

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0196/016/001

Case No: 2059595

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Septodont

58 Rue du Pont de Créteil, 94 107 Saint Maur-des-Fossés, Cedex, France

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Scandonest 2% w/v/1:100,000 Special, Solution for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **27/05/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Scandonest 2% w/v / 1:100,000 Special, Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mepivacaine hydrochloride	20.00	mg	per 1 ml
Epinephrine (Adrenaline)	0.01	mg	per 1 ml

Excipients - contains Potassium Metabisulphite (E224) 1.2mg (per 1ml)

Also contains Sodium (<1mmol/ml)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Local anaesthetic for dental use, where a vasoconstrictor effect is desirable.

4.2 Posology and method of administration

Administration:

Local injection (block or infiltration)

To minimise the likelihood of intravascular injection, aspiration should be performed before the local anaesthetic solution is injected. Inject slowly.

Adults:

Use 1 to maximum 3 cartridges per session of treatment.

The dosage depends on the extent of the area to be anaesthetized, and on the type of injection.

Children:

The quantity of solution to inject depends on the age of the child, on his weight and on the operation.

The average dose is 0.025 ml of solution per kg of weight.

Never exceed one cartridge per sitting.

The maximal dose of mepivacaine to be injected to a child is given in mg by this calculation : weight of the child expressed in kg x 1.33.

Do not use under three years of age.

4.3 Contraindications

The product is contraindicated in patients :

- presenting specific allergies to amide-type anaesthetic or any component of the solution,
- suffering from cardio-vascular diseases : severe disorders of the atrio-ventricular conduction not compensated by pace-maker, arterial hypertension, arrhythmia, valvular or coronary artery disease.
- Epilepsy manifestations not controlled by any treatment,
- Intermittent acute porphyria
- under tricyclic or MAOI anti-depressant treatment.

Usually, this medicinal product is contraindicated in combination with other medicinal products such as guanethidine and related products (see “Interactions with other medicinal products”)

4.4 Special warnings and precautions for use

Warnings

THIS PRODUCT 1/100,000 ADRENALINE CONTAINS.

The product should not be used on fingers, toes, tip of nose, penis and ears.

Take into account the risk of local necrosis in hypertensive and diabetic patients.

- Dose should be minimised for patients suffering from hepatic or renal disease.
- Take into consideration the risk of unintentional biting trauma.
- Use with caution when there is inflammation and/or sepsis in the area of the proposed injection site. Injection into highly vascular areas especially if these are inflamed or traumatised may result in reduced effect and increased absorption.
- In common with other local anaesthetics, Mepivacaine should be used cautiously in patients with epilepsy, impaired cardiac conduction, or impaired respiratory function.

The product containing a vasoconstrictor, it should not be injected repeatedly at the same site, because it may cause a necrosis at the injection site.

Athletes should be warned that this medicinal product contains an active substance likely to induce a positive reaction to tests undertaken in anti-doping controls.

Precautions for use

Dental practitioners who employ local anaesthetic agents should be well versed in diagnosis and management of emergencies which may arise from their use. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use.

Before using this medicinal product, it is imperative to :

- make inquiries into the patient's diathesis, current therapies and history,
- inject slowly, making repeated aspiration tests to check that the product is injected strictly out of the blood vessels
- Keep verbal contact with the patient.

The lowest dosage that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of mepivacaine may cause significant increases in blood levels with each repeat dose due to

slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical condition:

- Cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be monitored after each local anaesthetic injection.
- Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness should alert the practitioner to the possibility of central nervous system toxicity.
- Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position.

Monitoring should be increased in patients under anti-coagulants (monitoring of the INR).

Due to the presence of adrenaline, precautions and monitoring should be increased in the following cases:

- peripheral vascular disease : patients may exhibit exaggerated vasoconstrictor response.
- Arrhythmias except bradycardia,
- Coronary failure,
- Severe hypertension
- Hyperthyroidism

In case of severe hepatocellular insufficiency, it may be necessary to reduce the dose of mepivacaine, since amide type local anaesthetics are mainly metabolised by the liver.

Mepivacaine should be used with caution in patients with renal disease, since local anaesthetics are excreted by the kidneys, and the patient due to his condition is also at a greater risk of developing toxic plasma concentrations.

The posology should also be reduced in case of hypoxia, hyperkalaemia or metabolic acidosis.

In common with other local anaesthetics, mepivacaine should be used cautiously in patients with epilepsy, impaired cardiac conduction, or impaired respiratory function.

The concurrent administration of this anaesthetic with some other medicinal products (see “interactions with other medicinal products”) requires a rigorous monitoring of the patient's clinical and biological state.

4.5 Interaction with other medicinal products and other forms of interaction

Non-recommended combination

Due to the presence of adrenaline

- **Guanethidine and related products** (anti-glaucoma agents):

Important rise in blood pressure (hyper-reactivity linked to the reduction of the sympathetic tonus and/or to the inhibition of the adrenaline entry into the sympathetic fibres).

If this combination cannot be avoided, use smaller doses of sympathomimetic products (adrenaline) cautiously.

- Because of its adrenaline content, the product is contraindicated in case of MAOI or tricyclic antidepressant treatment. There may also be a risk of interaction with phenothiazines, vasopressor drugs, ergot-type oxytoxic drugs, antiarrhythmics and β -blocking agents.

Combinations which require precaution for use

Due to the presence of adrenaline:

- **Halogenated volatile anaesthetics:**

Severe ventricular arrhythmia (increased cardiac reactivity).

Precautions for use: Limit the anaesthetic dose, for instance: less than 0.1 mg of adrenaline within 10 minutes or 0.3 mg within one hour in adults.

- **Imipraminic antidepressants:**

Paroxysmal hypertension with possible arrhythmia (inhibition of adrenaline entry into the sympathetic fibres).

Precautions for use: Limit the anaesthetic dose, for instance: less than 0.1 mg of adrenaline with 10 minutes of 0.3 mg within one hour in adults.

- **Serotonergic and noradrenergic antidepressants (*described for minalcipran and venlafaxine*)**

Paroxysmal hypertension with possible arrhythmia (inhibition of adrenaline entry into the sympathetic fibres).

Precautions for use: Limit the anaesthetic dose, for instance: less than 0.1 mg of adrenaline within 10 minutes or 0.3 mg within one hour in adults.

- **Non-selective MAO inhibitors (*iproniazide*)**

Increased in the pressive action of adrenaline, most often moderate.

To be used under strict medical supervision.

- **A-selective MAO inhibitors (*moclobemide, toloratone*)**

by extrapolation from non-selective MAO inhibitors.

Risk of increase in the pressive action.

To be used under strict medical supervision

Due to the presence of mepivacaine:

- Increased serum levels of amide anaesthetics have been reported after concurrent administration of cimetidine.

- If sedatives are employed to reduce patient's apprehension, reduced doses of anaesthetic solution should be used since local anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

- **Antimyasthenics:**

Inhibition of neuronal transmission by local anaesthetics may antagonise the effects of antimyasthenics on skeletal muscle, especially if large quantities of the anaesthetic are rapidly absorbed; temporary dosage adjustment of myasthenics may be necessary to control symptoms of myasthenia gravis. Unlikely effect with doses used in dentistry.

4.6 Pregnancy and lactation

In pregnancy

On the basis on long usage, anaesthetics of the mepivacaine type are considered to be reasonably safe for use on pregnant women.

Retrospective studies of pregnant women receiving local anaesthetics for emergency surgery early in pregnancy have not shown that local anaesthetics cause birth defects.

However, no controlled studies have been carried out in pregnant women.

Moreover, no reproduction studies have been performed with the product.

Therefore, caution should be taken before administering this anaesthetic during early pregnancy.

Nursing mothers

It is not known whether local anaesthetics are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mepivacaine is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse experience following the administration of mepivacaine are similar in nature to those observed with other amide local anaesthetic agents.

These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or unintended intra-vascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central nervous system

CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, headache, nervousness, restlessness, yawning, apprehension, euphoria, logorrhoea, confusion, dizziness, drowsiness, tinnitus, nystagmus, blurred or double vision, nausea, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of mepivacaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular system

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position. Less commonly, they may result from a direct effect of the drug.

Failure to recognize the premonitory signs such as sweating, a feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and seizure or serious cardiovascular catastrophe. Management consists of placing the patient in the recumbent position and ventilation with oxygen. Supportive treatment of circulatory depression may require the administration of intravenous fluids by the clinical situation.

Respiratory system

Tachypnoea followed by bradypnoea which may result in apnoea.

Allergic reactions

Allergic reactions are characterized by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Allergic reactions as a result of sensitivity to mepivacaine are extremely rare and, if they occur, should be managed by conventional means. Facilities to deal with such reactions should be immediately available.

Due to Adrenaline

The clinical manifestations relate to CNS stimulation and include increasing fear and anxiety, tension, restlessness, throbbing headache, tremor, weakness, dizziness, pallor, respiratory difficult, and palpitation.

With increasing levels of adrenaline in the blood, cardiac dysrhythmias become more common; ventricular fibrillation is a rare but possible consequence. Dramatic increases in both systolic and diastolic pressures may be noted, which have lead to cerebral haemorrhage. Anginal episodes may be precipitated in patients with coronary insufficiency. Because of the rapid inactivation of adrenaline, the stimulatory phase of the overdose reaction is usually very brief.

Due to sulphites

Allergic-type reactions may occur in patients with bronchial asthma due to hypersensitivity to the sulphite component and may be manifested by dermatologic reactions, oedema, urticaria and other allergy symptoms.

4.9 Overdose

Acute emergencies from local anaesthetics are generally related to high plasma levels encountered during therapeutic use of excessive dosages of local anaesthetics, or to unintended intravascular injections of local anaesthetic solution. (see adverse reactions, warnings and precautions).

▪ Management of local anaesthetic emergencies

The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anaesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask.

Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate or a benzodiazepine may be administered intravenously.

The clinician should be familiar, prior to use of local anaesthetics, with these anticonvulsant drugs. Supportive treatment of circulation depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., Ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardio-pulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

Dialysis is of negligible value in the treatment of acute overdosage with mepivacaine.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group : local anaesthetic for dental use
ATC code : N01 BB 53

Mepivacaine is a local anaesthetic of amide type, acting rapidly and causing a long duration reversible block of the motor and sensorial nervous fibres and of the heart stimulation. Vasoconstriction reactions have been noted only in the case of intradermal administration.

5.1 Pharmacodynamic properties

Mepivacaine decreases the permeability of the membrane to the cations, more particularly sodium and potassium, when concentrations are high. The nervous fibres excitability decreases according to the concentrations, as the sudden increase of the permeability to sodium necessary to the formation of an action potential lowers. The neutral base comes through the myelinic tube more rapidly than the cation. The exact effect of the local anaesthetic effect has not yet been explained. The models developed until now are still hypothetical.

After having taken the axon internal pH, the cation is likely to induce the nerve block, as present active form of the local anaesthetic.

The activity of the membrane is modified, as well as regards cations as the local anaesthetic molecules which are not charged.

The absorption of the local anaesthetic depends on the physico-chemical properties (as lipid solubility), on the pharmacological properties (as vasodilator effect), and on the vascularisation and the irrigation of the injection area of the product.

The adrenaline added to the solution slows up the mepivacaine passage in the blood system and so ensures a steady long duration of the active concentration in the tissues, increasing mepivacaine efficiency and allowing to use smaller quantities of solution. The obtained ischaemia is more intense and allows to obtain a low haemorrhagic operative field.

5.2 Pharmacokinetic properties

The mepivacaine effect appears within 2 or 4 minutes in case of peripheral nerve blocks. The effect duration is determined by the progress from the tissues and by the diffusion in the blood vessels. The distribution ratio is 0.8. The plasma half-life is lengthened in patients suffering from liver disease or uraemia. The link of plasma proteins is 60-78 % for mepivacaine, mainly with Ó-glycoprotein acid. The mepivacaine pKa is 7.6.

The addition of adrenaline increases the anaesthesia duration and intensity and allows to use less mepivacaine (2 % solution) and to obtain as well lower plasma concentrations.

The blood half-life lasts between 2 and 3 hours after the administration of 600 mg of mepivacaine for a spine anaesthesia. The clearance of the amides depends strongly on the liver irrigation.

Methyl groups of mepivacaine and lidocaine are steric hindrances and influence the possibility of attack of the CONH groups, which confers to this molecule a great stability.

The metabolism occurs mainly through an oxidizing process in the liver. One notes the appearance of 2'-6'-pipecoloxylidide and of an aromatic hydroxylation which leads to the formation of 2'-6'-pipecoloxylidide-4' -hydroxymethyl and 3'-hydroxy-l-methyl.

The two metabolites are eliminated mainly by the bile and are glucuronised at 99 %. The metabolites are then resorbed by the intestines and eliminated by the urine. Only a small part of the metabolites can be found in the faeces. The urine pH has an influence on the elimination of the metabolites. The elimination can be increased by an urine acidification. In case of mepivacaine radioactive marking, 10 % of the radioactivity are eliminated by the lungs, in the form of CO₂.

In the adults, only 2.8 to 5.2 % of the mepivacaine are eliminated under the same form through kidneys. This percentage is of 43.3 % in the new-born children.

5.3 Preclinical safety data

The LD₅₀ is 39.9 mg/kg in the mouse and 27.8 mg/kg in the rat in the case of intravenous injection. The toxic dose (TD₅₀) is 7.2 mg/kg in the dog in case of intravenous administration.

The mepivacaine toxic threshold in the man ranges between 5 and 10 µg/ml. The relative toxicity is 0.81, compared to lidocaine and 1, compared to procaine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium edetate
Potassium metabisulphite (E224)
Hydrochloric acid
Sodium hydroxide solution
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the cartridge in the outer carton in order to protect from light.

6.5 Nature and contents of container

Cardboard box or can containing 50 cartridges of 1.8 ml or 2.2 ml.
Glass cartridges of type I with rubber closures.
Not all pack sizes may be marketed.
Clear, colourless, sterile injection solution, supplied in clear type I glass cartridges sealed with a rubber stopper and aluminium ring at one end and a rubber plunger at the other.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

One cartridge should be used on one patient during one session of treatment only. If only part is used, the remainder must be discarded.

7 MARKETING AUTHORISATION HOLDER

Septodont
58 Rue du Pont de Créteil
94 107 Saint Maur-des-Fosses
Cedex,
France

8 MARKETING AUTHORISATION NUMBER

PA 196/16/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th May 1999

Date of last renewal: 27th May 2009

10 DATE OF REVISION OF THE TEXT

April 2010