Scandonest 2% SPECIAL (WITH ADRENALINE)

A local and loco-regional anaesthetic for dental use

Description

The anaesthetic ingredient is N-Methyl pipecolic acid dimethyl-anilide hydrochloride, more commonly known as mepivacaine hydrochloride, a product which is quoted in several pharmacopoeias.

	cartridge 2.2 mL	cartridge 1.8 mL
Mepivacaine hydrochloride	44 mg	36 mg
Adrenaline base	22 µg	18 µg
Sodium chloride	14.3 mg	11.7 mg
Sodium edetate	0.55 mg	0.45 mg
Potassium metabisulphite	2.64 mg	2.16 mg
Sodium hydroxide (to adjust pH) Hydrochloric acid q.s. Water for injections q.s. to one cartridge of	2.2 mL	1.8 mL

Excipient(s) with known effect: Each ml contains 0.11 mmol of sodium (2,606 mg/mL) and 0.011 mmol of potassium.

Pharmacological properties

- **Pharmacodynamic properties**

Therapeutic class: Local anaesthetic

ATC Code: N01BB53

The mechanism underlying the anaesthetic action of mepivacaine is similar to that of other commonly used local 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 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 mepivacaine has been estimated at 7.7.

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

Onset (min)	Duration of pulpal anesthesia (min)	Duration of soft tissue anesthesia (min)
2 – 4	60-85	170 – 190

- **Pharmacokinetic properties**

Absorption

Peak plasma levels of combined solutions mepivacaine hydrochloride 20 mg/ml with adrenaline 0.1 mg/ml following peri-oral injections during dental usual procedures were determined in various clinical studies. Mepivacaine hydrochloride Cmax was reported to be between 0.62 – 1.3 µg/ml with one to two cartridges following intraoral injection.

Distribution

Mepivacaine is rapidly distributed to tissues and binds to plasmatic proteins up to around 75%.

Metabolism

As all amide-type local anaesthetics, mepivacaine is largely metabolised in the liver by microsomal enzymes undergoing extensive hepatic biotransformation with <5% urinary excretion of the unchanged drug. Metabolism is primarily through hydroxylation of the parent compound to inactive 3-OH-mepivacaine and 4-OH-mepivacaine by CYP1A2. Over 50% of a dose is excreted as metabolites into the bile undergoing entero-hepatic circulation as only small amounts appear in feces.

Elimination

The excretion in principally via the kidneys and metabolites are excreted in the urine with less than 5% of unchanged mepivacaine. The plasma elimination half-life is reported to be around 2 hours in adults.

- **Preclinical safety data**

General toxicity studies (Single dose toxicity, Repeat-dose toxicity) were performed with mepivacaine demonstrating a good safety margin. Adrenaline exhibits sympathomimetic effects.

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. However, some effects on fertility and teratogenicity were observed in animals treated with adrenaline only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

No specific carcinogenicity studies were performed.

Indications

SCANDONEST is indicated for the production of local anaesthesia for dental procedures by infiltration injection or nerve block.

Contraindications

- Hypersensitivity to mepivacaine (or any local anaesthesic agent of the amide type) or to adrenaline or to any of the excipients.
- Children below 3 years old (ca. 20 kg body weight).

Due to mepivacaine:

- Severe conduction disturbances;
- Poorly controlled epileptic patient.

Due to adrenaline:

- Uncontrolled / severe hypertension;
- Severe ischemic heart disease;

- Persistent / refractory tachyarrhythmia.

Special warnings and precautions for use

Before using this medicinal product, it is important:

- To make inquiries into the patient's diathesis, current therapies and history;
- To maintain verbal contact with the patient;
- To have resuscitative equipment at hand (see section Overdose).

- **Special warnings**

This product must be used with caution in:

Patients with cardiovascular disorders

- Peripheral vascular disease

- Arrhythmias particularly of ventricular origin

- Heart failure

- Hypotension.

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

Patients with cerebral circulation disturbances, history of strokes

It is recommended that dental treatment with mepivacaine / adrenaline be deferred for six months following a stroke due to the increased risk of recurrent strokes.

Epileptic patients

Because of their convulsive actions, all local anaesthetics should be used very cautiously.

For poorly controlled epileptic patients, see section Contraindications.

Patients with hepatic disease

Particular precaution should be used in order to administer the lowest dose leading to efficient anaesthesia in patients with hepatic impairment, in particular after repeated use

Patients with renal disease

The lowest dose leading to efficient anaesthesia should be used.

Patients receiving treatment with antiplatelets / anticoagulants

The increased risk of severe bleeding after accidental vessel puncture and during oro-maxillo-facial surgery should be considered. INR monitoring should be increased in patients taking anticoagulants. The higher risk of bleeding is more associated with the procedure, rather than with the medicine.

Patients with porphyria

Mepivacaine 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 uncontrolled diabetes

This product should be used very cautiously due to hyperglycemic effect of adrenaline.

Patients with susceptibility of acute angle-closure glaucoma

This product should be used very cautiously due to presence of adrenaline.

Elderly patients

Dosages should be reduced in elderly patients (lack of clinical data).

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.

Patients with thyrotoxicosis

The product should be used cautiously due to the presence of adrenaline

Patients with pheochromocytoma

The product should be used cautiously due to the presence of adrenaline

This product must be used safely and effectively under appropriate conditions:

Adrenaline impairs the flow of blood in the gums, potentially causing local tissue necrosis.

Injection of local anaesthetics into inflamed tissues is likely to result in a loss of effectiveness and/or increased dose requirement (due to acidosis and hyperaemia) and should be avoided where possible.

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 medicine contains potassium metabisulphite, a sulphite that may rarely cause hypersensitivity reactions and bronchospasm.

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

The medicine contains potassium, less than 1 mmol (39 mg) per cartridge, i.e. essentially 'potassium-free'.

The medicine contains less than 1 mmol sodium (23 mg) per cartridge, that is to say essentially 'sodium free'.

- **Precautions for use**

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 adrenaline and 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 or after any needle movement. 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 and the presence of adrenaline as it may impair the perineural blood supply and prevent mepivacaine local wash-out.

Risk of Takotsubo cardiomyopathy or stress-induced cardiomyopathy:

Stress cardiomyopathy induced by injected catecholamines has been reported.

Because of the presence of adrenaline, precautions and monitoring should be enhanced in the following situations: patients stressed prior dental procedure or conditions of use which may contribute to induce a systemic passage of adrenaline e.g. an administered dose higher than recommended or in case of an accidental intravascular injection.

Any previous knowledge of such underlying conditions in patients requiring dental anesthesia should be minded and a minimal dose of local anaesthetic with vasoconstrictor used.

Concomitant use of other medicinal products may require thorough monitoring (see section Interaction with other medicinal products and other forms of interaction).

Undesirable effects

a) Summary of the safety profile

Adverse reactions following administration of mepivacaine / adrenaline are similar to those observed with other local amide anaesthetics / vasoconstrictors. Adverse reactions following high systemic concentrations as caused by overdose, rapid absorption or unintended intra-vascular injection can be serious (see section Overdose). They may also result from hypersensitivity, idiosyncrasy, or diminished tolerance by the specific patient.

Serious adverse reactions are generally systemic. The presence of adrenaline increases the product's safety profile due to its sympathomimetic effects.

b) Tabulated list of adverse reactions

The reported adverse reactions 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) and "Not known (cannot be estimated form the available data)".

MedDRA System Organ Class	**Frequency**	**Adverse Reactions**
Infections and infestations	Not known	Gingivitis
Immune system disorders	Rare	Hypersensitivity[1]
Psychiatric disorders	Not known	Anxiety/Nervousness /Restlesness, agitation, Euphoric mood, Logorrhea
Nervous system disorders	Common	Headache
	Rare	Neuropathy[2]: Neuralgia (neuropathic pain) Hypoesthesia[2] Horner's syndrome, Tremor Dizziness (lightheadedness)
	Very rare	Paresthesia[2,3]
	Not known	Deep CNS depression[4]
Eye disorders	Rare	Amaurosis (blindness) Diplopia, Mydriasis Miosis, Visual impairment, Vision blurred, Accommodation disorder Eyelid ptosis, Enophthalmos, Exophtalmos
Ear and labyrinth disorders	Not known	Tinnitus Hyperacusis
Cardiac disorders	Common	Palpitations
	Rare	Conduction disorders, Atrioventricular block Bradyarrhythmia, Tachycardia, Bradycardia
	Not known	Cardiac arrest[5], Myocardial depression[5], Tachyarrhytmia (including ventricular extrasystoles and ventricular fibrillation)[5] Angina pectoris[6]

MedDRA System Organ Class	Frequency	Adverse Reactions
Vascular disorders	Common	Hypertension, Hypotension (with possible circulatory collapse) Pallor (local, regional, general)
	Not known	Vasodilatation, Vasoconstriction Local/ Regional hyperaemia
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression[7] Hypoxia[8] (including brain) Hypercapnia[8]
Gastrointestinal disorders	Rare	Nausea Vomiting
	Not known	Gingival/oral mucosal exfoliation (sloughing)/ulceration Swelling of tongue, lips, gums[9] Stomatitis, glossitis Salivary hypersecretion Diarrhoea
Skin and subcutaneous tissue disorders	Rare	Erythema
	Not known	Swelling face Hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Trismus
	Not known	Muscle twitching
General disorders and administration site conditions	Rare	Pain Injection site pain Injection site haematoma Injection site reaction including exfoliation / necrosis [10]
	Not known	Local swelling Injection site swelling Fatigue, asthenia (weakness) Feeling cold, feeling hot, feeling abnormal Discomfort Chills (shivering)

MedDRA System Organ Class	Frequency	Adverse Reactions
Injury, poisoning and procedural complications	Rare	Nerve injury

c) Description of selected adverse reactions

[1] Hypersensitivity should not be mistaken with syncopal episodes (cardiac palpitations due to adrenaline). It may characteristically occur with various symptoms e.g. rash (eruption), urticarial, pruritus, bronchospasm/asthma, wheezing, anaphylactic or anaphylactoid reactions and angioedema.

Angioedema include oedema of face / tongue / lip / throat / larynx / periorbital oedema.

Laryngo-pharyngeal oedema may characteristically occur with hoarseness and / or dysphagia. Bronchospasm (bronchoconstriction) may characteristically occur with dyspnoea;

[2] In the orofacial area;

[3] Paresthesia can be defined as transient anesthesia or altered sensation (i.e., burning, pricking skin sensation, tingling with no apparent physical cause or itching considered as partial anesthesia) well beyond the expected duration of anesthesia. Most cases of paresthesia reported after dental treatment are transient and resolve within days, weeks or months. Paraesthesia includes all abnormal sensation e.g. dysesthesia, burning sensation, numbness, dysgeusia (e.g., taste metallic, taste disturbance), ageusia. Persistent paresthesia, mostly following nerve blocks in the mandible, is characterized by slow, incomplete, or lack of recovery. Very rare cases of prolonged or irreversible nerve injury and gustatory loss have been reported after mandibular block analgesia;

[4] CNS depression may be characterised by various symptoms such as loss of consciousness, coma, convulsion (including tonic clonic seizure), presyncope, syncope, confusional state, disorientation, vertigo, speech disorder (e.g. dysarthria, logorrhea), balance disorder (disequilibrium), somnolence, nystagmus, yawning;

[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] Respiratory depression may occur through different symptoms, e.g; apnoea (respiratory arrest), hypoventilation, hyperventilation, tachypnea, bradypnea;

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

[9] By accidental biting or chewing of the lips or tongue while the anaesthesia persists;

[10] Due to excessive local effect of the vasoconstrictor.

d) Paediatric population

The safety profile was similar in children and adolescents from 4 to 18 years old compared to adults.

Dosage and administration

As with all local anaesthetics, the dose varies and depends upon the area to be anaesthetized, the vascularity of the tissues, individual tolerance and the technic used. Debilitated, elderly patients, acutely ill patients and children, should be given reduced doses commensurate with their age and physical status.

Adults

1 cartridge for routine work. This dose may be increased for long or difficult procedures or for mixed anaesthesia (block and local). As a rule, do not exceed 3 cartridges.

Children

6 to 14 years of age: usual dose : 1.35 mL. Do not exceed 2.7 mL

3 to 6 years of age: maximum recommended dose: 1.8 mL

The product is injected either locally or in the vicinity of a dental nerve trunk.

Any unused portion of a cartridge should be discarded.

Interactions with other medicinal products and other forms of interaction

- **Due to the presence of mepivacaine:**

Interactions requiring precautions for use:

Other local anesthetics

Mepivacaine should be used with caution in patients treated concomitantly with other products for local anesthesia, as the toxic effects are additive (risk of overdose).

Sedatives (central nervous system depressants):

Reduced doses of this product should be used due to additive effects.

Non-selective beta-adrenergic blockers (e.g., propranolol, nadolol):

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

CYP1A2 inhibitors

Mepivacaine is metabolised primarily by CYP1A2 enzyme. Inhibitors of this cytochrome (e.g. ciprofloxacin, enoxacin, fluvoxamine, verapamil) 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 Effects on ability to drive and use machines).

- **Due to the presence of adrenaline:**

Interactions that are not recommended:

Postganglionic adrenergic blocking agents (e.g., guanadrel, guanethidine, and rauwolfia alkaloids):

Reduced doses of this product should be used under strict medical supervision followed by careful aspiration due to possible increase response to adrenergic vasoconstrictors: risk of hypertension and other cardiovascular effects.

Interactions requiring precautions for use:

Halogenated volatile anaesthetics :

Reduced doses of this product should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia.

Tricyclic antidepressants (TCA) (e.g., amitriptyline, desipramine, imipramine, nortriptyline, maprotiline and protriptyline):

Dose and rate of administration of this product should be reduced due to strengthening of adrenaline activity.

MAO inhibitors [both A-selective MAO inhibitors (e.g., brofaromine, moclobemide, toloxatone) ***and non-selective MAO inhibitors*** (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.

Sympathomimetic vasopressors (e.g., mainly cocaine but also amphetamines, phenylephrine, pseudoephedrine, oxymetazoline) ***and other sympathomimetics*** (e.g., isoproterenol, levothyroxine, methyldopa, antihistamines (such as chlorpheniramine, diphehydramine):

There is a risk of adrenergic toxicity. Reduced doses of this product should be used.

If cocaine has been used within 24 hours, the planned dental treatment should be postponed.

Catechol-O-methyl transferase inhibitors (COMT inhibitors) (e.g., entacapone, tolcapone):

Arrhythmias, increased heart rate and blood pressure variations may occur.

Serotonin-norepinephrine reuptake inhibitors (SNRI) (e.g., venlafaxine, milnacipran):

Dose and rate of administration of this product should be reduced due to additive or synergistic effects on blood pressure and heart rate.

Drug with combination of adrenergic-serotoninergic effect (e.g., venlafaxine, milnacipran, sertraline):

Dose and rate of administration of this product should be reduced due to additive or synergistic effects on blood pressure and heart rate

Drugs causing arrhythmias in combination with adrenaline (e.g., antiarrhythmics like digitalis, quinidine):

Dose of administration of this product should be reduced due to additive or synergistic effects on heart rate.

Ergot-type oxytocic drugs (e.g., methysergide, ergotamine, ergonovine):

Use this product under strict medical supervision due to additive or synergistic increases in blood pressure and/or ischemic response.

Phenothiazines and other neuroleptics:

Use under caution in patient treated with phenothiazines considering the risk of hypotension due to possible inhibition of adrenaline effect.

Non-selective beta-adrenergic blockers (e.g., propranolol, nadolol):

Reduced doses of this product should be used due to possible increase in blood pressure.

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 literature reported cases of pregnant women injected with mepivacaine 20 mg/mL with adrenaline 0.01 mg/mL. Animal studies do not indicate direct or indirect harmful effects of mepivacaine with respect to reproductive toxicity. Adrenaline alone and at doses higher than maximal recommended dose is toxic to reproduction according to animal studies (see section Preclinical safety data).

In the event of inadvertent intravascular administration in the mother, adrenaline can reduce uterine perfusion.

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

- **Breastfeeding**

No nursing mothers were included in the clinical studies with the product. However, considering the lack of data for mepivacaine, a risk to the newborns/infants cannot be excluded. 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 14 hours following anesthesia.

Effects on ability to drive and use machines

Mepivacaine in combination with adrenaline solution 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 / adrenaline (see section Undesirable effects). Patients experiencing these symptoms should not drive or use machinery until any such symptoms have completely resolved.

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 the product.

- **Symptoms**

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.

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 Special warnings and precautions for use and Pharmacodynamic properties).

- **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 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.

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.

Pharmaceutical particulars

- **Special precautions for storage**

The product should be stored in a dry place below 25ºC (77°F).

Do not freeze.

Keep the cartridges in the outer carton in order to protect from light.

- **Presentations**

- Box of 50 cartridges containing each 2.2 mL of solution

- Box of 50 cartridges containing each 1.8 mL of solution

- **Special precautions for disposal and other handling**

As for any cartridge, the diaphragm should be disinfected just 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 circumstances be dipped into any solution whatsoever.

The solution for injection should not be mixed with any other product into the same syringe.

No open cartridge of anaesthetic solution should be reused.

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