Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
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TECHNICAL DATA SHEET: ODONTOCAINA 2% WITH EPINEPHRINE ®
PRFTPT-013

1 GENERAL PRODUCT INFORMATION

ODONTOCAINA 2% WITH EPINEPHRINE 1: 100 000
Anesthetic Injectable Solutions for Dental Use: MEPIVACAINE

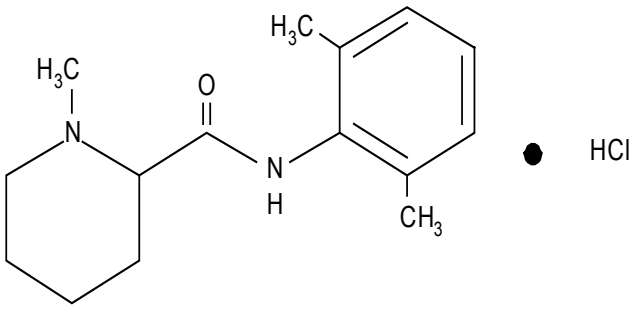
Mepivacaine 2% with Epinephrine 1:100000 is an anesthetic solution for injection (subcutaneous small volume) for dental use, indicated to produce local anesthesia, applied the techniques by infiltration or nerve block. This product should be used by personnel with professional certification, trained to perform dental procedures.

1.1 Commercial Name and International Nonproprietary Name (INN)

Odontocaína® 2%: Mepivacaine 2% with Epinephrine 1: 100 000

1.2 Structural Formula, Molecular Formula, and/or Empiric Formula of Active Ingredients

MEPIVACAINE



Molecular Form	$C_{15}H_{22}N_2O$. Hcl
Molecular Mass	282.81 g/mol

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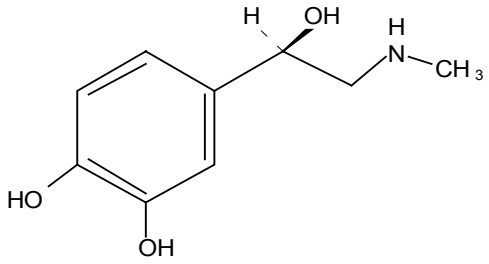
IUPAC Name 2-piperidin carboxamide (?)-*N*-(2,6-dimethylphenyl)- 1-methyl-monohydrochloride (?)-1-methyl-2', 6'-pipecoloxylidide monohydrochloride.

EPINEPHRINE



Molecular Formula	$C_9H_{13}NO_3$
Molecular Mass	183.21 g/mol

IUPAC Name: 1, 2- benzenediol, 4- [1-hydroxy-2-(methylamino)ethyl] -, *(R)* (-) – 3, 4-Dihydroxy-a-[(methylamino)methyl] benzyl alcohol.

2 INFORMATION ABOUT COMPOSITION ELEMENTS

Each dental Cartridgee of 1.8 ml.-contains.
Mepivacaine hydrochloride: 0.036 g.
Epinephrine: 0.000018 g.
Excipients q.s. a.d.: 1.8 ml.

3 PROPERTIES OF THIS PRODUCT

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Mepivacaine, a tertiary amino amide-type local anesthetic, appeared for the first time in 1957. It has a medium duration of action and its pharmacological properties are similar to those of Lidocaine. This local anesthetic stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses. (**See Figure nº 1**).

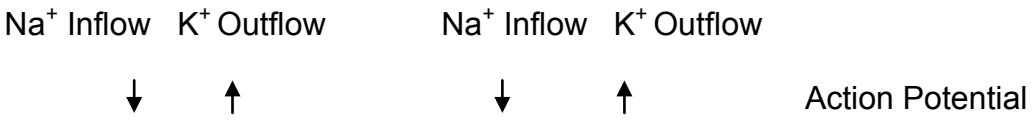
Its onset action is very similar to that of Lidocaine but its duration is a little bit longer (20%) than that of Lidocaine in absence of a vasoconstrictor agent associated with it. Mepivacaine has a slight vasoconstriction action and has no efficacy as a topical anesthetic. In local infiltration, Mepivacaine has no vasodilatation action. High plasma concentrations produced in paracervical blockade lead to uterine vasoconstriction and diminish the blood flow in the uterus. Children and elderly persons tend to be more sensitive to effects of Mepivacaine

Sympathomimetic amines such as Epinephrine (Adrenaline), Norepinephrine (Noradrenaline) and Levonordephrine are vasoconstrictors that exert their action on the alpha-adrenergic receptors existing in the vessels of the mucous membrane and diminish the blood flow in the injection area.

These vasoconstrictors are used to produce a longer-lasting action of the local anesthetic in the injection site and to diminishing the peak concentration of the anesthetic in the blood and therefore, the risk of systemic toxicity.

The vasoconstrictor also allows the use of a lesser concentration of the local anesthetic to block the conduction of nerve impulses and reduces the bleeding in the oral cavity. On the other hand, vasoconstrictors such as Epinephrine, Norepinephrine, and Levonordephrine may cause heart stimulation and irritability

Figure N° 1
Changes in polarity and action potential in the conduction of impulses by a nervous fiber



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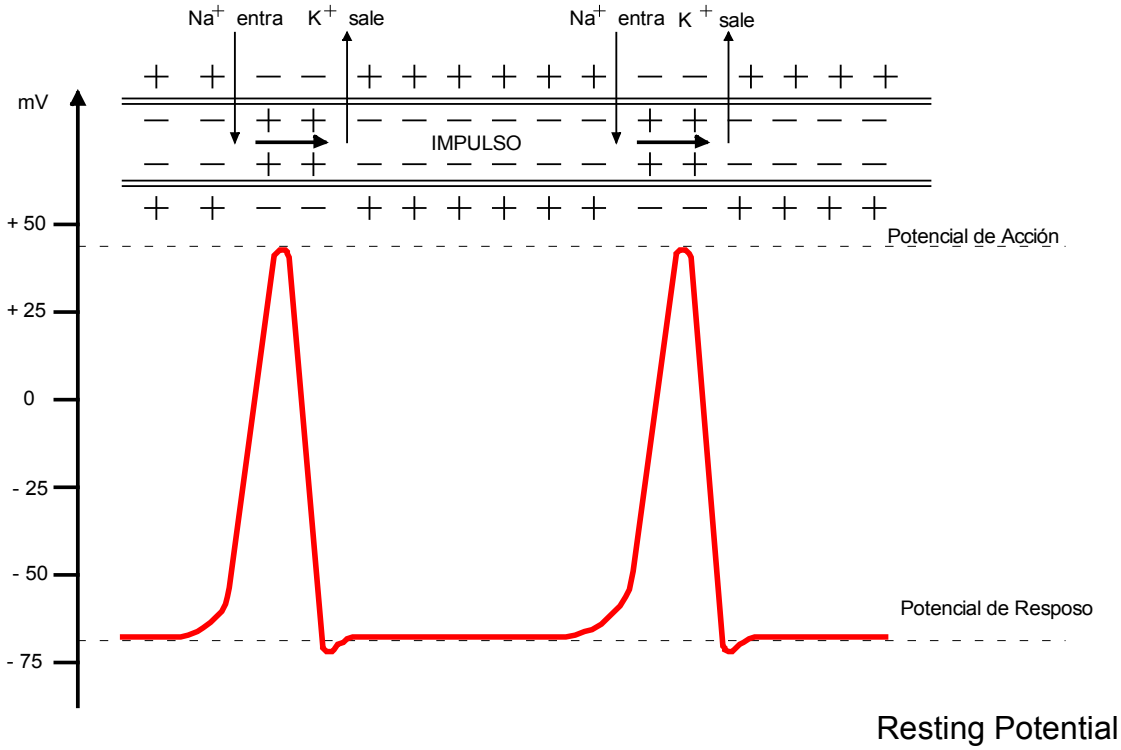

Resting Potential

METABOLISM

The amide structure of Mepivacaine is not catabolyzed by plasmatic stearases. This condition makes its metabolism much more restricted and slower than that of ester-type local anesthetics. The liver is the main site of metabolism. More than 50% of the injected dose of Mepivacaine is metabolized by the bile in the form of metabolites.

The most part of metabolized Mepivacaine will probably be reabsorbed by the intestine and excreted later on with urine, because only a very small percentage of this substance has been found in the feces.

The kidneys constitute the main excretion route. The most part of this anesthetic and its metabolites are eliminated in approximately 30 hours

More than 16% of the injected dose of Mepivacaine is excreted without change with urine. It has been observed that hydroxylation and N-desmethylation, two disintoxication reactions, play important roles in the metabolism of this anesthetic. The metabolites of Mepivacaine that have been identified in human adults are: two phenols that are almost exclusively excreted in their glucoronide conjugates, and one N-desmethylated compound (2' 6' – pipecoloxylidide)

Epinephrine is rapidly inactivated in the human body. The human liver produces two enzymes for the destruction of circulating epinephrine. The action of this organ is important but not indispensable in this degradation process. Most part of this substance is eliminated in the form of metabolites with urine

4 USAGE AND APPLICATIONS

Mepivacaine 2% with Epinephrine is a local anesthetic that is suitable for infiltration and nerve block anesthesia in dental procedures

WARNINGS

Dental professionals who work with local anesthetics must have a deep knowledge of diagnostic methods and the way they can manage local anesthetic emergencies that may happen in the dental office. Facilities for resuscitation, oxygen, and other resuscitation drugs should be available for immediate use when administering local anesthetics. This anesthetic must not be injected directly into the blood stream

Slow injection: Excessive pressure during an injection may cause local irritation and postoperative pain. A very rapid injection may also cause necrosis of palate tissues due to the firmness of the ligament on the bone

To reduce to a minimum the risk of intravascular injections, an aspiration must be made before the injection of the anesthetic solution. If the aspiration contains blood, the needle must be placed on another site where no aspirated blood appears. It must be noted, however, that the absence of blood in the syringe does not guarantee the

success of an intravascular injection. This is why a double aspiration is always recommended

The use of local anesthetics should be avoided if the injection site coincides with an inflamed or abscessed area

Intravascular injections of small doses of local anesthetics into the head and neck area may produce systemic adverse reactions similar to those observed in cases of inadvertent intravascular injections in higher doses

In patients with acidosis or hypoxia, the risk and severity of toxic reactions may be increased. Such reactions involve the Nervous Central System (CNS) and the Cardiovascular System. Local anesthetics must be administered with caution in patients suffering from anemia, severe cardiovascular diseases or circulatory dysfunctions of any kind

Solutions of local anesthetics which contain a vasoconstrictor agent must be administered with caution and according to the prescribed dose. These solutions must not be injected into distal sites of the body because the ischemia that is produced can lead to gangrene. In dental procedures, a vasoconstrictor should not be repeatedly injected into the same area because it reduces the blood flow and increases the oxygen consumption in the affected tissues which can lead to tissue anoxia, cicatricial delay of the edema or necrosis of the injection site

Mepivacaine with Epinephrine contains sodium metabisulfite that may cause allergic reactions such as anaphylactic shock, asthma episodes, and urticaria. Sensitivity to sulfites is more frequently observed in asthmatic patients

PRECAUTIONS

Cross- reactivity and /or other related problems can rarely occur with other amide-type local anesthetics

WARNINGS AND CONTRA-INDICATIONS

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The safety and efficacy of mepivacaine depend mainly on the following aspects: an appropriate dose, a correct technique, adequate precautionary measures, and emergency procedures. Facilities for resuscitation, oxygen, and other resuscitation drugs should be available for immediate use

The dentist should use the lowest possible dose that results in adequate anesthesia, in order to avoid high plasma levels and serious adverse effects

The administration of repeated doses of mepivacaine may cause significant increase of concentrations of this substance in the blood stream, due to the slow accumulation of this drug and its metabolites. Tolerance to high concentration levels in the blood plasma can vary from one patient to another. Feeble, elderly, and pediatric patients, as well as patients with acute sickness must be given reduced doses, according to their age and physical condition (See *Dosage and Administration Techniques)*

After each injection of a local anesthetic, the patient's cardiovascular and respiratory functions should be monitored (adequate ventilation) as well as his/her vital signs and consciousness. Symptoms like restlessness, anxiety, tinnitus, dyspnea, blurred vision, tremors, depression or drowsiness must constitute an alert to the dental professional about the possibility of toxicity at the level of the Central Nervous System. The signs and symptoms of depression of the cardio vascular function are commonly the result of a vasovagal reaction, in particular, if the patient is in upright position. If this situation appears, it is advisable to place the patient in an inclined position (See *Adverse Effects on the Cardiovascular System*)

The depuration of mepivacaine is reduced with the administration of beta-blockers and cimetidine. High concentration levels in the blood plasma may lead to convulsions and cardio-respiratory depression. Benzodiazepines, barbiturates, and volatile anesthetics increase the convulsive threshold. The duration of the anesthetic effect is prolonged with the addition of epinephrine to mepivacaine as well as with alpha 2-agonists (Chlonidine). The alkalization decreases the latency period and increases the anesthetic power. Contrary to ester-type anesthetics, amide-type anesthetics rarely cause allergic reactions

Mepivacaine should be avoided in spinal anesthesia and in obstetrical anesthesia. The use of this substance to produce paracervical block may produce bradycardia and fetal acidosis. Special precautions must be taken with patients suffering from dysrhythmias and cardiac blocks. The appearance of toxic levels in the blood plasma may lead to

cardiovascular collapse and convulsions, with symptoms characterized by tongue and perioral numbness, metallic taste restlessness, tinnitus and body tremor.

Circulatory support includes: intravenous solutions (vasopressor agents, intravenous $NaHC0_3$ at 1-2 mEq/kg, intravenous bretilium at 5 mg/kg, electrical cardioversion or defribillation of cardiac dysrhythmias if necessary), and ensure patent airways.

Convulsions can be managed with the following drugs: Sodium Thiopental (1-2 mg/kg, intravenous), Midazolam (20-40 mcg/kg, intravenous) or Diazepam (0.1 mg/kg, intravenous). The level of sympathic nerve block is proportional to the degree of arterial hypotension after the epidural block.

Hydration with crystalloid solutions (10-20 ml/kg of Ringer Solution or saline solution at 0.9%), vasopressor agents (such as ephedrine) and displacement of the uterus to the left (in order to avoid compression of the vena cava) must be some of prophilactic measures or treatments Atropine must be given in order to avoid bradycardia. Epidural or caudal punctions must be avoided in patients who are in hypovolemic shock or suffering from septicemia, coagulopathies or infection in the punction site The use of commercial solutions of Mepivacaine which contain sulfites increases the risk of anaphylactic or bronchospastic reactions. A harmful cardiac stimulation may be produced in patients suffering from hyperthyroidism.

Local anesthetic Mepivacaine should not be used in the following situations

Patient's hypersensitivity to this anesthetic (or to amide-type anesthetics);

Patients with hepatic disease (just because amide-type anesthetics are metabolized in the liver; patients with severe hepatic disease, due to their incapacity to normally metabolize local anesthetics and their high risk of presenting high toxic concentrations in their blood plasma

Patients with kidney disease (because local anesthetics are excreted through kidneys). These patients are also in high risk of presenting high toxic concentrations in their blood plasma.

Patients with a history of troubles in their cardiac rhythm or having suffered cardiac arrests (because the cardiopressor effect of these anesthetics may cause detriment to these patients

Medical history or predisposition to malignant hyper-rhythmia (because amide-type local anesthetics may contribute to the development of malignant hyper-rhythmia in case of requiring supplementary general anesthesia

Patients suffering from asthma, diabetes, atherosclerotic problems, hypertension, hyperthyroidism, and cerebrovascular failure

The use of the local anesthetic Mepivacaine should be carefully considered if ...

There is an inflamed and/or abscessed area around the injection site because this situation may alter the pH in this site and, as a result of this, the anesthetic effect decreases or fails. The plugging capacity of tissues will normally cause a stabilization of pH at the level of the tissue. Injections into infected areas will sometimes result in incomplete anesthesia because the infected focus produces residual acids that normally reduce the plugging capacity of tissues. An acid pH always reduces the anesthetic power of an injected solution.

INTERACTIONS WITH DRUGS AND DRUG-RELATED PROBLEMS\

If the dentist gives sedatives to reduce the patient's apprehension, the anesthetic dose must be lowered because local anesthetics and sedatives are depressors of the Central Nervous System. This combination may have addictive effects.

From a theoretical point of view, the use of topic Mepivacaine increases the effect of muscle relaxants

Mepivacaine may alter the results of analytic blood tests: (Biological) increase of Creatinine-Kinase

The use of sympathomimetic vasoconstrictors: such as epinephrine may cause addictive toxicity. The risk of a significant systemic effect resulting from the interactions of some of the drugs mentioned below with a vasoconstrictor contained in an anesthetic solution depends on the total dose (volume and concentration) of the administered vasoconstrictor and on factors that affect the absorption average of the

vasoconstrictor agent (site and route of administration, and the potential of intravascular administration.

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Adrenergic alpha-blockers such as Labetalol, Phenoxybenzamine, Phentolamine, Prazosin, tolazoline and other adrenergic alpha-blocker drugs such as: Droperidol, Haloperidol, Loxapine, Phenotiazines, Thioxantenes, or rapid-action Vasodilators (e.g. nitrates) can reduce the efficacy of the vasoconstrictor agent.

In patients who receive epinephrine, levonordephrine or norepinephrine but not phenylephrine, the alpha-adrenergic block may become a beta-adrenergic activity with risk of hypotension and severe tachycardia.

Vasoconstrictor agents may diminish the therapeutic effects of vasodilators, including the effects of nitrates against chest angina

Hydrocarbon anesthetics (chloroform, cyclopropane, halotane or trichloroetylene and to a much lesser degree, euflurane, isofluorane or metoxyfluorane), may sensitize the heart for the effects of a sympathomimetic vasoconstriction; If these drugs are associated with a vasoconstrictor agent, a cardiac arrhythmia may happen

Tricyclic antidepressants or maprotilen**e** in combination with lidocaine may increase the cardiovascular effects of a vasoconstrictor agent and, as a result of this, cardiac arrhythmias, tachycardia, severe hypertension or hyperpyrexia may happen.

Antihypertensors or diuretics used as antihypertensors: The hypertensor's effects may be diminished by the vasoconstrictor agents (It is highly recommended to control blood pressure.

Apart from a possible reduction of the antihypertensive effects of Guanadrel, Guanethidine, Mecamilamine, Methyldopa or Trimethaphan, the use of any of these agents in combination with vasoconstrictors may improve the response of these ones

The administration of a solution of a local anesthetic which contains epinephrine to patients who are receiving treatment with drugs that produce alteration in their blood pressure (e.g. monoaminoxydase (MAO) inhibitors, tricyclic antidepressants, or phenotiazines) may lead to a prolonged hypotension or hypertension.

Concurrent use of a vasopressor agent and oxytocic drugs such as ergotamine may cause persistent hypertension or cerebrovascular accidents

No incompatibilities of Mepivacaine with food have been found

PREGNANCY AND BREASTFEEDING

Pregnancy: Mepivacaine should be avoided in spinal anesthesia and in obstetrical anesthesia. The use of this substance to produce paracervical block may produce bradycardia and fetal acidosis.

Breastfeeding: The excretion of local anesthetics with human milk is not known. However, since many drugs are excreted jointly with human milk, Mepivacaine should be used with caution in lactating women

EFFECTS ON DRIVING SKILLS AND OPERATION OF MACHINERY

Not reported

ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) to Mepivacaine are similar to those produced by other amide-type local anesthetics. These adverse effects are generally produced by high blood plasma concentrations caused by excessive doses, fast absorption or inadvertent intravascular injections or may be due to an idiosyncratic hypersensitivity or diminished tolerance to local anesthetics on the part of the patient. Serious adverse effects are generally systemic

The most commonly reported adverse effects are the following

Central Nervous System (CNS):

CNS reactions may be excitatory and/or depressant and may manifest as photosensitivity, nervousness, apprehension, euphoria, confusion, vertigo, drowsiness,

double or blurred vision, sensations of heat/cold or numbness, tremors, convulsions, loss of consciousness, depression, and respiratory arrest. Excitatory symptoms may be

very short-lasting or totally absent. In any case, the first symptom of toxicity may be a sensation of sleepiness followed by loss of consciousness and respiratory arrest

The sleepiness sensation produced by mepivacaine is usually an early symptom of high concentrations of this anesthetic in the patient's blood plasma as a result of fast absorption of this drug

Cardiovascular System:

Cardiovascular reactions are usually depressant and may manifest as bradycardia, hypotension, and cardiovascular collapse that may lead to a cardiac arrest.

The signs and symptoms of a cardiovascular depression are commonly due to a vasovagal reaction, particularly, if the patient is in an upright position. Less frequent symptoms may result from a direct adverse reaction to the local anesthetic. Failing to recognize premonitory signs such as abundant perspiration, sensation of feebleness or changes in the pulse frequency may lead to a progressive cerebral hypoxia or to a serious cardiovascular catastrophe. An immediate treatment consists in placing the patient in an inclined position and then, to provide him/her with adequate ventilation with oxygen.

Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine)

Allergic Reactions: Allergic reactions to mepivacaine are extremely rare. They may be characterized by cutaneous lesions, urticaria, edema or other anaphylactoid reactions. These symptoms must be treated with conventional therapy.

The detection of a patient's sensitiveness by means of superficial cutaneous tests has not revealed to be a safe procedure

TREATMENT OF OVERDOSE

Serious emergencies caused by local anesthetics are commonly related to high concentration levels in blood plasma produced during the therapeutic use of the local anesthetic or resulting from excessive doses or inadvertent intravascular injections of

the solution of local anesthetic (See Adverse effects, Special Care, and Precautions for use)

Management of Local Anesthetic Emergencies

The first consideration has to do with prevention which is carried out by a constant and careful monitoring of the patient's cardiovascular and respiratory vital signs and his/her state of consciousness after each injection of a local anesthetic. When a first sign of change arrives, oxygen must be provided.

The first step has to do with the treatment of convulsions: The best way is the maintenance of the patient's airway and the provision of assisted or controlled ventilation with oxygen and to have close at hand an adequate system to immediately provide a positive air pressure, for example, a face mask Immediately after these supporting ventilatory measures, the patient's circulation must be evaluated, keeping in mind that anticonvulsive drugs sometimes depress the circulatory system when injected intravenously. Should convulsions persist despite adequate respiratory support, and if the patient's circulatory status permits, small increments of an ultra short-acting barbiturate (such as Sodium Thiopental, 50-100 mg increased, or Thiamilal) or a benzodiazepine (such as Diazepam, 2.5 mg increased) may be administered intravenously every 2 or 3 minutes in order to stop convulsions.

The dental professional should be familiar with the use of local anesthetics combined with anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If convulsions and cardiovascular depression are not treated immediately, they can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. In case of a cardiac arrest, cardiopulmonary resuscitation measures must be instituted

5 QUALITY ASSURANCE AND CONTROL

Odontocaine® 2%: Mepivacaine 2% with Epinephrine 1: 100 000 is manufactured under the most strict technical and quality controls. Its manufacturing process is carried

out in special manufacture areas with environmental, microbiological, and operational controls made by specially trained employees. Raw materials used in this product are

previously examined and approved according to requirements of pharmacopeias currently into effect. The control process includes the control of Blister Packing and secondary packaging materials. All raw materials are furnished by qualified providers.

Odontocaina® 2%: Mepivacaine 2% with Epinephrine 1: 100 000 conforms to all requisites of the United States Pharmacopeia USP 27 in terms of physical appearance and physical properties, contents of active ingredients, and microbiological controls. All these parameters are verified during the different steps of the manufacturing process with the use of high technology equipment, standardized procedures, areas for special analysis, and specially trained employees

6 INSTRUCTIONS FOR USE

Odontocaina® 2%: Mepivacaine 2% with Epinephrine 1: 100 000

Adult Patients

Infiltration and localized nerve block: 36 mg (1.8 ml of solution at 2% with Epinephrine 1: 100 000)

Infiltration and nerve block in all the oral cavity: 180 mg (9.0 ml of solution at 2% with Epinephrine 1: 100 000)

MAXIMUM RECOMMENDED DOSE: Do not exceed 6.6 mg/kg of body weight or 300 mg each dental session.

Children

Infiltration and nerve block: Do not exceed 6.6 mg/kg of body weight or 180 mg of Mepivacaine hydrochloride (9.0 ml of solution at 2% with Epinephrine 1: 100 000

REMARK

In pediatric patients up to 3 years of age, use concentrations between 0.2% and 0.5% of local anesthetic. In pediatric patients of more than 3 years of age and a body weight

>13.5 kg, use concentrations between 0.5% and 1.0% of local anesthetic. To obtain these concentrations, dilute the commercial concentration in the amount of sodium chloride at 9% for injections; for nerve block, use concentrations between 0.5% and 1.0%.

The dentist should use the lowest dose of the anesthetic solution that can provide the desired anesthetic effect the patient should be carefully monitored for possible adverse reactions Anesthetic solutions which contain epinephrine can be used in those oral procedures in which a longer effect is required in the injection site. Patients with decrease of hepatic blood flow or hepatic failure may require a lesser dose of Mepivacaine hydrochloride or a longer interval between doses.

CARTRIDGES DISINFECTION OF: Local anesthetic Cartridges must not be submerged in solutions made of anticorrosive tablets or in solutions of quaternary ammonium salts such as benzalkonium chloride. Some metal ions (e.g. mercury, zinc, cupper) are contained in disinfectant solutions and may be the cause of inflammations after anesthetic procedures. This is why local anesthetic Cartridges should not be submerged into these solutions.

For the chemical disinfection of the Cartridge surface, it is advisable to use isopropylic alcohol at 91% or ethylic alcohol at 70% without denaturalizing agents. Solutions which contain heavy metals are not recommended.

Mepivacaine with Epinephrine 1:100 000 should not be used if the solution is colored (pink or brownish colors) or if it contains a precipitate

The local anesthetic Mepivacaine with Epinephrine 1:100 000 should not be submitted to autoclave sterilization because of the thermal decomposition of epinephrine

(thermolabilitye) Any amount of anesthetic solution that remains in the Cartridgee must be discarded.

7 COMMERCIAL PRESENTATIONS OF THIS PRODUCT

The anesthetic solution Odontocaina® 2%: Mepivacaine 2% with Epinephrine 1: 100 000 is marketed in the following types of packaging

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Primary Packaging

Glass Cartridges: Cylindrical ampoules made of type I- glass (**Borosilicate** glass)
Plastic Cartridges: Cylindrical ampoules made of virgin polypropylene

Both types of primary packaging have the same sliding plug and top cap:
Natural-rubber plug, and metal cap with diaphragm (aluminium and natural rubber)

Secondary Packaging

Two types of secondary packaging are available
Blister in cardboard box per 50 Cartridges
Plastic Box per 50 Cartridges

8. EXPIRATION DATE

Two (2) years.

9. STORAGE AND CONSERVATION MEASURES

The injectable solution Odontocaina® 2%: Mepivacaine 2% with Epinephrine must be stored in dry and cool areas, away from direct heat and light or intense light sources. It should be stored at a temperature below 30º C. (111,6°F).