartridges, closed on one end with a self-aspirating bromobutyl rubber plunger and at the other end by a bromobutyl disk covered by an aluminium cap.

#### 4 CLINICAL PARTICULARS

##### 4.1 THERAPEUTIC INDICATIONS

4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 is indicated for local or regional anaesthesia for both simple and complex dental procedures in adults, adolescents and children 4 years of age and older.

4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 is indicated only for dental procedures.

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## **4.2 DOSE AND METHOD OF ADMINISTRATION**

One or more cartridges should be used on a single patient on one occasion only during each session of treatment. If only a portion of a cartridge is used, the remainder must be discarded.

Administer 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 by submucosal injection.

### **Use in Adults**

Table 1 summarises the recommended volumes and concentrations of 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 for various types of anaesthetic procedures. For most common operations, one infiltration with 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 is sufficient. In all cases, the injection must be done slowly (about 1 mL/min).

For an infiltration in the interdental septum, a quantity of 0.3 to 0.5 mL is generally sufficient. Higher volumes should rarely be required.

MAXIMUM RECOMMENDED DOSE for normal health adults of articaine hydrochloride administered by submucosal infiltration and/or nerve block should not exceed 7 mg/kg of body weight. This corresponds, for a subject weighing 60 kg, to five (5) standard 2.2 mL cartridges (doses of 7 mg/kg were not exceeded in clinical trials). Anaesthesia is obtained rapidly (1 to 6 minutes).

**Table 1. Recommended Dosages in Adults**

<b>Procedure</b>	<b>4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000</b>	
	<b>Volume (mL)</b>	<b>Total dose of articaine hydrochloride (mg)</b>
Infiltration	0.5 – 2.5	20 – 100
Nerve block	0.5 – 3.4	20 – 136
Oral surgery	1.0 – 5.1	40 - 204

The above-suggested volumes serve only as a guide for normal health adults.

Other volumes may be used provided that the total maximum recommended dose is not exceeded.

The duration of the anaesthesia during which an operation can be performed is about one hour (pulpal analgesia) depending on the technique used, and on the procedure.

### **Use in Children**

Safety and effectiveness in paediatric patients below the age of 4 years have not been established. Dosages in paediatric patients (over 4 years) should be reduced, commensurate with age, body weight, and physical condition. Please refer to Table 2 below. Use of 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 in children under 4 years of age is not recommended due to the absence of safety and efficacy data.

MAXIMUM RECOMMENDED DOSE for normal health children must not exceed 7 mg/kg of body weight.

**Table 2. Dosage Adjustments for Use in Children**

	<b>20 Kg child</b>	<b>40 Kg child</b>
<b>Maximum Dose:</b> 0.175 mL/Kg	3.5 mL (i.e. ~1.5 cartridges of 2.2 mL)	7.0 mL (i.e. ~3 cartridges of 2.2 mL)
<b>Recommended dose:</b>		
0.06 mL/kg for simple procedure	1.2 mL (i.e. ≈ ½ cartridge of 2.2 mL)	2.4 mL (i.e. ≈ 1 cartridge of 2.2 mL)
0.07 mL/kg for complex procedure	1.4 mL (i.e. ≈ ½ cartridge of 2.2 mL)	2.8 mL (i.e. ≈ 1 cartridge of 2.2 mL)

### **4.3 CONTRAINDICATIONS**

These may be of the following types:

a) Contraindications to articaine:

- specific allergies to articaine or to other anaesthetics of the amide type,
- hypersensitivity to any local anaesthetic agent.

b) Contraindications to the vasoconstrictor:

- arterial hypertension,
- coronary disease,
- valvular cardiac disease (particularly sequelae to acute rheumatic fever),
- thyrotoxicosis, untreated,
- known sensitivity to sympathomimetic amines.

c) Hypersensitivity to sulfites (sodium metabisulfite is present in the formula as an antioxidant).

d) Injection by intravenous route.

e) Inflammation or sepsis in the region of the proposed injection.

f) Patients who have experienced bronchospasm after administration of any product, which contains sulfites, should not be given 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000.

g) Hypersensitivity to any other component of 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000.

h) Patients who are known or who have a history, which suggests a deficiency in plasma cholinesterase activity (see Section 5.2 Pharmacokinetic Properties).

i) Patients receiving monoamine oxidase inhibitors (or who have received such an agent within two weeks), or tricyclic antidepressants.

j) Patients in whom there is a possibility that general anaesthesia might be required to complete the procedure.

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k) Do not use in children under 4 years of age.

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND RESUSCITATIVE DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS.

Because of the possibility of hypotension and bradycardia following major blocks, an intravenous cannula should be inserted before the local anaesthetic is injected. Delay in proper management of dose-related toxicity, under ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and death.

INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION, WHICH CAN PRODUCE CEREBRAL SYMPTOMS EVEN AT LOW DOSES.

Note, however, that the absence of blood in the syringe does not assure that intravascular injection will be avoided. There should be careful monitoring of cardiovascular and respiratory vital signs after each injection.

Intravascular injection is strictly contraindicated. An accidental injection into a blood vessel may be associated with systemic adverse effects due to the circulating levels of adrenaline (epinephrine) and/or articaine. Therefore, it is imperative to ensure that the needle being used for the injection does not go into a blood vessel.

Since amide-type local anaesthetics are also metabolised by the liver, 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolise local anaesthetics normally, are at greater risk of developing toxic plasma concentration.

Due to the presence of adrenaline (epinephrine), the product is not advised for diabetic subjects and for patients with thyrotoxicosis.

#### **Use with caution in the following circumstances:**

- The lowest dosage that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should also be used with caution in patients with heart block.
- Local anaesthetic solutions containing a vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypersensitive vascular disease may exhibit exaggerated vasoconstrictor response. Ischaemic injury or necrosis may result. 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anaesthetic agents, since cardiac arrhythmias may occur under such conditions.

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- Many drugs used during the conduct of anaesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anaesthetics may trigger this reaction, and since the need for supplemental general anaesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available.
- Solutions containing adrenaline (epinephrine) should be used with caution in patients with hypertension, cardiac disease, and/or cerebrovascular insufficiency.
- Prostatic hypertrophy.
- 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should be administered with caution to subjects with cardiovascular disease, abnormalities of cardiac conduction, or a history of epilepsy.
- 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should not be used in patients with a deficiency of plasma cholinesterase activity.

Systemic absorption of local anaesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal.

However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic 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.

Small doses of local anaesthetics injected in dental blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anaesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should be observed constantly. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded.

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

**Use in hepatic impairment**

*In vitro* studies show that about 5% to 10% of articaine is metabolised 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. 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of atrioventricular (AV) conduction produced by these drugs.

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**Use in the elderly**

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 anaesthetic for complete anaesthesia compared with 11% of patients between 17 and 65 years old who required additional injections. See Section 5.1 Pharmacodynamic Properties – Clinical Trials for description of studies in the Elderly.

**Paediatric use**

4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should not be used in children younger than 4 years of age as safety and effectiveness has not been established in this age group.

See Section 5.1 Pharmacodynamic Properties – Clinical trials for description of studies in children and adolescents (4 years of age to 16 years of age). See also Section 4.2 Dose and Method of Administration.

**Effects on laboratory tests**

No data available.

**4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

No drug interaction studies have been performed.

Due to the possibility that clinically significant increases in circulating adrenaline (epinephrine) concentrations may occur post-injection, 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should be administered with caution to any patient receiving drugs with sympathomimetic properties or with agents whose therapeutic actions may be antagonized by adrenaline (epinephrine).

The administration of local anaesthetic solutions containing adrenaline (epinephrine) to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines may produce severe prolonged hypotension or hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of adrenaline (epinephrine). Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Concurrent administration of vasopressor drugs and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should be administered with caution to patients under the following treatments:

- Hypoglycaemics: adrenaline (epinephrine)-induced hyperglycaemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemics.
- Anti-arrhythmic agents (e.g. procainamide, mexilitine, disopyramide).
- Antiepileptic skeletal muscle relaxant.
- Cardiac glycosides (e.g. digoxin): adrenaline (epinephrine) may interact with cardiac

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glycosides resulting in cardiac arrhythmias.

- Adrenergic neuron blocking agents (e.g. guanethidine) since the product contains adrenaline (epinephrine).
- Quinidine: combination with adrenaline (epinephrine) may lead to cardiac arrhythmias.
- Cimetidine.
- Amiodarone.
- Phenytoin and other antiepileptic drugs such as phenobarbitone, primidone and carbamazepine.
- Inhalational anaesthetics: serious cardiac arrhythmias may occur if preparations containing adrenaline (epinephrine) are employed in patients following the administration of inhalational anaesthetics.
- Beta adrenoreceptor antagonists - Propranolol and metoprolol, timolol. Administration of adrenaline (epinephrine) may result in dose-dependent hypertension and bradycardia with possible heart block.
- Thyroid hormones: may potentiate the actions of adrenaline (epinephrine).

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

No effects on male or female fertility were observed in rats given articaine hydrochloride with adrenaline (epinephrine) subcutaneously from prior to mating until mating (males) or early gestation (females) at doses up to 80 mg/kg/day (approximately twice the maximum recommended human dose on a mg/m<sup>2</sup> basis).

### **Use in pregnancy**

Category B3

#### **[Definitions of the Australian categories for prescribing medicines in pregnancy for Category B3**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.]

No clinical experience of the use in pregnancy and lactating women is available. Safe use of local anaesthetics during pregnancy has not been established with respect to adverse effects on fetal development. The product should only be used in pregnancy when the benefits are considered to outweigh the risks.

No effects on embryofetal development were observed when articaine hydrochloride with adrenaline (epinephrine) was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg/day in rabbits and 80 mg/kg/day in rats (approximately 2 times the

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maximum recommended human dose on a mg/m<sup>2</sup> basis). In rabbits, fetal death and increased fetal skeletal variations were observed at the maternotoxic dose of 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m<sup>2</sup> basis).

When articaine hydrochloride alone was administered subcutaneously to rats throughout gestation and lactation, 80 mg/kg/day (approximately 2 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) increased the number of stillbirths, delayed eye opening, and adversely affected passive avoidance, a measure of learning, in pups, along with maternal toxicity were observed. A dose of 40 mg/kg/day (approximately the maximum recommended human dose on a mg/m<sup>2</sup> basis) did not produce these effects. A similar study using articaine hydrochloride with adrenaline (epinephrine) produced maternal toxicity, but no effects on the offspring.

**Use in lactation**

The excretion of articaine or its metabolites in human milk is unknown. As many drugs are excreted in human milk, caution should be exercised when 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 is administered to a nursing woman. If administered, nursing women should not breast feed for at least 48 hours following anaesthesia with 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000.

For effects of articaine hydrochloride in rat pups being suckled. See Section 4.6 Fertility, Pregnancy and Lactation – Use in pregnancy.

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

In a controlled study on healthy volunteers articaine was shown to have no effect on the level of attentiveness, reaction time to visual stimulations or motor co-ordination.

Patients who experience systemic adverse effects during or immediately following administration of 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 should be advised to avoid driving or operating machinery until resolution of signs or symptoms.

**4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

Articaine and adrenaline (epinephrine) may reach sufficient concentrations in blood to provoke systemic adverse effects. Reactions to 4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 are characteristic of those associated with other amide-type local anaesthetics. 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.

**Adverse Reactions from Clinical Trials:**

The reported adverse events are derived from clinical trials in the US and UK.

Of the 1,325 patients treated in the primary clinical trials, 882 were exposed to articaine hydrochloride 4% (40 mg/mL) with epinephrine (adrenaline) 1:100,000 injection.



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**Table 3. Adverse events in controlled trials with an incidence of 1% or greater in patients administered articaine hydrochloride 4% (40 mg/mL) with epinephrine (adrenaline) 1:100,000 injection**

Body system	Articaine hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection N (%)
<b>Number of Patients</b>	882 (100%)
<b>Body as a whole</b>	
Face oedema	13 (1%)
Headache	31 (4%)
Infection	10 (1%)
Pain	114 (13%)
<b>Digestive system</b>	
Gingivitis	13 (1%)
<b>Nervous system</b>	
Paraesthesia	11 (1%)

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

- *Body as a Whole* - abdominal pain, accidental injury, asthenia, back pain, injection site pain, malaise, neck pain.
- *Cardiovascular System* - hemorrhage, migraine, syncope, tachycardia.
- *Digestive System* - constipation, diarrhea, dyspepsia, glossitis, gum hemorrhage, mouth ulceration, nausea, stomatitis, tongue edemas, tooth disorder, vomiting.
- *Hemic and Lymphatic System* - ecchymosis, lymphadenopathy.
- *Metabolic and Nutritional System* - edema, thirst.
- *Musculoskeletal System* - arthralgia, myalgia, osteomyelitis.
- *Nervous System* - dizziness, dry mouth, facial paralysis, hyperesthesia, increased salivation, nervousness, neuropathy, paresthesia, somnolence.
- *Respiratory System* - pharyngitis, rhinitis.
- *Skin and Appendages* - pruritis, skin disorder.
- *Special Senses* - ear pain, taste perversion.
- *Urogenital System* - dysmenorrhea.

**Adverse Reactions Due to Articaine:**

Toxic reactions (showing an abnormally high concentration of local anaesthetic in the blood) may appear either immediately, by accidental intravascular injection or later, by true overdose following an injection of an excessive quantity of anaesthetic solution.

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Symptoms include:

- *Symptoms showing effects on the central nervous system:* nervousness, shaking, yawning, trembling, apprehension, nystagmus, logorrhoea, headache, nausea, buzzing in the ears. These signs, when they appear, require rapid corrective measures to prevent possible worsening.
- *Respiratory symptoms:* tachypnoea, then bradypnoea, which could lead to apnoea.
- *Cardiovascular signs:* reduction in the contractile power of the myocardium, lowering of heart rate and drop in blood pressure.

**Common  $\geq 1\%$  and  $<10\%$**

Headache, facial oedema, gingivitis.

Disruption of nerve transmission (para-, hypo- and dysaesthesia) may appear after articaine administration. Resolution usually occurs within two weeks.

**Uncommon  $\geq 0.1\%$  and  $<1\%$**

Nausea

**Other Adverse Reactions:**

Serious adverse experiences following the administration of articaine are similar in nature to those observed with other amide local anaesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption, unintended intravascular injection or may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature.

The following types are those most commonly reported:

- *Central nervous system:* CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, agitation, difficulty in swallowing and slurred speech, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest which are less common.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

- *Cardiovascular system:* Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest. Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position.

Less commonly, they may result from a direct effect of the drug. Failure to recognize the premonitory signs such as sweating, a feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and seizure or serious cardiovascular catastrophe. Management consists of placing the patient in the recumbent position and ventilation with oxygen. Supportive treatment of circulatory depression may require the administration of intravenous fluids and resuscitative

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drugs as directed by the clinical situation.

- *Hypersensitivity:* One may observe manifestations of hypersensitivity to articaine as rash, pruritis, urticaria or anaphylaxis.

The administration of large doses of articaine may produce methaemoglobinaemia in patients with subclinical methaemoglobinaemia.

- *Allergic reactions:* Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions.
- *Allergic reaction to sulfites:* Allergic-type reactions may occur in patients with bronchial asthma due to hypersensitivity to the sulfite component and may be manifested by dermatologic reactions, oedema, urticaria and other allergy symptoms.

### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

## 4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) and 0800 764 766 (New Zealand).

The most serious effects of articaine intoxication are on the CNS and cardiovascular system. The type of toxic reaction is unpredictable and depends on such factors as dosage, rate of absorption, and clinical status of the patient. Two types of reactions that effect stimulation and/or depression of the central cortex and medulla may result from systemic absorption.

### Symptoms

Slow onset symptoms following overdose include stimulation leading to nervousness, dizziness, blurred vision, nausea, tremors, convulsions, hypotension, cardiovascular depression, and respiratory arrest.

Rapid onset symptoms following overdose include depression, leading primarily to respiratory arrest, cardiovascular collapse, and cardiac arrest. Since cardiac arrest symptoms may occur rapidly and with little warning, treatment should be readily available.

### Treatment of overdose

*For all symptoms:* If acute toxicity occurs the injection should be stopped immediately. A patent airway should be established and maintained, oxygen should be administered, and assisted or controlled ventilation should be provided as required.

*Circulatory collapse:* toxic cardiovascular reactions can include peripheral vasodilation, hypotension, bradycardia and cardiac arrest. Immediately resuscitate with oxygen and commence cardiovascular resuscitation procedures as appropriate.

*Convulsions:* Appropriate medication for the management of convulsions should be used. If not treated immediately, both convulsions and cardiovascular depression may result in

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hypoxia, acidosis, bradycardia, arrhythmia and cardiac arrest.

Supportive treatment should be given; standard cardiopulmonary resuscitative therapy, including respiratory support may be required to counter adverse effects on the cardiovascular and/or respiratory systems and to control convulsions. There is no specific antidote.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

Articaine is a local anaesthetic of the amide type. Preclinical pharmacodynamic studies show that the mechanism of action of articaine is similar to that of other commonly used anaesthetics (lidocaine, procaine, prilocaine). Inhibition of the generation and the conduction of the action potential but no change in resting potential is shown.

Articaine blocks sodium channels and, with lower sensitivity, potassium channels at neutral pH. Inhibition of muscle activation after nerve stimulation and depression of cardiac electrophysiologic measurements demonstrate that articaine has the same pharmacologic activities as other local anaesthetics. When injected close to sensitive nerve filaments, articaine has the reversible effect of blocking the conduction of painful sensations.

Adrenaline (epinephrine) added to the solution reduces bleeding during surgery, slows down the passage of articaine into the general circulation and thus ensures the prolonged maintenance of an active tissue concentration.

Adrenaline (epinephrine) acts on both adrenergic receptors of tissue innervated by sympathetic nerves, except for the sweat glands and arteries of the face. It is the most important alpha receptor activator. Adrenaline (epinephrine) stimulates the heart to increase output, raises the systolic blood pressure, lowers the diastolic blood pressure, relaxes bronchial spasm and mobilises liver glycogen, resulting in hyperglycaemia and possibly glycosuria.

The mean time to onset of anaesthesia after administration of articaine 4% with adrenaline (epinephrine) 1:100,000 is about 3.5 minutes with a range of 1 to 6 minutes, and the mean duration of anaesthesia is about 68 minutes with a range of 20 to 175 minutes. The pulpal analgesia lasts 75 minutes and the bleeding during surgery is significantly reduced.

#### **Clinical trials**

Three randomized, double-blind, active-controlled studies were designed to evaluate the effectiveness of articaine hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection as a dental anaesthetic. A total of 882 patients received articaine hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection. Of these, 7% were between 4 and 16 years old, 87% were between 17 and 65 years old, and 6% were at least 65 years old. In addition, 53% of patients were female and 47% were male, with a racial/ethnic distribution of 73% white, 11% Hispanic, 8% black, 5% Asian and 3% 'other' races/ethnicities.

These patients underwent simple dental procedures, single apical resections and single crown procedures, and complex dental procedures such as multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures on the bone.

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Articaine hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection was administered as submucosal infiltration and/or nerve block. Efficacy was measured immediately following the procedure by having the patient and investigator rate the patient's procedural pain using a 10 cm visual analog scale (VAS), in which a score of zero represented no pain, and a score of 10 represented the worst pain imaginable.

Mean patient and investigator VAS pain scores were 0.3 - 0.4 cm for simple procedures and 0.5 - 0.6 cm for complex procedures. These values are summarized in Table 4 below.

**Table 4. Summary of VAS Pain Scores**

	<b>Articaine HCl 4% with adrenaline (epinephrine) (as acid tartrate) 1:100,000</b>	
	<b>Simple procedures</b>	<b>Complex procedures</b>
Number of patients	674	207
Investigator score (cm)		
Mean	0.3	0.5
Median	0.0	0.2
Range	0 – 9.0	0 – 7.3
Patient score (cm)		
Mean	0.4	0.6
Median	0.0	0.2
Range	0 – 8.0	0 – 8.7

In clinical trials, 61 paediatric patients between the ages of 4 and 16 years received articaine hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection. Among these paediatric 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 hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection at doses greater than 7.00 mg/kg in order to assess its safety in paediatric patients. No unusual adverse events were noted in these patients. Approximately 13% of these paediatric patients required additional injections of anaesthetic for complete anaesthesia.

In the clinical trials 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received articaine hydrochloride 4% with adrenaline (epinephrine) 1:100,000 injection. Among all patients between 65 and 75 years, doses from 0.43 mg/kg to 4.76 mg/kg (0.9 to 11.9 mL) were administered safely to 35 patients for simple procedures and doses from 1.05 mg/kg to 4.27 mg/kg (1.3 to 6.8 mL) were administered safely to 19 patients for complex procedures. Among the 11 patients ≥ 75 years old, doses from 0.78 mg/kg to 4.76 mg/kg (1.3 to 11.9 mL) were administered safely to 7 patients for simple procedures and doses of 1.12 mg/kg to 2.17 mg/kg (1.3 to 5.1 mL) were administered to 4 patients for complex procedures.

## **5.2 PHARMACOKINETIC PROPERTIES**

### **Absorption**

Following dental injection by the submucosal route of a 4% articaine solution containing 1:200,000 adrenaline (epinephrine), articaine reaches peak blood concentration about 25

**Product Information**

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minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 minutes and 204 mg doses are 385 and 900 ng/mL, respectively.

**Distribution**

Approximately 60 to 80% of articaine hydrochloride is bound to human serum albumin and  $\gamma$ -globulins at 37°C in vitro.

**Metabolism**

Articaine hydrochloride is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid which is inactive. Articainic acid concentration reaches its peak about 30 to 60 minutes following the peak in articaine concentration. *In vitro* studies show that the human liver microsome P450 isoenzyme system metabolises approximately 5% to 10% of the available articaine with nearly quantitative conversion to articainic acid.

**Excretion**

The elimination half-life of articaine is about 1.8 hours and that of articainic acid is about 1.5 hours. Articaine is excreted primarily through urine with 53 - 57% of the administered dose eliminated in the first 24 hours following submucosal administration. Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide, is also excreted in urine. Articaine constitutes only 2% of the total dose in excreted urine.

**Special Populations**

Effect of Age: No pharmacokinetic data is available in the following populations: elderly, children.

Race: No pharmacokinetic data is available for different racial groups.

Renal and Hepatic Insufficiency: No pharmacokinetic data is available for patients with hepatic or renal impairment.

**5.3 PRECLINICAL SAFETY DATA**

**Genotoxicity**

Articaine was negative in bacterial and mammalian assays for gene mutation and a chromosomal aberration test in Chinese hamster ovary cells. *In vivo* clastogenicity (mouse micronucleous) assays with articaine alone and with adrenaline (epinephrine) were negative at a low subcutaneous dose (same as the maximal recommended clinical dose on a mg/m<sup>2</sup> basis).

**Carcinogenicity**

Studies to evaluate the carcinogenic potential of articaine hydrochloride in animals have not been conducted.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 LIST OF EXCIPIENTS**

4% Articadent DENTAL with Adrenaline (epinephrine) 1:100,000 injection contains the excipients sodium chloride, sodium metabisulfite, water for injection. Hydrochloric acid

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and/or sodium hydroxide may be present and are used to adjust the pH of the solution during manufacture.

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light. Do not freeze.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Each carton consists of 50 x 2.2 mL Type I glass cartridges.

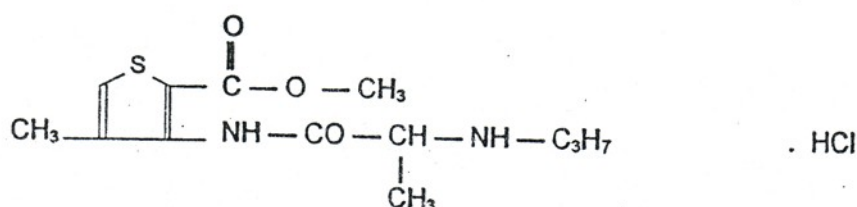
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Chemical structure of articaine hydrochloride



Chemical name: Articaine hydrochloride: Methyl 4-methyl-3-[

[(2RS)-2-(propylamino)propanoyl]amino]-thiophene-2-carboxylate hydrochloride

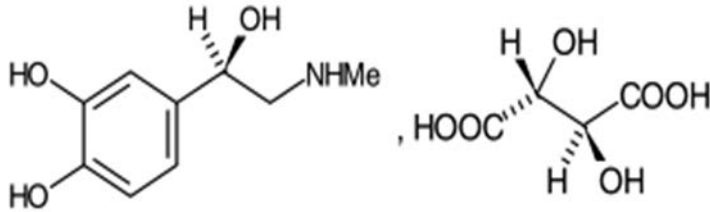
Molecular formula: C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S.HCl

Molecular weight: 320.84

**Product Information**

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Chemical structure of adrenaline (epinephrine) acid tartrate



Chemical name: Adrenaline (epinephrine) acid tartrate: (1*R*)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)ethanol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate

Molecular formula: C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>.C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>

Molecular weight: 333.3

**CAS number**

Articaine hydrochloride: 23964-57-0

Adrenaline (epinephrine) acid tartrate: 51-42-3

**7 MEDICINE SCHEDULE (POISONS STANDARD)**

S4 - Prescription Only Medicine

New Zealand Medicine Classification: Prescription Medicine

**8 SPONSOR**

**Australia**

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**9 DATE OF FIRST APPROVAL**

22 October 2015

**10 DATE OF REVISION**

29 August 2018



Articadent is a registered trademark of DENTSPLY International Inc.

**SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
All sections	<ul style="list-style-type: none"><li>• Updated PI format according to the new requirements</li><li>• Updated expression of the Drug Product and Drug Substance to ensure consistency of the ingredient name with the Australian Approved Name for therapeutic substances</li></ul>
Section 8	Updated sponsor information