The format of this leaflet has been determined by the Ministry of Health and its content has been examined and approved in November 2016

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Articaine HCl 4% and Epinephrine 1:200,000

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Articaine HCl 4% and Epinephrine 1:200,000 contains articaine hydrochloride 4% with 1:200,000 epinephrine (adrenaline) as bitartrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
The solution is a clear and colourless liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For infiltration anaesthesia and nerve block anaesthesia in clinical dentistry.

4.2 Posology and method of administration

The following dosage instructions apply:
The smallest possible volume of solution which will lead to an effective anaesthesia should be used.

For extraction of maxillary teeth, 1.7 ml Articaine HCl 4% and Epinephrine 1:200,000 per tooth suffices in most cases; painful palatal injections can thus be avoided. In the case of serial extractions of neighbouring teeth, a reduction of the injection volume is often possible.
If a cut or suture is required in the palate, a palatal injection of approx 0.1 ml per puncture is indicated.
For smooth extractions of mandibular premolar teeth, infiltration anaesthesia of 1.7 ml Articaine HCl 4% and Epinephrine 1:200,000 per tooth is mostly sufficient; in single cases a buccal re-injection of 1 to 1.7 ml is required. An injection into the mandibular foramen can be indicated in rare cases.
Vestibular injections of 0.5 - 1.7 ml Articaine HCl 4% and Epinephrine 1:200,000 per tooth enable cavity and crown-stump preparations.
Nerve-block anaesthesia should be used in the treatment of mandibular molar teeth.
Generally, in children weighing about 20 - 30 kg, doses of 0.25 - 1 ml are sufficient; in children weighing 30 - 45 kg, 0.5 - 2 ml.
Articaine HCl 4% and Epinephrine 1:200,000 must not be used with children aged under 4 years (see section 4.3).
Increased plasma levels of Articaine HCl 4% and Epinephrine 1:200,000 can occur in older patients due to diminished metabolic processes and lower distribution volume. The risk of accumulation of Articaine HCl 4% and Epinephrine 1:200,000 is increased in particular after repeated application (e.g.

re-injection). A similar effect can ensue from the reduced general condition of the patient, as well as severely impaired hepatic and renal function (see also section 4.4).
A lower dosage range is thus recommended in all such cases (minimum quantity for sufficient anaesthetic depth).
The dose has to be likewise reduced in patients with certain pre-existing diseases (angina pectoris, arteriosclerosis) (see also section 4.4).
Maximum Recommended Dosage:
Adults:
For healthy adults, the maximum dose is 7 mg/kg body weight articaine (500 mg for a 70 kg patient), equivalent to 12.5 ml Articaine HCl 4% and Epinephrine 1:200,000.
The maximum dose represents 0.175 ml of solution per kg.
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 7 mg articaine/kg (0.175 ml Articaine HCl 4% and Epinephrine 1:200,000 /kg) of body weight.
Espestesin 4 % articaine with 1/100:000 adrenaline (epinephrine) is also available and may be more appropriate for procedures of longer duration and when there is a risk of significant bleeding into operative field (see section 5.1 for more information on duration of analgesia).
Method of administration
For injection/oromucosal use
FOR USE IN DENTAL ANAESTHESIA ONLY

To avoid intravascular injection, aspiration control at least in two planes (rotation of the needle by 180°) must always be carefully undertaken, although a negative aspiration result does not safely rule out an unintentional and unnoticed intravascular injection.
The injection rate should not exceed 0.5 ml in 15 seconds, i.e. 1 cartridge per minute.
Major systemic reactions as a result of accidental intravascular injection can be avoided in most cases by an injection technique – after aspiration slow injection of 0.1 – 0.2 ml and slow application of the rest – not earlier than 20 – 30 seconds later.
Opened cartridges must not be used in other patients. Residues must be discarded.

4.3 Contraindications

Articaine HCl 4% and Epinephrine 1:200,000 is not allowed to be used in the event of
- children under 4 years of age
- hypersensitivity to the active substances, sodium sulphite (E221) or to any of the other
excipients
Due to the local anaesthetic ingredient articaine, Espestesin 4 % articaine with 1/200 000 adrenaline
(epinephrine) is not allowed to be used in the event of
− known allergy or hypersensitivity to local anaesthetics of the amide type
− severe impairment of the impulse initiation and conduction system of the heart (e.g. 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
− haemorrhagic diatheses – particularly with nerve-block anaesthesia
− injection into an inflamed area

Due to the content of epinephrine as a vasoconstrictor admixture, Espestesin 4 % articaine with 1/200 000 adrenaline (epinephrine) is not allowed to be used in the event of

− Heart diseases 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 severe hypertension
- untreated or uncontrolled congestive heart failure

− concomitant treatment with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants
(see section 4.5)

Due to the content of sulphite as excipient, Espestesin 4 % articaine with 1/200 000 adrenaline (epinephrine) is not allowed to be used in the event of

- allergy or hypersensitivity to sulphite
- severe bronchial asthma

Articaine HCl 4% and Epinephrine 1:200,000 can provoke acute allergic reactions with anaphylactic symptoms (e.g. bronchospasm).

4.4 Special warnings and precautions for use

Articaine HCl 4% and Epinephrine 1:200,000 must be used with particular caution in the event of

− severe impairment to the renal function
− angina pectoris (see section 4.2 and 4.3)
− arteriosclerosis
− considerably impaired blood coagulation (see section 4.5)
− thyrotoxicosis
− narrow-angle glaucoma
− diabetes mellitus
− lung diseases – particularly allergic asthma
− pheochromocytoma

Accidental intravascular injection may be associated with convulsions, followed by central nervous system or cardiorespiratory arrest. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Since amide-type local anaesthetics are also metabolised by the liver, Articaine HCl 4% and Epinephrine 1:200,000 should be used with caution in patients with hepatic diseases.

Patients with severe hepatic diseases are at greater risk of developing toxic plasma concentration.

The product should be administered 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.

The product should be administered with caution to patients with history of

epilepsy.
There is a possibility of positive results on doping tests performed on sportsmen.
It should be taken into consideration that during treatment with blood coagulation inhibitors (e.g. heparin or acetylsalicylic acid), an inadvertent vasopuncture when administering the local anaesthetic can lead to serious bleeding, and that in general the hemorrhagic tendency is increased (see section 4.5)
Inadvertant intravascular application must be avoided (see section 4.2)
Fascilities for resuscitation should be available when local anesthetics are administered.

The lower blood flow in the pulp tissue due to the content of epinephrine and thus the risk to overlook an opened pulp has to be taken into account regarding cavity or crown preparations.
The medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, i.e. essentiall “sodiumfree”.

Precautions for use:

Each time a local anaesthetic is used the following drugs/therapy should be available:
Anti-convulsant medicines (benzodiazepines or barbiturates), myorelaxants, atropine and vasopressors or adrenaline for a severe allergic or anaphylactic reaction.
- Resuscitating equipment (in particular a source of oxygen) enabling artificial ventilation if necessary.
- Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be monitored after each local anaesthetic injection. Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity (see section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking MAO inhibitors or tricyclic antidepressants
The sympathomimetic effect of epinephrine can be intensified by the simultaneous intake of MAO inhibitors or tricyclic antidepressants. (see also section 4.3)
Patients taking oral antidiabetics
Epinephrine can inhibit insulin release in the pancreas and thus diminish the effect of oral antidiabetics.
Patients taking non-selective beta-blockers
The concomitant administration of non-cardioselective ß-blockers can lead to an increase in blood pressure due to the epinephrine in Espestesin 4% articaine with 1:200 000 adrenaline (epinephrine).
Patients taking phenothiazines
Phenothiazines may reduce or reverse the pressor effect of epinephrine.
Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.
Patients taking blood coagulation inhibitors
During treatment with blood coagulation inhibitors, the hemorrhagic tendency is increased (see also section 4.4).
Inhalational anesthestics

Certain inhalational anaesthetics, such as halothane, can sensitise the heart to catecholamines and therefore induce arrhythmias following administration of Articaine HCl 4% and Epinephrine 1:200,000.

4.6 Fertility, Pregnancy and lactation

For Articaine HCl 4% and Epinephrine 1:200,000 no clinical data on exposed pregnancies are available. In regard of articaine animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Animal studies carried out with epinephrine have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Caution should be exercised when prescribing to pregnant women.
It is unknown whether articaine and epinephrine is excreted in human breast milk. The excretion of articaine and epinephrine in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Articaine HCl 4% and Epinephrine 1:200,000 should be made taking in to account the benefit of breastfeeding to the child and the benefit of Articaine HCl 4% and Epinephrine 1:200,000 therapy to the women. Therefore, nursing mothers should milk and discard the first mother's milk following anaesthesia with articaine.

4.7 Effects on ability to drive and use machines

Although test patients have shown no impairment of their normal reactions when driving a vehicle, the dentist has to assess in each case the possible impairment of safety when operating a motor vehicle or machinery. The patient should not leave the dental office earlier than at least 30 minutes after the injection.

4.8 Undesirable effects

Due to the local anaesthetic ingredient articaine, the following adverse effects can occur.

Cardiovascular disorders
Rare (>.1/10,000 to < 1/1,000)
Decrease in heart rate, hypotension.
Drop in blood pressure, cardiac impulse conduction disorders, bradycardia, asystolia, cardiovascular arrest.

Nervous system disorders
Rare (>.1/10,000 to < 1/1,000)
Metallic taste, tinnitus, dizziness, nausea, vomiting, restlessness, anxiety, yawning, shaking, nervousness, nystagmus, logorrhoea, headache, increase in respiratory rate. Paresthesias (loss of sensation, burning, tingling) of the lip, tongue, or both.
When these signs appeared rapid corrective measures are required to prevent possible worsening:
Drowsiness, confusion, tremor, muscle twitching, tonic-clonic seizures, coma and respiratory paralysis.

Respiratory disorders
Rare (>.1/10,000 to < 1/1,000)
Tachypnea, then bradypnea, which could lead to apnoea.

Allergic reactions

Very rare (< 1/10,000)
One may observe manifestation of hypersensitivity to articaine as rash, pruritus edema, pruritus, and erythema as well as nausea, diarrhea, wheezing or anaphylaxis. Cross-reactivity to articaine has been reported in a patient with delayed hypersensitivity to prilocaine.
In general, patients with demonstrated hypersensitivity to articaine or other amides should receive an ester-group local anaesthetic for subsequent procedures.
The administration of large doses of articaine may produce methaemoglobinemia in patients with subclinical methaemoglobinemia.
Due to the content of epinephrine as a vasoconstrictor admixture, the following undesirable effects can occur

Cardiovascular disorders
Rare (>.1/10,000 to < 1/1,000)
Heat sensation, sweating, heart racing, migrainelike headache, blood pressure increase, angina pectoris disorders, tachycardias, tachyarrhythmias and cardiovascular arrest and acute oedematous thyroid swelling.
Due to the content of sulphite as excipient, the following undesirable effects can occur in very rare cases:
Allergic reactions or hypersensitivity reactions, particularly in bronchial asthmatics, which are manifested as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of consciousness or shock.
Due to the content of both articaine and epinephrine, the following undesirable effects can occur

Nervous system disorders
2 weeks delayed onset of facial nerve paralysis has been described with articaine/epinephrine, the event still occur 6 months later.
Interferences in the clinical picture can result from the simultaneous occurrence of various complications and side effects.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il)

4.9 Overdose

Undesirable effects (showing an abnormally high concentration of local anaesthetic in the blood) may appear either immediately, caused by accidential intravascular injection or abnormal absorption conditions, e.g. in inflamed or intensive vascularised tissue, or later, caused by true overdose following an

injection of excessive quantity of anaesthetic solution, and manifest themselves as central nervous and/or vascular symptoms.

Symptoms caused by the local anaesthetic ingredient articaine:

Milder central nervous symptoms involve metallic taste, tinnitus, dizziness, nausea, vomiting, restlessness, anxiety, initial increase in respiratory rate.

More severe symptoms are drowsiness, confusion, tremor, muscular twitching, tonic-clonic seizures, coma and respiratory paralysis.

Severe cardiovascular episodes are seen in the form of a drop in blood pressure, cardiac impulse conduction disorders, bradycardia, cardiovascular arrest.

Symptoms caused by epinephrine as a vasoconstrictor:

Cardiovascular symptoms such as heat sensation, sweating, heart racing, migrainelike headache, blood pressure increase, angina pectoris disorders, tachycardias, tachyarrhythmias, cardiovascular arrest and acute oedematous thyroid swelling.

Interferences in the clinical picture can result from the simultaneous occurrence of various complications and side effects.

Therapy

If adverse reaction arise the application of the local anaesthetic has to be stopped.

General basic measures:

Diagnostics (respiration, circulation, consciousness), maintenance/restoration of the vital functions of respiration and circulation, oxygen administration, intravenous access.

Special measures:

Hypertension: Elevation of the upper body, if necessary sublingual nifedipine.

Convulsions: Protect patients from concomitant injuries, if necessary benzodiazepins (e.g. diazepam iv).

Hypotension: Horizontal position, if necessary intravascular infusion of a whole electrolyte solution, vasopressors (e.g. etilefrine iv).

Bradycardia: Atropine iv.

Anaphylactic shock: Contact emergency physician, in the meantime shock positioning, generous infusion of a whole electrolyte solution, if necessary epinephrine iv, cortisone iv.

Cardiovascular arrest: Immediate cardiopulmonary resuscitation, contact emergency physician.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, ATC code N01B B58

Articaine HCl 4% and Epinephrine 1:200,000 contains articaine which is a local anaesthetic of the amide type for dentistry and leads to a reversible inhibition of the irritability of vegetative, sensory and motor nerve fibres. The blocking of voltage dependent Na+ channels on the membrane of the nerve fibre is supposed to be the mechanism of effect of articaine.

The rapid onset of anaesthesia - latency period of 1 - 3 minutes - the reliable effect with strong analgesic effect and good local tolerability are characteristic. The duration of effect of Articaine HCl 4% and Epinephrine 1:200,000 in pulpal anaesthesia lasts at least 45 minutes, and in soft-tissue anaesthesia 120 to 240 minutes.

Epinephrine leads locally to vasoconstriction, whereby the absorption of

articaine is delayed. The result is a higher concentration of the local anaesthetic at the site of effect over a longer period, as well as the reduction in the occurrence of systemic adverse side effects.

5.2 Pharmacokinetic properties

Articaine HCl 4% and Epinephrine 1:200,000 is rapidly and almost completely absorbed.

The maximum plasma level of articaine from intraoral injection is achieved approximately after 10 -

15 minutes (Tmax). The distribution volume is 1.67 l/kg and the elimination half-life is approximately 20 minutes.

Articaine is bound up to 95% in the serum to plasma proteins.

Articaine is rapidly hydrolysed by plasma cholinesterases to its primary metabolite articainic acid which is further metabolised to articainic acid glucuronide. Articaine and its metabolites are mainly eliminated in urine.

Epinephrine is rapidly catabolized in the liver and other tissues. The metabolites are excreted renally.

5.3 Preclinical safety data

Symptoms of articaine toxicity were independent of the route of administration (IV, IM, SC and PO) and of the animal species and included trembling, vertigo, and tonic and clonic convulsions. The duration and intensity of these symptoms were dose-dependent; at high doses (single dose of approx 50-100 mg/kg) the convulsions resulted in death and at low doses all symptoms dissipated in 5 to 10 minutes. Lethal doses of articaine resulted in pulmonary oedema in mice (IV and SC) and in rats (IV, IM, SC and PO).

In rats, rabbits and cats, articaine showed no effect on embryo or fetal development in utero and no skeletal or organ abnormalities. Cups of lactating rats receiving articaine in high doses (80 mg/kg/day) causing maternal toxicity showed delayed eye opening and increased likelihood of failure in the passive avoidance test.

Epinephrine was potentially teratogenic in rats albeit at doses 25 times the human therapeutic dose.

Following IV administration, the presence of 1:100 000 epinephrine increased the toxicity of articaine in the rat, mouse, but not in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite

Sodium chloride

Hydrochloric acid Sodium hydroxide Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light. Do not freeze.

6.5 Nature and contents of container

Glass Cartridge Type I, grey bromobutyl rubber stopper, gold lacquered aluminum cap 50 cartridges of 1.7 ml each.

6.6 Special precautions for disposal

The product should be inspected visually for particulate matter, discoloration or damage of container prior to administration. The product should not be used if such defects are observed.
The product is for single use only. Any unused product should be discarded immediately after first use.

7 Manufacturer

Novocol Pharmaceutical of Canada, Inc., Cambridge, Ontario, Canada, N1R 6X3 25 Wolseley Court

8 License Holder

HENRY SCHEIN SHVADENT (2009) LTD, RACHEL IMENU 7A,JERUSALEM 9314507