SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Scandonest 3% Plain, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 30 mg of mepivacaine hydrochloride.

Each cartridge of 1.7 ml of solution for injection contains 51 mg of mepivacaine hydrochloride.
Each cartridge of 2.2 ml of solution for injection contains 66 mg of mepivacaine hydrochloride.

Excipient(s) with known effect
Each ml contains 0.11 mmol of sodium (2.467 mg/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.
pH: 6.0-6.8

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Scandonest 3% Plain, solution for injection is a local anaesthetic indicated for the local and loco-regional anaesthesia in dental surgery in adults, adolescents and children above 4 years of age (c.a. 20 kg of body weight).

4.2 Posology and method of administration

The medicinal product should only be used by or under the supervision of dentists, stomatologists or other clinicians sufficiently trained and familiar with diagnosis and treatment of systemic toxicity. The availability of appropriate resuscitation equipment and medication and adequately trained staff is recommended before induction of regional anaesthesia with local anaesthetics to enable prompt treatment of any respiratory and cardiovascular emergencies. The patient's state of consciousness should be monitored after each local anaesthetic injection.

Posology
As the absence of pain is related to the patient individual sensibility, the lowest dose of anaesthetic leading to effective anaesthesia should be used. For more extensive procedures one or more cartridges may be required, without exceeding the maximum recommended dose.

For adults, the maximum recommended dose is of 4.4 mg/kg of body weight with an absolute maximum recommended dose of 300 mg for the individuals above 70 kg of body weight corresponding to 10 ml of solution.

Of note, the maximum quantity has to take into account the patient's body weight. As patients possess different body weights, each patient possess a different maximum allowed quantity of mepivacaine that can tolerate. Additionally, there are important individual variations with regards to the onset and duration of action.

The following table lists the maximum allowed doses in adults for the most commonly used anaesthetic techniques and the equivalent in number of cartridges:

Weight (kg)	Mepivacaine hydrochloride dose (mg)	Volume (ml)	Equivalent* in cartridge numbers (1.7 ml)	Equivalent* in cartridge numbers (2.2 ml)
50	220	7.3	4.0	3.0
60	264	8.8	5.0	4.0
≥70	300	10.0	5.5	4.5

* Rounded to the nearest half-cartridge

Paediatric population
Scandonest 3% Plain is contraindicated in children below 4 years of age (ca. 20 kg body weight) (see section 4.3).

Recommended therapeutic dose:
The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average dosage is 0.75 mg/kg = 0.025 ml of mepivacaine solution per kg body weight: ~ ¼ cartridge (15 mg of mepivacaine hydrochloride) for a 20 kg child.

Maximum recommended dosage:
The maximum recommended dose in pediatric population is 3 mg of mepivacaine/kg (0.1 ml mepivacaine/kg).

The following table lists the maximum allowed dose in children and the equivalent in number of cartridges:

Weight (kg)	Mepivacaine hydrochloride dose (mg)	Volume (ml)	Equivalent* in cartridge numbers (1.7 ml)	Equivalent* in cartridge numbers (2.2 ml)
20	60	2	1.2	0.9
35	105	3.5	2.0	1.5
45	135	4.5	2.5	2.0

* Rounded to the nearest half-cartridge

Special populations
Due to the lack of clinical data, particular precaution should be used in order to administer the lowest dose leading to efficient anaesthesia in:
- elderly people,
- patients with renal or hepatic impairment.

Mepivacaine is metabolized by the liver and can lead to elevated plasma levels in patients with hepatic impairment, in particular after repeated use. In case a reinjection is required, patient should be monitored, to identify any sign of relative overdose.

Concomitant use of sedatives to reduce patient anxiety:

If sedative medication is administered, the maximum safe dose of mepivacaine may be reduced due to an additive effect of the combination on central nervous system depression (see section 4.5).

Method of administration
Infiltration and perineural use
For single use

Precautions to be taken before administering the medicinal product
The medicinal product should not be used if cloudy and discoloured.
The rate of injection should not exceed 1 ml of solution per minute.
Local anaesthetics should be injected with caution when there is inflammation and/or infection at the site of the injection. The injection rate shall be very slow (1 ml/min).

Risk associated with an accidental intravascular injection
Accidental intravascular injection (e.g.: inadvertent intravenous injection into the systemic circulation, inadvertent intravenous or intra-arterial injection in the head area and neck area) may be associated with severe adverse reactions, such as convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest, due to the sudden high level of mepivacaine in the systemic circulation.
Thus, to ensure that the needle does not penetrate a blood vessel during injection, aspiration should be performed before the local anaesthetic 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 mepivacaine's potential chemical neurotoxicity as it may impair the perineural blood supply and prevent mepivacaine local wash-out.

4.3 Contraindications

- Hypersensitivity to the active substance (or any local anaesthetics agent of the amide type) or to any of the excipients listed in section 6.1,
- Children below 4 years of age (ca. 20 kg body weight),
- Severe disorders of atrioventicular conduction not compensated by pace maker,
- Poorly controlled epileptic patient.

4.4 Special warnings and precautions for use

Special warnings

If there is any risk of an allergic reaction, choose different medicine for anaesthesia (see Section 4.3).

Mepivacaine must be used safely and effectively under appropriate conditions:

The local anaesthetic effects may be reduced when Scandonest 3% Plain is injected into an inflamed or infected area.

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.

Mepivacaine must be used with caution in:

Patients with cardiovascular disorders:
- Peripheral vascular disease,
- Arrhythmias particularly of ventricular origin,
- Atrio-ventricular conduction disorders,
- Heart failure,
- Hypotension.

Mepivacaine should be administered with caution in patients with impaired cardiac function since they may be less able to compensate or worsen changes due to prolongation of atrio-ventricular conduction.

Epileptic patients:
Because of their convulsive actions, all local anaesthetics should be used very cautiously.
For poorly controlled epileptic patients, see section 4.3.

Patients with a hepatic disease:
The lowest dose leading to efficient anaesthesia should be used.

Patients with a kidney disease:
The lowest dose leading to efficient anaesthesia should be used.

Patients with porphyria
Scandonest 3% Plain should only be used to patients with acute porphyria when no safer alternative is available. Caution should be taken in all patients with porphyria, as this medicinal product may trigger porphyria.

Patients with acidosis
Caution should be used in case of acidosis such as worsened of renal insufficiency or poorly control of type 1 diabetes mellitus.

Elderly patients:
Dosages should be reduced in elderly patients (due to lack of clinical data).

Mepivacaine should be administered with caution in patients, who are using antiplatelet/anticoagulant medicines or are suffering from a coagulation disorder, because of higher risk of bleeding. The higher risk of bleeding is more associated with the procedure, rather than with the medicine.

<u>Precautions for use</u>

Local anaesthetics should only be employed by healthcare professionals who are well versed in diagnosis and management of dose-related toxicity and other acute emergencies which might arise from the block to be employed. The immediate availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies should be considered (see section 4.2). 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, possibly, death.

Hypoxaemia and metabolic acidosis may potentiate the cardiovascular toxicity. Early control of seizures and aggressive airway management to treat hypoxaemia and acidosis may prevent cardiac arrest.

Concomitant use of the other medicinal products may require thorough monitoring (see section 4.5).

This medicinal product contains 24.67 mg sodium per 10 ml (maximum recommended dose), equivalent to 1.23 % of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Additive interactions with other local anaesthetics
Toxicity of local anaesthetics is additive. The total dose of administered mepivacaine should not exceed the maximum recommended dose.

H2 antihistaminics (cimetidine)
Increased serum levels of amide anaesthetics have been reported after concomitant administration of cimetidine. Cimetidine reduces the clearance of mepivacaine.

Sedatives (central nervous system depressants)
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.

Antiarrhythmic drugs
Patients who are being treated with antiarrhythmic drugs may encounter an accumulation of side effects after the use of mepivacaine due the similarity of structures (such as Class I drug i.e. lidocaine).

CYP1A2 inhibitors
Mepivacaine is metabolised primarily by CYP1A2 enzyme. Inhibitors of this cytochrome (e.g. ciprofloxacin, enoxacin, fluvoxamine) may decrease its metabolism, increase the risk of adverse effects and contribute to prolonged or toxic blood levels. Increased serum levels of amide anaesthetics have also been reported after concomitant administration of cimetidine, which is probably due to the inhibitory effect of cimetidine on CYP1A2. Caution is advised when associating the product of interest with these medications as dizziness may last longer (see section 4.7.).

Propranolol
The clearance of mepivacaine may be reduced when associated with propranolol and it may result in higher serum concentrations of the anaesthetic. Caution should be exercised when mepivacaine is administered concomitantly with propranolol.

4.6 Fertility, pregnancy and lactation

Fertility
No relevant data reported any toxic effects on fertility in animals with mepivacaine. To date, no data are available on humans.

Pregnancy
Clinical studies were not performed in pregnant women and no cases of pregnant women injected with mepivacaine 30 mg/ml were reported in the literature. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Therefore, as a precautionary measure, it is preferable to avoid the use of mepivacaine during pregnancy, unless necessary.

Breastfeeding
No nursing mothers were included in the clinical studies with Scandonest 3% Plain. However, considering the lack of data for mepivacaine, a risk to the newborns/infants cannot be excluded. Therefore, nursing mothers are advised not to breastfeed within 10 hours following anaesthesia with Scandonest 3% Plain.

4.7 Effects on ability to drive and use machines

Scandonest 3% Plain 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 mepivacaine (see section 4.8). 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

Summary of the safety profile

Adverse reactions following administration of Scandonest 3% Plain are similar to those observed with other local amide anaesthetics. These adverse reactions are, in general, dose-related and may result from high plasma levels caused by overdose, rapid absorption or unintended intra-vascular injection. They may also result from hypersensitivity, idiosyncrasy, or diminished tolerance by patient.
Serious adverse experiences are generally systemic.

Tabulated list of adverse reactions

The reported adverse effects come from spontaneous reporting 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).
Frequency "not known": "not known (cannot be estimated from the available data)".

MedDRA Sytem Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Rare	Hypersensitivity Anaphylatic / anaphylactoid reactions Angioedema (Face / tongue / lip / throat / larynx[1] / periorbital oedema) Bronchospasm / asthma[2] Urticaria
Psychiatric disorders	Not Known	Euphoric mood Anxiety/Nervousness[3]
Nervous system disorders	Common	Headache
	Rare	Neuropathy[4] : Neuralgia (Neuropathic pain) Paresthesia (i.e., burning, prickling, itching, tingling, local sensation of heat or cold, with no apparent physical cause) of oral and perioral structures Hypoesthesia / numbness (oral and perioral) Dysesthesia (oral and perioral), including dysgeusia (e.g., taste metallic, taste distorted), ageusia Dizziness (light headedness) Tremor[3] Deep CNS depression: Loss of consciousness Coma Convulsion (including tonic-clonic seizure) Presyncope, syncope;

		Confusional state, disorientation Speech disorder[3] (e.g., dysarthria, logorrhea) Restlessness / agitation[3] Balance disorder (disequilibrium) Somnolence
	Not known	Nystagmus
Eye disorders	Rare	Visual impairment Vision blurred Accommodation disorder
	Not known	Horner's syndrome Eyelid ptosis Enophthalmos Diplopia (paralysis of oculomotor muscles) Amaurosis (blindness) Mydriasis Miosis
Ear and labyrinth disorders	Rare	Vertigo
	Not Known	Ear discomfort Tinnitus Hyperacusis
Cardiac disorders	Rare	Cardiac arrest Bradyarrhythmia Bradycardia Tachyarrhythmia (including ventricular extrasystoles and ventricular fibrillation)[5] Angina pectoris [6] Conduction disorders (atrioventricular block) Tachycardia Palpitations
	Not known	Myocardial depression
Vascular disorders	Rare	Hypotension (with possible circulatory collapse)
	Very rare	Hypertension
	Not known	Vasodilatation Local/ Regional hyperaemia
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression Bradypnoea Apnoea (respiratory arrest) Yawning Dyspnoea[2] Tachypnea
	Not known	Hypoxia[7] (including cerebral) Hypercapnia[7] Dysphonia (Hoarseness[1])

Gastrointestinal disorders	Rare	Nausea Vomiting Gingival / oral mucosal exfoliation (sloughing) / ulceration Swelling[8] of tongue, lip, gums
	Not known	Stomatitis, glossitis, gingivitis Salivary hypersecretion
Skin and subcutaneous tissue disorders	Rare	Rash (eruption) Erythema Pruritus Swelling face Hyperhidrosis (sweating or perspiration)
Musculoskeletal and connective tissue disorders	Rare	Muscle twitching Chills (shivering)
General disorders and administration site conditions	Rare	Local swelling Injection site swelling
	Not known	Chest pain Fatigue, asthenia (weakness) Feeling hot Injection site pain
Injury, poisoning and procedural complications	Not known	Nerve injury

Description of selected adverse reactions

[1] laryngo-pharyngeal oedema may characteristically occur with hoarseness and/or dysphagia;

[2] bronchospasm (bronchoconstriction) may characteristically occur with dyspnoea;

[3] 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.)

[4] neural pathologies that may occur with the various symptoms of abnormal sensations (i.e., paresthesia, hypoesthesia, dysesthesia, hyperesthesia, etc) of the lips, tongue and oral tissues. These data originated in post-marketing reports, mostly following nerve blocks in mandible, involving various branches of the trigeminal nerve;

[5] mostly in patients with underlying cardiac disease or those receiving certain drugs;

[6] in predisposed patients or those with risk factors of ischemic heart disease;

[7] hypoxia and hypercapnia are secondary to respiratory depression and / or to seizures and sustained muscular exertion;

[8] by accidental biting or chewing of the lips or tongue while the anaesthesia persists.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Types of overdose
Overdose of local anaesthetics may be absolute, resulting from the injection of excessive doses, or relative, resulting from the injection of a normally non-toxic dose under particular circumstances. These include inadvertent intravascular injection or abnormal rapid absorption into the systemic circulation, or delayed metabolism and elimination of the product.

Symptoms
In case of relative overdose, patients generally present symptoms within 1-3 minutes. Whereas in case of absolute overdose, signs of toxicity, depending on the injection site, appear about 20-30 minutes after the injection.
Toxic effects are dose-dependent, comprising progressively more severe neurological manifestations, followed by vascular, respiratory and finally cardiovascular signs such as hypotension, bradycardia, arrhythmia and cardiac arrest

CNS toxicity occurs gradually, with symptoms and reactions of progressively increasing severity. Initial symptoms include agitation, a feeling of intoxication, a sensation of numbness in the lips and tongue, paraesthesia around the mouth, dizziness, visual and hearing disturbances, and buzzing in the ears. Manifestation of these effects during injection of the product is a warning signal and the injection should be stopped immediately.

Cardiovascular symptoms occur at plasma levels exceeding those inducing CNS toxicity and are therefore generally preceded by signs of CNS toxicity, unless the patient is under general anaesthesia or is heavily sedated (e.g. by a benzodiazepine or barbiturate). Loss of consciousness and the onset of generalized seizures may be preceded by premonitory symptoms such as joint and muscle stiffness, or twitching. Seizures may last from a few seconds to several minutes and rapidly lead to hypoxia and hypercapnia, as a result of increased muscular activity and insufficient ventilation. In severe cases, respiratory arrest may occur.

Undesirable toxic effects may appear at plasma concentrations upper than 5 mg/l, and convulsions could appear with 10 mg/l or higher. Limited data of overdose are available.

Acidosis exacerbates the toxic effects of local anaesthetics.

If a rapid intravascular injection is administered, a high blood concentration of mepivacaine in the coronary arteries may lead to myocardial failure, possibly followed by cardiac arrest, before the CNS is affected. The data on this effect remains controversial (see Sections 4.4 and 5.1).

Management
If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately.
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 are of vital importance.
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.
Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

Dialysis is not effective in treating an overdose of Mepivacaine. Elimination can be accelerated by acidifying the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous System/Anaesthetics/Local anaesthetics/Amides/Mepivacaine
ATC code: N01 BB 03

Mechanism of action
Mepivacaine is an amide local anaesthetic.
Mepivacaine reversibly inhibits the conduction of nerve impulses by decreasing or blocking sodium (Na+) flow during propagation of the nerve action potential. 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. Mepivacaine has a rapid onset, a high potency of anaesthesia and a low toxicity.
The mepivacaine displays slight vasoconstrictive properties leading to a longer duration of action than with most other local anesthetics when administered without a vasoconstrictor. Studies revealed, that mepivacaine has vasoconstrictive properties. This property could be beneficial when the use of vasoconstrictor is contraindicated. Several factors such as pH of tissue, pKa, lipid solubility, local anaesthetic concentration, diffusion in the nerve of local anaesthetic, etc., may influence the onset and the duration of the local anaesthetic.

Onset of action

When a dental peripheral nerve block is performed, mepivacaine effect occurs rapidly (generally within 3 to 5 minutes).

Analgesia duration

Pulp anaesthesia generally lasts approximately 25 minutes after maxillary infiltration and around 40 minutes after inferior alveolar block, whereas anaesthesia of soft tissue was maintained around up to 90 minutes after maxillary infiltration and approximatively 165 minutes after inferior alveolar nerve block.

Bioavailability
The bioavailability is 100% at the action site.

5.2 Pharmacokinetic properties

Absorption
Peak plasma levels of mepivacaine 30 mg/ml solution following peri-oral injections during dental usual procedures were determined in various clinical studies. The maximum plasma level of mepivacaine is achieved approximately after 30-60 minutes. Mepivacaine maximum concentrations were reported to be between 0.4 – 1.2 µg/ml at around 30 minutes post-intraoral injection with one cartridge and between 0.95-1.70 µg/ml with two cartridges. The ratio of the average plasma levels following one and two cartridges were approximately 50%, evidencing a dose proportionality at these dose levels. These plasmatic concentrations are well below the threshold of CNS and CVS toxicity, respectively 10 to 25 fold lower.

Distribution
Mepivacaine distribution covers all body tissues. Higher concentrations are found in highly perfused tissues such as liver, lungs, heart and brain. Mepivacaine binds to plasmatic proteins up to around 75% and can cross placental barrier by simple diffusion.

Metabolism
As all amide-type local anaesthetics, mepivacaine is largely metabolised in the liver by microsomal enzymes (cytochrome P450 1A2 (CYP1A2)). Given this fact, inhibitors of P450 isoenzymes may decrease its metabolism and increase the risk of adverse effects (see section 4.5.). Over 50% of a dose is excreted as metabolites into the bile but these probably undergo entero-hepatic circulation as only small amounts appear in the faeces.

Elimination
The plasma elimination half-life is 2 hours for adults. Clearance of amides is dependent on hepatic blood flow. The plasma half-life is prolonged if the patient is suffering from liver and renal insufficiency. The duration of the local anaesthetic is unrelated to the half-life as its action is terminated when the drug is removed from the receptor. Metabolites are excreted in the urine with less than 10% of unchanged mepivacaine.
Elimination can be accelerated by acidifying the urine (See section 4.9).

5.3 Preclinical safety data

General toxicity studies (Single dose toxicity, Repeat-dose toxicity) were performed with mepivacaine demonstrating a good safety margin. *In vitro* and *in vivo* testing carried out on mepivacaine hydrochloride did not reveal any genotoxic effect of this product.
No relevant reproductive and development toxicity study demonstrated teratogenic effects with mepivacaine.
No specific carcinogenicity studies were performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH-adjustment)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with any other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Single use type I glass cartridge, sealed at its base by a mobile type I synthetic rubber and at the top by a type I synthetic rubber seal kept in place by an aluminium cap.
Cartridges of 1.7 ml or 2.2 ml.
Box containing 50 cartridges.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridges are intended for single use. The drug administration to the patient should take place immediately after the opening of the cartridge.

As for any cartridge, the diaphragm should be disinfected prior to use. It should be carefully swabbed either with 70% ethyl alcohol or with 90% pure isopropyl alcohol for pharmaceutical use.

The cartridges should under no circumstance be dipped into any solution whatsoever.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Septodont Limited
Units R & S, Orchard Business Centre
St Barnabas Close, Allington
Maidstone, Kent ME16 0JZ
UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER(S)

PL 08313/0023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02/11/1987

Date of latest renewal: 29/01/2005

10. DATE OF REVISION OF THE TEXT

27/03/2020