Physician's Prescribing Information

Septanest N and Septanest SP

1) Name of the medicinal product(s):
SEPTANEST N
SEPTANEST SP

2) Qualitative and quantitative composition:

SEPTANEST N:
1 ml of solution for injection contains 40 mg of articaine hydrochloride and 5 micrograms of adrenaline (as adrenaline tartrate).
Each cartridge of 1.7 ml of solution for injection contains 68 mg of articaine hydrochloride and 8.5 micrograms of adrenaline (as adrenaline tartrate).

SEPTANEST SP:
1 ml of solution for injection contains 40 mg of articaine hydrochloride and 10 micrograms of adrenaline (as adrenaline tartrate).
Each cartridge of 1.7 ml of solution for injection contains 68 mg of articaine hydrochloride and 17 micrograms of adrenaline (as adrenaline tartrate).

Excipient(s) with known effect: sodium metabisulfite (E223), sodium chloride, disodium edetate, sodium hydroxide.
SEPTANEST N and SEPTANEST SP contain 0.804 mg sodium per 1 ml of solution i.e. 1.44 mg/1.7 ml.
For the full list of excipients, see section 6.1.

3) Pharmaceutical Form: Solution for Injection. Clear and colourless solution, practically free from particles.

4) CLINICAL PARTICULARS:

4.1) Therapeutic indications: SEPTANEST N and SEPTANEST SP are indicated for infiltration anaesthesia and nerve block anaesthesia in clinical dentistry. This includes local or loco-regional dental anaesthesia suitable for operations such as: single extractions, with no complications; multiple extractions; extractions of impacted teeth; trephinement; apical resections; removal of cysts; alveolectomies; preparation of cavity; biopulpectomies; and maxillo-facial surgery.
SEPTANEST N and SEPTANEST SP are also suitable for muco-gingival operations and other surgical operations on the bone when long lasting ischaemia and analgesia are required.

4.2) Posology and method of administration: As with all local anaesthetics the dosage varies and depends upon the area to be anaesthetized, the vascularity of the tissues, the number of numeral segments to be blocked, individual tolerance and the technique of anaesthesia.

Adults:
- For most common operations, one infiltration with 1.7 ml SEPTANEST N or SEPTANEST SP is sufficient. In all cases, the injection must be administered slowly (About 1 ml/min).
- For an infiltration in the interdental septum, a quantity of 0.3 to 0.5 ml is indicated as generally sufficient.

Do not exceed the equivalent of 7 mg/kg articaine hydrochloride body weight which corresponds, for a subject weighing 60 Kg, to 6 standard 1.7 ml cartridges. The duration of anaesthesia during which an operation can be performed using SEPTANEST N is up to 45 minutes. The duration of anaesthesia during which an operation can be performed using SEPTANEST SP is up to 75 minutes. The lowest dosage needed to provide effective anaesthesia should be administered.

Children: For SEPTANEST N and SEPTANEST SP, use in children under 4 years of age is not recommended. The quantity to be injected should be determined by the age of the child and the size of the operation. Do not exceed the equivalent of 7 mg articaine hydrochloride per kilogram of body weight.

4.3) Contraindications:
- Hypersensitivity to articaine (or any local anaesthetic agent of the amide type), to adrenaline or to any of the excipients listed in section 6.1.
- Patients with epilepsy not controlled by treatment.

4.4) Special warnings and precautions for use:
Before using this medicinal product, it is important:
- To make inquiries into the patient's current therapies and history
- To maintain verbal contact with the patient
- To have resuscitative equipment at hand (see section 4.9)

Special warnings: This medicinal product must be used with special caution in patients with the following disorders and postponement of dental surgery should be considered if the condition is severe and/or unstable.

Patients with cardiovascular disorders: The lowest dose leading to efficient anaesthesia should be used in case of:
- Cardiac impulse formation and conduction disturbances (e.g. 2nd or 3rd degree atrioventricular block, marked bradycardia)
- Acute decompensated heart failure (acute congestive heart failure)
- Hypotension
- Patients with paroxysmal tachycardia or absolute arrhythmias with rapid heart rate
- Patients with unstable angina or a history of recent (less than 6 months) myocardial infarction
- Patients with recent (3 months) coronary artery bypass surgery
- Patients taking non-cardioselective beta-blockers (e.g. propranolol) (risk of hypertensive crisis or severe bradycardia), (see section 4.5)
- Patients with uncontrolled hypertension
- Concomitant treatment with tricyclic antidepressants, as these active substances can intensify the cardiovascular effects of adrenaline (see section 4.5)

This medicinal product must be used with caution in patients with the following disorders:

Patients with epileptic disease: Because of their convulsive actions, all local anaesthetics should be used very cautiously.

Patients with plasma cholinesterase deficiency: A plasma cholinesterase deficiency can be suspected when clinical signs of overdose occurs with usual dosage of anesthesia and when a vascular injection has been excluded. In this case, caution shall be used for the next injection and reduced dose shall be applied.

Patients with renal disease: The lowest dose leading to effective anaesthesia should be used.

Patients with severe hepatic disease: This medicinal product should be used cautiously due to the presence of hepatic disease although 90% of articaine is first inactivated by unspecific plasma esterases in the tissue and blood.

Patients with myasthenia gravis treated by acetylcholinesterase inhibitors: The lowest dose leading to effective anaesthesia should be used.

Patients with porphyria: SEPTANEST N and SEPTANEST SP should only be used in patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in all patients with porphyria, as this medicinal product can trigger porphyria.

Patients with concomitant treatment with halogenated inhalation anaesthetics: The lowest dose of the medicinal product leading to effective anaesthesia should be used (see section 4.5).

Patients receiving treatment with antiplatelets / anticoagulants: SEPTANEST N and SEPTANEST SP should be administered with caution in patients, who are using antiplatelet/anticoagulant medicines or are suffering from coagulation disorder, because of higher risk of bleeding. The higher risk of bleeding is more associated with the procedure, rather than with the medicine.

Elderly patients: Elevated product plasma levels may occur in elderly patients in particular after repeated use. In case of required reinjection, patient should be strictly monitored, to identity any sign of relative overdose (see section 4.9). Therefore, the lowest dose leading to effective anaesthesia should be used. The use of SEPTANEST N over SEPTANEST SP should be considered on account of its lower adrenaline content of 5 micrograms/ml in:
- *Patients with cardiovascular diseases* (e.g. heart failure, coronary heart disease, history of myocardial infarction, cardiac arrhythmia, hypertension)
- *Patients with cerebral circulation disturbances, history of strokes:* It is recommended that dental treatment with articaine/adrenaline be deferred for six months following a stroke due to the increased risk of recurrent strokes.
- *Patients with uncontrolled diabetes:* This medicinal product should be used cautiously due to hyperglycemic effect of adrenaline.
- *Patients with thyreotoxicosis:* This medicinal product should be used cautiously due to the presence of adrenaline.
- *Patients with pheochromocytoma:* This medicinal product should be used cautiously due to the presence of adrenaline.
- *Patients with susceptibility of acute angle-closure glaucoma:* This medicinal product should be used cautiously due to the presence of adrenaline.

The lowest dose leading to effective anaesthesia should be used.

This medicinal product must be used safely and effectively under appropriate conditions: Adrenaline impairs the flow of blood in the gums, potentially causing local tissue necrosis.

Very rare cases of prolonged or irreversible nerve injury and gustatory loss have been reported after mandibular block analgesia.

The local anaesthetic effects may be reduced when this medicinal product is injected into an inflamed or infected area.

The dose must also be reduced in case of hypoxia, hyperkalaemia and metabolic acidosis.

Risk of biting trauma (lips, cheeks, mucosa, and tongue) exists, especially in children; the patient should be told to avoid chewing gum or eating until normal sensation is restored.

This medicinal product contains sodium metabisulfite, a sulfite that may rarely cause hypersensitivity reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per cartridge, i.e. it is considered as essentially "sodium free".

If there is any risk of an allergic reaction, choose a different medicine for anesthesia (see section 4.3).

Precautions for use:
Risk associated with accidental intravascular injection: Accidental intravascular injection may cause sudden high levels of adrenaline and articaine in the systemic circulation. This may be associated with severe adverse reactions, such as convulsions, followed by central nervous and cardiorespiratory depression and coma, progressing to respiratory and circulatory arrest.
Thus, to ensure that the needle does not penetrate a blood vessel during injection, aspiration should be performed before the local anaesthetic medicinal product is injected. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Risk associated with intraneural injection: Accidental intraneural injection may lead the drug to move in retrograde manner along the nerve.
In order to avoid intraneural injection and to prevent nerve injuries in connection with nerve blockades, the needle should always be slightly withdrawn if electric shock sensation is felt by the patient during injection or if the injection is particularly painful. If needle nerve injuries occur, the neurotoxic effect could be aggravated by articaine potential chemical neurotoxicity and the presence of adrenaline as it may impair the perineural blood supply and prevent articaine local wash-out.

4.5) Interaction with other medicinal products and other forms of interaction

Interactions with articaine:

Interactions requiring precautions for use:
Other local anaesthetics: Toxicity of local anaesthetics is additive.
The total dose of all local anaesthetics administered should not exceed the maximum recommended dose of the drugs used.

Sedatives (central nervous system depressants e.g. benzodiazepine, opioids): If sedatives are employed to reduce patient's apprehension, reduced doses of anaesthetics should be used since local anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect (see section 4.2).

Interactions with adrenaline

Interactions requiring precautions for use:
Halogenated volatile anaesthetics (e.g., halothane): Reduced doses of this medicinal product should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia. Discussion with the anaesthetist before local anaesthetic administration during general anaesthesia is recommended.

Postganglionic adrenergic blocking agents (e.g., guanadrel, guanethidine, and rauwolfia alkaloids): Reduced doses of this medicinal product should be used under strict medical supervision with careful aspiration due to possible increase response to adrenergic vasoconstrictors: risk of hypertension and other cardiovascular effects.

Non-selective beta-adrenergic blockers (e.g., propranolol, nadolol): Reduced doses of this medicinal product should be used due to possible increase in blood pressure and an increased risk of bradycardia.

(TCAs) Tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, maprotiline and protriptyline): Dose and rate of administration of this medicinal product should be reduced due to an increased risk of severe hypertension.

COMT inhibitors (Catechol-O-methyl transferase inhibitors) (e.g., entacapone, tolcapone): Arrhythmias, increased heart rate and blood pressure variations may occur.
A reduced amount of adrenaline in dental anaesthesia should be given to patients on COMT inhibitors.

MAO inhibitors (both A-selective (e.g. moclobemide) and non-selective (e.g. phenelzine, tranylcypromine, linezolide): If the concurrent use of these agents cannot be avoided, the dose and rate of administration of this product should be reduced, and the product should be used under strict medical supervision due to possible potentiation of the effects of adrenaline leading to the risk of hypertensive crisis."

Drugs causing arrhythmias (e.g., antiarrhythmics like digitalis, quinidine): Dose of administration of this medicinal product should be reduced due to the increased risk of arrhythmia when both adrenaline and digital glucosides are administered concomitantly to patients. Careful aspiration prior to administration is recommended.

Ergot-type oxytocic drugs (e.g., methysergide, ergotamine, ergonovine): Use this medicinal product under strict medical supervision due to additive or synergistic increases in blood pressure and/or ischemic response.

Sympathomimetic vasopressors (e.g., mainly cocaine but also amphetamines, phenylephrine, pseudoephedrine, oxymetazoline): There is a risk of adrenergic toxicity.
If any sympathomimetic vasopressor has been used within 24 hours, the planned dental treatment should be postponed.

Phenothiazines (and other neuroleptics): Use with caution in patients taking phenothiazines considering the risk of hypotension due to possible inhibition of adrenaline effect.

4.6) Fertility, pregnancy and lactation:

Pregnancy: Animal studies with articaine 40 mg/ml + adrenaline 10 micrograms/ml, as well as with articaine alone, have not shown adverse effects on pregnancy, embryonal/foetal development, birth or postnatal development (see section 5.3).
Animal studies have shown that adrenaline is toxic to reproduction at doses higher than maximal recommended dose (see section 5.3).
There is no experience of the use of articaine in pregnant women, except during childbirth. Adrenaline and articaine cross the placental barrier, although articaine does so to a lesser extent than other local anaesthetics. Serum concentrations of articaine measured in newborn infants were approx. 30% of maternal levels. In the event of inadvertent intravascular administration in the mother, adrenaline can reduce uterine perfusion.

During pregnancy, SEPTANEST SP should only be used after a careful analysis of the benefit-to-risk ratio has been made.

On account of its lower adrenaline content, the use of SEPTANEST N over SEPTANEST SP should be preferred.

Breastfeeding: As a result of the rapid drop in serum levels and rapid elimination, clinically relevant quantities of articaine are not found in breast milk. Adrenaline passes into breast milk but also has a short half-life.
It is not usually necessary to suspend breast-feeding for short-term use, starting from 5 hours following anesthesia.

Fertility: Animal studies with articaine 40 mg/ml + adrenaline 10 micrograms/ml have not shown effects on fertility (see section 5.3). At therapeutic doses, adverse effects on human fertility are not expected.

4.7) Effects on ability to drive and use machines
The combination articaine hydrochloride with adrenaline tartrate solution for injection may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of SEPTANEST N and SEPTANEST SP (see Section 4.8 of SmPC). So, patients should not leave the dental office until they recover their abilities (generally within 30 minutes) following the dental procedure.

4.8) Undesirable effects:

a) Summary of the safety profile: Adverse reactions following administration of articaine / adrenaline 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, or diminished tolerance by patient. Nervous system disorders, local injection site reaction, hypersensitivity, cardiac disorders and vascular disorders are the most frequently occurring adverse reactions.
Serious adverse reactions are generally systemic.

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 (cannot be estimated from the available data)".

MedDRA Sytem Organ Class	Frequency	Adverse Reactions
Infections and infestations	Common	Gingivitis
Immune system disorders	Rare	Allergic[1], anaphylactic / anaphylactoid reactions
Psychiatric disorders	Rare	Nervousness / anxiety[4]
	Not known	Euphoric mood
Nervous system disorders	Common	Neuropathy: Neuralgia (neuropathic pain) Hypoesthesia / numbness (oral and perioral)[4] Hyperesthesia Dysesthesia (oral and perioral), *including* Dysgeusia (e.g., taste metallic, taste disturbance) Ageusia Allodynia Thermohyperesthesia Headache
	Uncommon	Burning sensation
	Rare	Facial nerve disorder[2] (palsy, paralysis and paresis) Horner's syndrome (eyelid ptosis, enophthalmos, miosis). Somnolence (Drowsiness) Nystagmus
	Very rare	Paresthesia[3] (persistent hypoesthesia and gustatory loss) after mandibular or inferior alveolar nerve blocks

MedDRA Sytem Organ Class	Frequency	Adverse Reactions
Eye disorders	Rare	Diplopia (paralysis of oculomotor muscles)[4] Visual impairment (temporary blindness) [4] Ptosis Miosis Enophthalmos
Ear and labyrinth disorders	Rare	Hyperacusis Tinnitus[4]
Cardiac disorders	Common	Bradycardia Tachycardia
	Rare	Palpitations
	Not known	Conduction disorders (atrioventricular block)
Vascular disorders	Common	Hypotension (with possible circulatory collapse)
	Uncommon	Hypertension
	Rare	Hot flush
	Not known	Local / Regional hyperaemia Vasodilatation Vasoconstriction
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm / asthma Dyspnoea[2]
	Not known	Dysphonia (Hoarseness)[1]
Gastrointestinal disorders	Common	Swelling of tongue, lip, gums
	Uncommon	Stomatitis, glossitis Nausea, vomiting, diarrhoea
	Rare	Gingival / oral mucosal exfoliation (sloughing) / ulceration
	Not known	Dysphagia Swelling of cheeks Glossodynia
Skin and subcutaneous tissue disorders	Uncommon	Rash (eruption) Pruritus
	Rare	Angioedema (face / tongue / lip / throat / larynx / periorbital oedema) Urticaria
	Not known	Erythema Hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Neck pain
	Rare	Muscle twitching[4]
	Not known	Aggravation of the neuromuscular manifestations in Kearns-Sayre syndrome Trismus
General disorders and administration site conditions	Uncommon	Injection site pain
	Rare	Injection site exfoliation / necrosis Fatigue, asthenia (weakness) / Chills
	Not known	Local swelling Feeling hot Feeling cold

c) Description of selected adverse reactions:

1 Allergic reactions should not be mistaken with syncopal episodes (cardiac palpitations due to adrenaline).

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

3 These neural pathologies may occur with various symptoms of abnormal sensations. Paresthesia can be defined as spontaneous abnormal usually non-painful sensation (e.g., burning, pricking, tingling or itching) well beyond the expected duration of anesthesia. Most cases of paresthesia reported following dental treatment are transient and resolve within days, weeks or months. Persistent paresthesia, mostly following nerve blocks in the mandible, is characterized by slow, incomplete, or lack of recovery.

4 Several adverse events, like agitation, anxiety / nervousness, tremor, speech disorder may be warning signs before CNS depression. In attendance of these signs, patients should be requested to hyperventilate and surveillance should be instituted (see Section 4.9).

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 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:
https://sideeffects.health.gov.il /

4.9) Overdose:

Types of overdose: Local anaesthetic overdose in the largest sense is often used to describe:
- absolute overdose,
- relative overdose such as:
  - inadvertent injection into a blood vessel, or
  - abnormal rapid absorption into the systemic circulation, or
  - delayed metabolism and elimination of drug.

In case of relative overdose, patients generally present symptoms within the first minutes. Whereas in case of absolute overdose, signs of toxicity, depending on the injection site, appear later after the injection.

Symptoms: Due to an overdose (absolute or relative), since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Due to articaine: The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations (presyncope, syncope, headache, restlessness, agitation, confusional state, disorientation, dizziness (lightheadedness), tremor, stupor, deep CNS depression, loss of consciousness, coma, convulsion (including tonic-clonic seizure), speech disorder (e.g., dysarthria, logorrhea), vertigo, balance disorder (disequilibrium)), eyes manifestations (mydriasis, vision blurred, accommodation disorder) followed by vascular (pallor (local, regional, general)), respiratory (apnoea (respiratory arrest), bradypnoea, tachypnoea, yawning, respiratory depression) and finally cardiac (cardiac arrest, myocardial depression) toxicity.
Acidosis exacerbates the toxic effects of local anaesthetics.

Due to adrenaline: The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations (restlessness, agitation, presyncope, syncope) followed by vascular (pallor (local, regional, general)), respiratory (apnoea (respiratory arrest), bradypnoea, tachypnoea, respiratory depression) and finally cardiac (cardiac arrest, myocardial depression) toxicity.

Treatment of overdose: The availability of resuscitation equipment and medication should be ensured before administration of regional anaesthesia with local anaesthetics to enable prompt treatment of any respiratory and cardiovascular emergencies.
The seriousness of overdose symptoms should have physicians/dentists to implement protocols that foresee the necessity of timely securing the airway and providing assisted ventilation.
The patient's state of consciousness should be monitored after each local anaesthetic injection.
If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately. Change patient position to supine position if necessary.
CNS symptoms (convulsions, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.
Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis may prevent cardiac arrest.
If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and/or inotropic agents should be considered. Children should be given doses commensurate with age and weight.
In case of cardiac arrest, immediate initiation of cardiopulmonary resuscitation should be performed.

5) PHARMACOLOGICAL PROPERTIES

5.1) Pharmacodynamic properties: Pharmacotherapeutic group: Nervous System / Local Anaesthetics / Anaesthetics, local / Amides / Articaine, combinations. ATC code: N01BB58.

Mechanism of action and pharmacodynamic effects: Articaine, a local amide anaesthetic, reversibly blocks nerve conduction through a well-known mechanism commonly observed with other local amide anaesthetics. This consists in decreasing or preventing the large transient increase in the permeability of excitable membranes to sodium (Na^+) that is normally produced by slight

depolarisation of the membrane. These actions lead the anaesthetic action. As the anaesthetic action progressively develops in the nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines and impulse conduction slows. The pKa of articaine has been estimated at 7.8.

Adrenaline, as vasoconstrictor, acts directly on both α- and β-adrenergic receptors; β-adrenergic effects predominate. Adrenaline prolongs the effect duration of the articaine, and reduces the risk of excessive uptake of articaine into the systemic circulation.

Clinical efficacy and safety: SEPTANEST N and SEPTANEST SP have an onset of 1.5-1.8 min for infiltration and 1.4-3.6 min for nerve block.
The anaesthetic duration of articaine 40 mg/mL with adrenaline 1:100,000 is of 60 to 75 minutes for pulpal anaesthesia and 180 to 360 minutes for soft tissue anaesthesia.
The anaesthetic duration of articaine 40 mg/mL with adrenaline 1:200,000 is of 45 to 60 minutes for pulpal anaesthesia and 120 to 300 minutes for soft tissue anaesthesia.
No difference was observed in pharmacodynamic properties between the adult and the paediatric population.

5.2) Pharmacokinetic properties

• ***Articaine***

Absorption: In three published clinical studies describing the pharmacokinetic profile of the combination articaine hydrochloride 40 mg/ml with adrenaline 10 or 5 micrograms/ml, T_{max} values were between 10 and 12 minutes, with C_{max} values ranging from 400 to 2100 ng/ml.
In clinical trials performed in children, C_{max} was 1382 ng/ml and T_{max} 7.78 min following infiltration of a dose of 2 mg/kg body weight.

Distribution: High protein binding of articaine was observed with human serum albumin (68.5-80.8%), and α/β-globulins (62.5-73.4%). Binding to γ-globulin (8.6-23.7%) was much lower. Adrenaline is a vasoconstrictor added to articaine to slow down absorption into the systemic circulation and thus prolong maintenance of active articaine tissue concentration.The volume of distribution in plasma was about 4 l/kg.

Biotransformation: Articaine is subject to hydrolysis of its carboxyl group by unspecific esterases in the tissue and in blood. Since this hydrolysis is very fast, about 90% of articaine is inactivated by this way. Articaine is additionally metabolised in the liver microsomes. Articainic acid is the major product of cytochrome P450-induced metabolism of articaine, further metabolised to form articainic acid glucuronide.

Elimination: Following dental injection, the elimination half-life of articaine was c.a. 20-40 min. In a clinical trial, plasma concentrations of articaine and articainic acid were shown to decrease rapidly following submucosal injection. Very little articaine was detected in plasma from 12 to 24 hours following injection. More than 50% of the dose was eliminated in the urine, 95% as articainic acid, within 8 hours of administration. Within 24 hours, approximately 57% (68 mg) and 53% (204 mg) of the dose was eliminated in the urine. Renal elimination of unchanged articaine accounted for only about 2% of total elimination.

5.3) Preclinical safety data

Preclinical data reveal no special hazard for humans at therapeutic doses, based on conventional studies of safety pharmacology, chronic toxicity, reproductive toxicity and genotoxicity.

At supratherapeutic doses, articaine has cardiodepressant properties and can exert vasodilatory effects.
Adrenaline exhibits sympathomimetic effects.
Subcutaneous injections of articaine combined with adrenaline induced adverse effects from 50 mg/kg/day in rats and 80 mg/kg/day in dogs after 4 weeks daily repeated administrations. However, these findings are of little relevance to its clinical use as acute administration.

In embryotoxicity studies with articaine, no increase in the foetal mortality rate or malformations were observed at daily i.v. doses of up to 20 mg/kg in rats and 12.5 mg/kg in rabbits.
Teratogenecity was observed in animals treated with adrenaline only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Reproductive toxicity studies conducted with articaine 40 mg/ml + adrenaline 10 micrograms/ml administered by the subcutaneous route at doses up to 80 mg/kg/day revealed no adverse effects on fertility, embryonal/foetal development, or pre- and postnatal development.

No genotoxicity effect was observed during in-vitro and in-vivo studies conducted with articaine alone or in an in vivo study conducted with articaine in combination with adrenaline.
Contradictory findings were raised from in-vitro and in-vivo genotoxicity studies with adrenaline.

6) PHARMACEUTICAL PARTICULARS

6.1) List of excipients: Sodium chloride, Sodium metabisulfite (E223), Sodium edetate, Sodium hydroxide (for pH-adjustment), Water for injections.

6.2) Incompatibilities: Not applicable.

6.3) Shelf life: The expiry date of the product is indicated on the label and packaging. Do not use after the expiry date.

6.4) Special precautions for storage: Store below 25°C. Do not freeze. Protect from light. Keep the cartridges in the tightly closed outer carton.

6.5) Nature and content of container: Single use cylindrical class I glass cartridge sealed at its base by a mobile rubber plunger and at the top by a rubber seal kept in place by an aluminium cap.
Cartridges of 1.7 ml. Box containing 10, 20, 30, 40 or 50 cartridges.
Not all pack sizes may be marketed.

6.6) Special precautions for disposal: To avoid risk of infection (e.g. hepatitis transmission), syringe and needles used to draw up the solution must always be fresh and sterile.
This medicinal product should not be used if the solution is cloudy or discoloured.
The cartridges are intended for single use. If only a portion of a cartridge is used, the remainder must be discarded.
Use immediately after the opening of the cartridge.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7) Israeli drug registration number:
SEPTANEST N: 121-48-30084-00; SEPTANEST SP: 121-52-30088-00

8) Manufacturer: Septodont, Saint-Maur-Des-Fossés, France.

9) Israeli marketing authorization holder: A. Levy Dental Co. Ltd., VAT # 510917768, 27 Kalisher Street, Tel Aviv 65165, Israel.

10) REVISED ON: 03/2021
[SPTNST-N+SP-DCTR-03/21 dated 25/03/2021]

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