SCANDONEST INJECTION 3% WITHOUT VASOCONSTRICTOR

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	66 mg	54 mg
Sodium chloride	13.2 mg	10.8 mg
Sodium hydroxide (to adjust pH) Water for injections q.s. to one cartridge of	2.2 mL	1.8 mL

Excipient with known effect: Each ml contains 0.11 mmol of sodium (2,467 mg/ml).

Pharmacological properties

- **Pharmacodynamic properties**

Therapeutic class: Local anaesthetic

ATC Code: N01BB03

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.

The anesthetic effect of mepivacaine appeared within 5 min after injection and lasted for 25 to 40 min for infiltration and alveolar nerve block respectively and 90 to 165 min for soft tissue.

- **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. 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.

Biotransformation

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 Interactions with other medicinal products and other forms of interaction). 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 5% of unchanged mepivacaine.

Elimination can be accelerated by acidifying the urine (See section Overdose).

- **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.

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 any of the excipients.
- Children below 3 years of age (ca. 20 kg body weight).
- Severe disorders of atrioventicular conduction not compensated by pace maker.
- Poorly controlled epileptic patient.

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;
- Atrio-ventricular conduction disorders;
- 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.

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 effective anaesthesia in patients with hepatic impairment, in particular after repeated use.

Patients with renal disease:

The lowest dose leading to effective 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 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:

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

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

The injection rate shall be very slow (1 ml/min).

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.

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

Precautions

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 or after injection site change. 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.

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

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

Undesirable Effects

a) Summary of the safety profile

Adverse reactions following administration of mepivacaine are similar to those observed with other local amide anaesthetics. 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 patient.

Serious adverse reactions are generally systemic.

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 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000) and Very rare (< 1/10,000) and "Not known (cannot be estimated from 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	Euphoric mood Anxiety/Nervousness/Agitation/ Restlesness
Nervous system disorders	Common	Headache
	Rare	Neuropathy[2] : Neuralgia (neuropathic pain)[2] Paresthesia[2, 3] Hypoesthesia[2] Horner's syndrome Dizziness (lightheadedness) Tremor Deep CNS depression[4]
Eye disorders	Rare	Visual impairment Vision blurred Accommodation disorder
	Not known	Eyelid ptosis Enophthalmos Exophtalmos Diplopia (paralysis of oculomotor muscles) Amaurosis (blindness) Mydriasis Miosis
Ear and labyrinth disorders	Not known	Tinnitus Hyperacusis

Cardiac disorders	Rare	Cardiac arrest[5] Bradyarrhythmia Bradycardia Tachyarrhytmia (including ventricular extrasystoles and ventricular fibrillation)[5] Angina pectoris[6] Conduction disorders (atrioventricular block) Tachycardia Palpitations
	Not known	Myocardial depression[5]
Vascular disorders	Rare	Hypotension (with possible circulatory collapse)
	Very rare	Hypertension
	Not known	Vasodilatation Local/regional hypereamia
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression[7]
	Not known	Hypoxia[8] (including cerebral) Hypercapnia[8]
Gastrointestinal disorders	Rare	Nausea Vomiting Gingival/oral mucosal exfoliation (sloughing)/ulceration Swelling[9] of tongue, lips, gums
	Not known	Stomatitis, glossitis
Skin and subcutaneous tissue disorders	Rare	Erythema Swelling face Hyperhidrosis (sweating or perspiration)
Musculoskeletal and connective tissue disorders	Rare	Muscle twitching
	Not known	Trismus
General disorders and administration site conditions	Rare	Local swelling Injection site swelling Chills (shivering)

	Not known	Injection site reaction Chest pain Fatigue, asthenia (weakness) Feeling hot, Feeling cold, Feeling abnormal Injection site pain
Injury, poisoning and procedural complications	Not known	Nerve injury

c) Description of selected adverse reactions

[1] Hypersensitivity may characteristically occur with various symptoms e.g. rash (eruption), urticaria, 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 (dysphonia) and/or dysphagia. Bronchospasm (bronchoconstriction) may characteristically occur with dyspnoea.

Anaphylactic or anaphylactoid reactions were described with the product with a very rare frequency;

[2] In the orofacial area;

[3] Paresthesia can be defined as transient anesthesia or altered sensation (e.g., burning, prickling, skin sensation, tingling, local sensation of heat or cold 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, hyperesthesia, 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.

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

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.

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).

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

The clearance of mepivacaine may be reduced when associated with non-selective beta-adrenergic blockers and it may result in higher serum concentrations of the anaesthetic. Caution should be exercised when mepivacaine is administered concomitantly with non-selective beta-adrenergic blockers.

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 also 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 (Section Effects on ability to drive and use machines).

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 30 mg/mL. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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 mepivacaine 30 mg/mL. 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 14 hours following anaesthesia with the product.

Effects on ability to drive and use machines

Mepivacaine 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 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**

Store below 25°C (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.

Product Owner

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