# 1 PRODUCT NAME

UBISTESIN 1/200 000 solution for injection

UBISTESIN FORTE 1/100 000 solution for injection

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amount per 1.7 mL cartridge

| **Component** | **Ubistesin 1/200 000** | **Ubistesin Forte 1/100 000** |
|---|---|---|
| **Active ingredients:** | | |
| Articaine hydrochloride | 68 mg | 68mg |
| Adrenaline (epinephrine) hydrochloride<br>*Equivalent to adrenaline (epinephrine)* | 0.0102 mg<br><br>*0.0085 mg* | 0.0204 mg<br><br>*0.017 mg* |
| **Excipients with known effect:** | | |
| Sodium chloride | 1.91 mg | 1.91 mg |
| Sodium sulfite | 1.02 mg | 1.02 mg |

The cartridges contain sodium sulfite as an antioxidant and are free from preservatives.
For a full list of excipients, see section 6.1

# 3 PHARMACEUTICAL FORM

UBISTESIN and UBISTESIN FORTE are sterile isotonic aqueous solutions for injection. The solution is a clear, not opalescent, colourless solution, practically free from visible particles with a pH value of 3.6-4.4.

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

Infiltration anaesthesia and nerve block anaesthesia in dentistry.

UBISTESIN FORTE is especially indicated for more complex dental procedures requiring prolonged anaesthesia.

UBISTESIN and UBISTESIN FORTE must not be used in children under the age of 4 years.

## 4.2 Dose and method of administration

UBISTESIN and UBISTESIN FORTE are exclusively for use in dentistry.

The following dosage instructions apply:

The smallest possible volume of solution that will lead to effective anaesthesia should be used.

Adults:
For extraction of maxillary teeth, 1.7mL UBISTESIN or UBISTESIN FORTE per tooth suffices in most cases, thereby avoiding painful palatal injections. A smaller injection volume is often possible for serial extractions of neighbouring teeth.

If a cut or suture is required in the palate, a palatal injection of approximately 0.1mL per puncture is indicated.

For uncomplicated extractions of mandibular premolar teeth, infiltration anaesthesia of 1.7mL UBISTESIN or UBISTESIN FORTE per tooth is mostly sufficient; in single cases a buccal re-injection of 1 to 1.7mL is required. In rare cases an injection into the mandibular foramen can be indicated. Vestibular injections of 0.5-1.7mL per tooth enable cavity and crown stump preparations.

In surgical procedures, UBISTESIN FORTE should be dosed individually depending on the extent and duration of the operation and factors relating to the patient.

Nerve-block anaesthesia should be used in the treatment of mandibular molar teeth.

Special populations:
*Elderly population:* Increased plasma levels can occur in older patients due to diminished metabolic processes and lower distribution volume. The risk of accumulation is increased, in particular, after repeated administration (eg re-injection). Dosages should be reduced from adult recommendations, taking into consideration any cardiac or liver disease (*see section 4.4 Special warnings and precautions for use*).

*Patients with hepatic impairment:* Articaine is also metabolised by the liver. Lower doses of articaine may be required in patients with hepatic dysfunction due to prolonged effects and systemic accumulation (*see Section 4.4 Special warnings and precautions for use*).

*Patients with renal impairment:* Articaine and its metabolites are mainly eliminated in urine. Lower doses of articaine may be required in patients with severe renal dysfunction due to prolonged effects and systemic accumulation (*see Section 4.4 Special warnings and precautions for use*).

*Patients with particular genotype:* In patients who are known to have an inborn or acquired deficiency in plasma cholinesterase activity, the use of UBISTESIN and UBISTESIN FORTE is contraindicated (*see Section 4.3 Contraindications).*

*Other relevant special populations:* The dose should also be reduced where the general condition of the patient is poor, in patients with certain pre-existing diseases (angina pectoris, arteriosclerosis (see Section 4.3 *Contraindications* and Section 4.4 *Special Warnings and precautions for use*) and patients concurrently taking medications known to interact with articaine and/or adrenaline (epinephrine) (see Section 4.4 *Special warnings and precautions for use and* Section 4.5 *Interaction with other medicines and other forms of interaction)*.

Dose recommendation for special populations:
A lower dosage range is recommended in all such cases (i.e. minimum volume of UBISTESIN or UBISTESIN FORTE for sufficient anaesthetic effect).

Paediatric population:
UBISTESIN and UBISTESIN FORTE is contraindicated in children aged below 4 years (see Section 4.3 *Contraindications*).
The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation.
Generally, in children weighing about 20-30kg, doses of 0.25-1mL are sufficient; and in children weighing 30-40kg, 0.5-2mL. UBISTESIN and UBISTESIN FORTE must not be used in children under the age of 4 years.

Maximum Recommended Dosage

*Adults*: For healthy adults the maximum dose is 7mg/kg body weight articaine (500mg for a 70kg patient), equivalent to 12.5mL UBISTESIN or UBISTESIN FORTE. The maximum dose represents 0.175mL of solution per kg of body weight.

*Children*: The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 7mg articaine/kg (0.175mL/kg) of body weight.

UBISTESIN FORTE may be more appropriate for procedures of longer duration and when there is a risk of significant bleeding into the operative field (see *Section 5.1 Pharmacodynamics* for information on duration of analgesia). The duration of anaesthesia during which an operation can be performed using UBISTESIN FORTE is up to 75 minutes.

Method of Administration

**For injection / oromucosal use in dental anaesthesia only**.

To avoid intravascular injection, aspiration control in at least two planes (rotation of the needle by 180$^{o}$) must always be carefully undertaken, although a negative aspiration result does not rule out an unintentional and unnoticed intravascular injection.

The injection rate should not exceed 0.5mL in 15 seconds ie 1 cartridge per minute.

Major systemic reactions resulting from accidental intravascular injection can in most cases be avoided by the injection technique: after aspiration slow injection of 0.1-0.2mL followed by slow injection of the remainder no sooner than 20-30 seconds later.

Opened cartridges must not be used in other patients. Residues must be discarded (See section 6.6 *Special precautions for disposal)*.

## 4.3 Contraindications

*UBISTESIN and UBISTESIN FORTE must not be used in:*

- children under the age of 4 years
- hypersensitivity to any ingredients. In general, patients with demonstrated hypersensitivity to articaine and other amides should receive an ester-group local anaesthetic for subsequent procedures.

Due to the local anaesthetic ingredient articaine, do not use in the event of:

- known allergy or hypersensitivity to local anaesthetics of the amide type;
- severe, uncontrolled or untreated excitation and conduction disorders of the heart (eg grade II and III AV block, pronounced bradycardia);
- acutely decompensated cardiac insufficiency;
- severe hypotension;
- patients who are known to have a deficiency in plasma cholinesterase activity also drug induced forms;
- haemorrhagic diatheses, particularly with nerve-block anaesthesia.

Do not inject into inflamed or infected areas. The reduced penetration of articaine into inflamed tissue can result in failure of anaesthesia.

Due to the content of adrenaline (epinephrine) as a vasoconstrictor admixture, do not use in the event of:

- heart disease such as
  - unstable angina pectoris
  - recent myocardial infarction
  - recent coronary artery bypass surgery
  - refractory arrhythmias and paroxysmal tachycardia or high-frequency continuous arrhythmia
  - untreated or uncontrolled hypertension
  - untreated or uncontrolled congestive heart failure;
- concomitant treatment with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants (see *Section 4.5 Interaction with other medicines and other forms of interaction).*
- thyrotoxicosis, untreated

Do not use in acra of extremities.

UBISTESIN and UBISTESIN FORTE must not be used in persons who are allergic or hypersensitive to sulfite, as well as in persons with severe bronchial asthma. UBISTESIN and UBISTESIN FORTE can provoke acute allergic reactions with anaphylactic symptoms (eg bronchospasm).

## 4.4 Special warnings and precautions for use

Use with particular caution in the event of:

- severe impairment to renal function;
- angina pectoris (see *Section 4.2 Dose and method of administration* and *Section 4.3 Contraindications)*;
- arteriosclerosis;
- considerably impaired blood coagulation or concomitant treatment with anticoagulants or platelet aggregation inhibitors, the overall risk of bleeding is increased;
- uncontrolled or untreated hyperthyroidism
- narrow-angle glaucoma;
- diabetes mellitus;
- lung diseases, particularly allergic asthma;
- pheochromocytoma.

Since amide-type local anaesthetics are metabolised in the liver, use 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 levels.

Administer with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Administer with caution to patients with a history of epilepsy.

There is the possibility of a positive doping test result.

This medicinal product contains less than 1 mmol (23 mg) sodium per 1.7 ml, i.e. essentially ‘sodium free’.

Precautions for use

The patient should be advised to exert caution to avoid inadvertent trauma to the lips, tongue, cheek mucosa or soft palate while these structures are anaesthetised. The patient should therefore avoid eating until the anaesthetic has worn off.

In the case of cavity or crown preparations, the risk of overlooking an opened pulp must be taken into account since adrenaline (epinephrine) reduces blood flow in the pulp tissue.

Avoid inadvertent intravascular injection (see *Section 4.2 Dose and method of administration).*

Accidental intravenous injection may be associated with convulsions, followed by central nervous system or cardiorespiratory arrest (see Section 4.9 *Overdose)*.

Dental practitioners who use local anaesthetic agents should be well versed in diagnosis and management of emergencies which may arise from their use.

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use.

Before a local anaesthetic is used the following drugs/therapy as well as an indwelling venous cannula set should be available: anti-convulsant medicines (benzodiazepines or barbiturates), myorelaxants, glucocorticoids, atropine and vasopressors or adrenaline (epinephrine) for a severe allergic or anaphylactic reaction; resuscitating equipment (in particular a source of oxygen) enabling artificial ventilation if necessary.

Cardiovascular and respiratory (adequate oxygen supply) vital signs and the patient's state of consciousness should be carefully and constantly monitored after each local anaesthetic injection. Restlessness, anxiety, tinnitus, dizziness, blurred vision, visual disturbances, tremors, depression or drowsiness may be early signs of central nervous system toxicity and require rapid corrective measures to prevent possible worsening (see *Section 4.9 Overdose*).

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

## 4.5 Interaction with other medicines and other forms of interaction

*Interactions affecting the use of this medicinal product:*

- Contraindications of concomitant use:
  Patients taking MAO inhibitors or tricyclic antidepressants
  The sympathomimetic effect of adrenaline (epinephrine) can be intensified by the simultaneous intake of MAO inhibitors or tricyclic antidepressants (see *Section 4.3 Contraindications).*

- Concomitant use is not recommended in:
  Patients taking non-selective beta-blockers
  The concomitant administration of non-cardioselective beta-blockers can lead to an increase in blood pressure and bradycardia due to the adrenaline (epinephrine) in UBISTESIN and UBISTESIN FORTE.

  Patients taking phenothiazines:
  Phenothiazines may reduce or reverse the pressor effect of adrenaline (epinephrine). Concurrent use of these agents should generally be avoided. In situations where concurrent therapy is necessary, careful patient monitoring is essential.

  Concurrent administration of vasopressors and ergot-type oxytocic medicines may cause severe, persistent hypertension or cerebrovascular accidents.

  Inhalation anaesthetics:
  Certain inhalational anaesthetics, such as halothane, can sensitise the heart to catecholamines and therefore induce arrhythmias following administration of UBISTESIN or UBISTESIN FORTE.

The use of UBISTESIN or UBISTESIN FORTE during or following treatment with general anaesthesia administered by inhalation should be avoided, if possible.

Precautions including dose adjustment:
Local anaesthetics
Caution is advised if articaine with adrenaline (epinephrine) is used concurrently with other local anaesthetics. The toxic effects of local anaesthetics is additive.

Cross-reactivity to articaine has been reported in a patient with delayed hypersensitivity to prilocaine.

Thyroid hormones may potentiate the actions of adrenaline (epinephrine).

Administer with caution to patients under the following treatments: adrenergic neuron blocking agents (eg guanethidine), quinidine, amiodarone, procainamide, mexiletine, disopyramide, digoxin, cimetidine, antiepileptic skeletal muscle relaxants, phenytoin, phenobarbitone, primidone and carbamazepine.

*Interactions resulting in clinically relevant changes in the use of other medicinal products:*

- Concomitant use is not recommended in:
  Patients taking oral antidiabetics
  Adrenaline (epinephrine) can inhibit insulin release in the pancreas and thus diminish the effect of oral anti-diabetics.

*Paediatric population:*
No significant differences can be expected between the adult and paediatric populations with regards to drug interactions.

## 4.6 Fertility, pregnancy and lactation

*Fertility:*
No effects on male or female fertility were observed in rats given articaine hydrochloride with adrenaline 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$^2$ basis).

*Pregnancy:*
No clinical experience of use in pregnant and lactating women is available.
Safe use of local anaesthetics during pregnancy with respect to adverse effects on foetal development has not been established. Caution should be exercised when prescribing to pregnant women. The medicine should only be used if the expected benefit to the patient outweighs the risk to the foetus.

*Breast-feeding:*

The excretion of articaine and its metabolites in human milk is unknown. It is unknown whether adrenaline (epinephrine) is excreted into the human milk.
Preclinical safety data suggests that the amount of articaine in breast milk does not reach clinically relevant levels.
A decision as to whether to continue or discontinue breast feeding or to continue or discontinue therapy with UBISTESIN or UBISTESIN FORTE should be made taking in to account the benefit of breast feeding to the child and the benefit of therapy to the women. Following anaesthesia with UBISTESIN or UBISTESIN FORTE, it is recommended that nursing mothers express and discard the first mother's milk following anaesthesia with articaine.

## 4.7 Effects on ability to drive and use machines

Although trial patients have shown no impairment of their normal reactions when driving, possible impairment on the ability to drive or operate machinery should be assessed. The physician must decide on an individual basis whether the patient may drive or operate machinery. The patient should not leave the dental surgery earlier than at least 30 minutes after the injection.

## 4.8 Undesirable effects

a) Summary of the safety profile:
Adverse reactions following the administration of articaine / adrenaline (epinephrine) are similar to those observed with other local amide anaesthetics / vasoconstrictors. These adverse reactions are, in general, dose-related. They may also result from hypersensitivity, idiosyncrasy, diminished tolerance by the patient or unintentional intravascular injection. Nervous system disorders, local injection site reactions, hypersensitivity, cardiac disorders and vascular disorders are the most frequently occurring adverse reactions.

Serious adverse reactions are generally systemic. Early symptoms and signs of CNS toxicity include metallic taste, tinnitus, lightheadedness and confusion, followed by tremors and shivering. Seizures and cardiorespiratory arrest may ultimately occur (see Section 4.9 *Overdose*).

b) Tabulated list of adverse reactions
The reported adverse reactions come from spontaneous reporting, clinical studies and literature.

The frequencies classification follows the convention: Very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). "Not known" indicates the frequency cannot be estimated from the available data

| MedDRA System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Immune System Disorders | Rare | Angioedema (face / tongue / lip / throat/ larynx / periorbital oedema)<br>Bronchospasm / asthma<br>Allergic[1], anaphylactic / anaphylactoid reactions<br>Urticaria |
| | Not known | Hypersensitivity Type I hypersensitivity, anaphylactic shock, |
| Psychiatric Disorders | Rare | Nervousness / anxiety |
| | Not Known | Euphoric mood |
| Nervous System Disorders | Common | Neuropathy:<br>Neuralgia (neuropathic pain)<br>Hypoaesthesia / numbness (oral and perioral)<br>Hyperaesthesia<br>Dysaesthesia (oral and perioral), including<br>Dysgeusia (e.g., taste metallic, taste disturbance)<br>Ageusia<br>Allodynia<br>Thermohyperaesthesia<br>Presyncope, syncope<br>Headache<br>Restlessness, agitation<br>Confusional state, disorientation<br>Dizziness (lightheadedness)<br>Tremor |
| | Uncommon | Burning sensation |
| | Rare | Deep CNS depression:<br>Loss of consciousness<br>Coma<br>Convulsion (including tonic-clonic seizure)<br>Facial nerve disorder[2] (palsy, paralysis and paresis)<br>Speech disorder (e.g., dysarthria, logorrhea)<br>Vertigo<br>Balance disorder (disequilibrium)<br>Somnolence (Drowsiness) |

| MedDRA System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| | | Nystagmus, peripheral neuropathy |
| | Very Rare | Paraesthesia[3] (persistent hypoaesthesia and gustatory loss) after mandibular or inferior alveolar nerve blocks |
| | Not known | Depressed level of consciousness, hypergeusia, hypotonia, VIth nerve paralysis, IVth nerve paralysis, sensory disturbance |
| Eye Disorders | Rare | Horner's syndrome (eyelid ptosis, enophthalmos, miosis).<br>Diplopia (paralysis of oculomotor muscles)<br>Visual impairment (temporary blindness)<br>Ptosis, Blepharospasm<br>Miosis<br>Enophthalmos<br>Mydriasis<br>Blurred vision<br>Accommodation disorder |
| | Not known | Visual acuity reduced |
| Ear and labyrinth Disorders | Uncommon | Vertigo, ear pain |
| | Rare | Hyperacusis<br>Tinnitus |
| Cardiac Disorders | Common | Bradycardia<br>Tachycardia |
| | Rare | Palpitations<br>Cardiac arrest<br>Myocardial depression<br>Tachyarrhythmia (including ventricular extrasystoles and ventricular fibrillation)<br>Angina pectoris |
| | Not known | Conduction disorders (atrioventricular block, ventricular arrhythmias) |
| Vascular disorders | Common | Hypotension (with possible circulatory collapse)<br>Pallor |

| MedDRA System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| | Uncommon | Hypertension |
| | Rare | Hot flush, haemorrhage |
| | Not known | Vasodilatation<br>Vasoconstriction |
| Respiratory, thoracic and mediastinal disorders | Rare | Apnoea (respiratory arrest)<br>Dyspnoea[2]<br>Hypoxia<br>Hypercapnia<br>Bradypnoea<br>Tachypnoea<br>Yawning, Sinus Congestion |
| | Not known | Dysphonia (Hoarseness)[1]<br>Respiratory depression, Laryngeal oedema, Pharyngeal Oedema, Pulmonary Oedema |
| Gastrointestinal disorders | Common | Gingivitis<br>Swelling of tongue, lip, gums |
| | Uncommon | Stomatitis, glossitis<br>Nausea, vomiting, diarrhoea |
| | Rare | Gingival / oral mucosal exfoliation (sloughing) /<br>Ulceration, abdominal pain, cheilitis, constipation, dry mouth, dyspepsia, salivary hypersecretion, sensitivity of teeth |
| | Not known | Dysphagia, mouth oedema, oral paraesthesia |
| Skin and subcutaneous tissue disorders | Uncommon | Rash (eruption)<br>Pruritus, hyperhidrosis |
| | Not known | Erythema, angioedema, |
| Musculoskeletal | Uncommon | Neck pain |
| | Rare | Muscle twitching<br>Chills (shivering), back pain, muscle tightness, trismus |
| | Not known | Aggravation of the neuromuscular manifestations in Kearns-Sayre syndrome, osteonecrosis |
| General disorders and administration site conditions | Common | Pain, tenderness, swelling |
| | Uncommon | Injection site pain, face oedema, injection site |

| MedDRA System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| | | swelling, injection site haematoma |
| | Rare | Injection site exfoliation/necrosis, Fatigue, malaise, asthenia (weakness), chills, thirst |
| | Not known | Local swelling, post-operative swelling, feeling hot, feeling cold, mucosal inflammation, mucosal oedema |
| Investigations | Uncommon | Blood pressure decreased, heart rate increased, blood pressure increased |
| | Rare | ECG signs of myocardial ischaemia, abnormal vital functions, positive allergy test |
| | Not known | Blood pressure immeasurable, heart rate decreased |
| Injury, poisoning and procedural complications | Common | Procedural pain |
| | Rare | Accidental injury, mouth injury, incorrect route of drug administration, nerve injury |
| | Not known | Gingival injury, wound complication, Vth nerve injury |

**c) Description of selected adverse reactions**

[1] Allergic reactions should not be mistaken with syncopal episodes.

[2] A 2 week delay in the onset of facial paralysis has been described following administration of articaine combined with adrenaline (epinephrine), and the condition was unchanged 6 months later.

[3] These neural pathologies may occur with various symptoms of abnormal sensations. Paraesthesia can be defined as spontaneous abnormal usually non-painful sensations (e.g., burning, pricking, tingling or itching) well beyond the expected duration of anaesthesia. Most cases of paraesthesia reported following dental treatment are transient and resolve within days, weeks or months.

Persistent paraesthesia, mostly following nerve blocks in the mandible, is characterised by slow, incomplete, or lack of recovery. The risk of nerve damage is

likely to be greater if repeated injections are given into a previously anaesthetized site or if higher concentration local anaesthetic solutions are administered.

Symptoms and signs of depressed cardiovascular function may result from a vasovagal reaction, particularly if the patient is in upright position.

**d) Paediatric population**

The safety profile was similar in children and adolescents from 4 to 18 years old compared to adults. However, accidental soft tissue injury was observed more frequently, especially in 3 to 7 year old children, due to the prolonged soft tissue anaesthesia.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

## 4.9 Overdose

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.

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:**

*For all symptoms.* If acute toxicity occurs the injection should be stopped immediately. A patient 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 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, ATC code N01B B58
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 electrophysiological measurements demonstrate that articaine has the same pharmacological 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.

Complete anaesthesia can be achieved within 1-3 minutes of administration. The mean duration of effect in pulpal anaesthesia is 48-54 minutes for UBISTESIN and at least 75 minutes for UBISTESIN FORTE. For surgical interventions in soft tissue the mean duration of effect is 120-240 minutes.

Clinical efficacy and safety:

**Clinical trials**
Three randomised, double blind, active controlled studies were designed to evaluate effectiveness of articaine and adrenaline (epinephrine) 1:100,000 injection as a dental

anaesthetic. A total of 882 patients received 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, mucogingival operations and other surgical procedures on the bone.

Articaine and 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 10cm visual analogue scale (VAS), in which a score of zero represented no pain, and a score of ten represented the worst pain imaginable. Mean patient and investigator VAS pain scores were 0.3 to 0.4 cm for simple procedures and 0.5 to 0.6 cm for complex procedures. These values are summarised in Table 1 below.

**Table 1: Summary of VAS pain scores**

| | **Articaine HCl 4% with adrenaline (epinephrine) 1:100,000)** | |
|---|---|---|
| | **Simple procedures** | **Complex procedures** |
| **Number of patients** | **674** | **207** |
| Investigator score (cm)<br>Mean<br>Median<br>Range | <br>0.3<br>0.0<br>0 – 0.9 | <br>0.5<br>0.2<br>0 – 7.3 |
| Patient score (cm)<br>Mean<br>Median<br>Range | <br>0.4<br>0.0<br>0 – 8.0 | <br>0.6<br>0.2<br>0 – 8.7 |

In the clinical trials 54 patients between the ages of 65 and 75 years and eleven patients 75 years and over received articaine and adrenaline (epinephrine) 1:100,000 injection. Among all patients between 65 and 75 years, doses from 0.43 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 to 4.27 mg/kg (1.3 to 6.8 mL) were administered safely to 19 patients for complex procedures. Among the eleven patients greater than or equal to 75 years old, doses from 0.78 to 4.76 mg/kg (1.3 to 11.9 mL) were administered safely to seven patients for simple procedures and doses of 1.12 to 2.17 mg/kg (1.3 to 5.1 mL) were administered to four patients for complex procedures.

Paediatric population:
In clinical trials, 61 paediatric patients between the ages of 4 and 16 years received articaine and adrenaline (epinephrine) 1:100,000 injection. Among these paediatric patients, doses from 0.76 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 and 7.48 mg/kg (0.7 to 3.9 mL) were administered safely to ten patients for complex procedures. However, there was insufficient exposure to articaine and 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.

## 5.2 Pharmacokinetic properties

Absorption
Following dental injection by the submucosal route of an articaine 4% solution containing adrenaline (epinephrine) 1:200,000, articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 minutes and 204 mg doses are 385 and 900 nanogram/mL, respectively.

Distribution
Approximately 60 to 80% of articaine hydrochloride is bound to human serum albumin and gamma-globulins at 37 deg. C *in vitro.*

Metabolism
Articaine hydrochloride is rapidly metabolised 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 to 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 are available in the following populations: elderly, children.

*Race:* No pharmacokinetic data are available for different racial groups.

*Renal and hepatic insufficiency:* No pharmacokinetic data are available for patients with hepatic or renal impairment.

### 5.3 Preclinical safety data

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 maximum recommended human dose on a mg/m² 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/m² 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/m² 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/m² basis) did not produce these effects. A similar study using articaine hydrochloride with adrenaline produced maternal toxicity, but no effects on the offspring.

*Genotoxicity:* Articaine was negative in bacterial and mammalian assays for gene mutation and a chromosomal aberration test in Chinese hamster ovary cells. In vivo clastogenecity (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/m² 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

Sodium sulfite
Sodium chloride
Hydrochloric acid 14% (for pH adjustment)
Sodium hydroxide solution 9% (for pH adjustment)
Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 25ºC. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

Tin with 50 glass cartridges of 1.7ml each.

Cartridge made of colourless neutral glass I.
Stopper and rubber disc are made of butyl rubber.
Aluminium cap made of aluminium-iron-silicon-alloy.

### 6.6 Special precautions for disposal

Prior to administration, the product should be visually inspected for particulate matter, discolouration or damage to the container. The product should not be used if such defects are observed.
The cartridges are intended for single-use only. Opened cartridges must not be used in other patients. Residues must be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MEDICINE SCHEDULE

Prescription Medicine

## 8 SPONSOR

3M New Zealand Limited
94 Apollo Drive,
Rosedale, Auckland 0632
Telephone: 09 477 4040

## 9 DATE OF FIRST APPROVAL

31 January 2008

## 10 DATE OF REVISION OF THE TEXT

8 March 2019

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 2 | Amended active ingredients section to clearly indicate the proportions of active ingredient ‘adrenaline (epinephrine) hydrochloride’ and the ‘adrenaline (epinephrine)’ component within each 1.7mL cartridge. |