SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MEDICAINE 2% with adrenaline, injectable solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains:
Mepivacaine hydrochloride..... 20,00 mg
Adrenaline.....0,01 mg
One 1.8 ml cartridge of solution for injection contains 36 mg of mepivacaine hydrochloride and 0.018 mg of adrenaline.
Excipient(s) with known effect: Sodium metabisulfite and sodium. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injectable Solution.

4. CLINICAL DATA

4.1. Therapeutic indications

Local or loco-regional anesthesia in odonto-stomatological practice.

4.2. Posology and method of administration

Use reserved for dentists and stomatologists.

Posology

Adults

As the absence of pain depends on the individual sensitivity of the patient, the smallest dose providing effective anesthesia should be used.
For a routine operation, the usual dose in adults is one cartridge but a lower volume may be sufficient to ensure effective anesthesia. If the dentist deems it necessary, he can use more cartridges during heavier procedures, while respecting the maximum recommended dose.
In a healthy adult weighing 70 kg, the maximum dose of mepivacaine administered by submucosal infiltration and/or neuronal block should not exceed 4.4 mg/kg (0.22 ml/kg) of body weight with an absolute dose 300 mg of mepivacaine hydrochloride per session.
The maximum recommended doses are listed in the table below according to cartridge volume and patient weight.

				Equivalent in number of cartridges
Weight (kg)	*Dose of Mepivacaine Hydrochloride (mg)*	*Dose of Adrenaline (mg)*	*Volume (ml)*	*1,8 ml*
60	*264*	*0,132*	*13,2*	*7*
≥70	*300*	*0,150*	*15,0*	*8*

Pediatric population

According to the European Pediatric Consensus Conference, the injection is not recommended in pediatric patients under 4 years of age.
Patients aged 4 years (approximately 20 kg body weight) or older (see section 4.3).

Recommended therapeutic dose:

Special precautions should be used in pediatric population. The anesthesia technique must be chosen carefully and avoid painful techniques. The child's behavior during the procedure should be carefully monitored.

For a routine operation, the usual dose for a child is one cartridge but a lower volume may be sufficient to ensure effective anesthesia. If the dentist deems it necessary, he can use more cartridges during heavier procedures, while respecting the maximum recommended dose.

The average dose to be expected for a child is 0.5 mg of mepivacaine hydrochloride (0.025 mL of anesthetic solution) per kilogram of body weight.

Recommended maximum dose:

Do not exceed the equivalent of 3 mg mepivacaine hydrochloride/kg (0.15 ml mepivacaine/kg) of body weight.

The recommended maximum dose is shown in this table:

				Equivalent in number of cartridges
Weight (kg)	*Dose of Mepivacaine Hydrochloride (mg)*	*Dose of Adrenaline (mg)*	*Volume (ml)*	*1,8 ml*
20	*60*	*0,030*	*3,0*	*2*
30	*90*	*0,045*	*4,5*	*2*
40	*120*	*0,06*	*6*	*3*
50	*150*	*0,075*	*7,5*	*4*

Special populations

In the absence of clinical data, special precautions must be taken to administer the smallest dose allowing effective anesthesia to be obtained in:

· The elderly

· Patients with renal or hepatic insufficiency

Method of administration

Infiltration and perineural use in the oral cavity.

Before injection, it is always recommended to perform aspiration to avoid intravascular injection.

Major systemic reactions may occur following accidental intravascular injection. They can be avoided in most cases by aspiration then injecting slowly: the injection speed should not exceed 1mL of solution per minute.

To avoid any risk of infection (i.e., transmitting hepatitis), the syringes and needles used to draw up the solution must be new and sterile.

For single use. Any unused solution should be discarded.

This medicine should not be used if it is unclear or has changed color.

4.3. Contraindications

· Hypersensitivity to active substances or to any of the excipients mentioned in section 6.1.

· Children under 4 years old (approximately 20 kg of body weight).

Because of mepivacaine:

· Severe cardiac conduction disorders.

· Uncontrolled epilepsy.

Because of the adrenaline:

· Uncontrolled/severe hypertension.

· Severe ischemic heart disease.

· Persistent/severe tachyarrhythmias.

· Thyrotoxicosis.

· Pheochromocytoma.

4.4. Special warnings and precautions for use

Special warnings

This medicine should be used with caution in the following patients:

Patients with cardiovascular diseases:

· Peripheral vascular diseases

· Arrhythmias mainly of ventricular origin

· Heart failure

· Hypotension.

This medication should be administered with caution in patients with reduced cardiac function because they are less able to compensate for prolonged atrioventricular conduction.

Epileptic patients:

Because of their convulsant effects, all local anesthetics should be used with caution. In patients with uncontrolled epilepsy, see section 4.3.

Patients with liver disease:

The lowest dose to achieve effective anesthesia should be used.

Patients with kidney disease:

The lowest dose to achieve effective anesthesia should be used.

Patients receiving antiplatelet/anticoagulant therapy:

The increased risk of serious bleeding after accidental vessel perforation and during Oro-maxillofacial surgery must be considered. Monitoring of the INR (International Normalized Ratio) must be increased in patients taking anticoagulants.

Patients with uncontrolled diabetes:

This medication should be used with caution because of the hyperglycemic effect of adrenaline.

Patients with a predisposition to acute angle closure glaucoma

This medication should be used with caution due to the presence of adrenaline.

Elderly:

Doses should be reduced in patients aged over 70 years (lack of clinical data).

This medicine should be used safely and effectively, under appropriate conditions:

The effects of the local anesthetic may be reduced when this medication is injected into an area with inflammation or infection.

There is a risk of bite injury (lips, cheeks, mucous membrane, and tongue), particularly in child; the patient should be warned to avoid chewing gum or eating until normal sensations are restored.

A risk of local necrosis must be considered in hypertensive or diabetic patients.

This medicine contains sodium metabisulfite, a sulfite which may, in rare cases, cause hypersensitivity reactions and bronchospasm.

This medicine contains less than 1 mmol sodium (23 mg) per cartridge. It is therefore considered essentially “sodium-free”.

Precautions for use

The use of this product absolutely requires:

· To interview the patient to find out their background, their current treatments, and their medical history

· Maintain verbal contact with the patient

· To have a resuscitation kit ready (see section 4.9).

Risk associated with accidental intravascular injection:

Accidental intravascular injection (i.e., inadvertent intravenous injection into the systemic circulation, intravenous or intra-arterial injection in the head and neck region) may be associated with serious adverse reactions, such as convulsions, followed by cardiorespiratory depression and central nervous system, , and coma, progressing to respiratory and circulatory arrest, because of the sudden increase in the levels of adrenaline and mepivacaine in the systemic circulation.

Therefore, to ensure that the needle does not enter a blood vessel during injection, aspiration should be performed before injecting the local anesthetic. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Risk associated with an accidental intraneural injection:

Accidental intraneural injection may cause retrograde movement of the drug along the nerve.

To avoid intraneural injections and to prevent nerve damage related to nerve blockage, the needle should always be withdrawn slightly if the patient feels a sensation of electric shock during the injection, or if the injection is particularly painful. In cases of nerve injury caused by the needle, the neurotoxic effect may be aggravated by the potential chemical neurotoxicity of mepivacaine, and the presence of adrenaline, which may impair perineural blood flow and prevent evacuation of mepivacaine on a local level.

Risk of Takotsubo cardiomyopathy or stress cardiomyopathy:

Cases of stress cardiomyopathy induced by catecholamine injection have been reported.

Due to the presence of adrenaline, precautions and monitoring must be increased in the following cases: patients stressed before the intervention or conditions of use which could contribute to the systemic passage of adrenaline, for example: administration of a dose higher than the recommended dose or accidental intravascular injection.

If the dentist becomes aware of such underlying conditions in a patient requiring dental anesthesia, it will be up to him to take them into account.

Concomitant use of other medications may require increased monitoring (see section 4.5).

4.5. Interactions with other medicinal products and other forms of interactions

Due to the presence of adrenaline:

Not recommended combinations:

Associations subject to precautions for use:

Volatile halogenated anesthetics:

Reduced doses of this medication should be used because of sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmias.

The patient's hemodynamic parameters should be closely monitored.

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

The dose and speed of administration of this medication should be reduced due to increased adrenaline activity.

Close cardiovascular monitoring is recommended.

Monoamine oxidase inhibitors (MAOIs) [both A-selective inhibitors (such as brofaromine, moclobemide or toloxatone) and non-selective ones (such as phenelzine, tranylcypromine or linezolid), tranylcypromine, linezolid]:

Use under strict medical supervision due to the possible potentiation of the effects of adrenaline.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, milnacipran): The dose and rate of administration of this medication should be reduced due to additive or synergistic effects on blood pressure and heart rate.

Cardiovascular monitoring (preferably by an ECG) is recommended.

4.6. Fertility, pregnancy, and breastfeeding

Pregnancy

No clinical studies have been carried out in pregnant women and there are no reports in the literature in pregnant women having received injections of mepivacaine 20 mg/mL plus adrenaline 0.01 mg/ml. Animal studies do not indicate any direct or indirect effects with respect to reproductive toxicity.

Therefore, as a precaution, it is better to avoid using this medication during pregnancy.

Breastfeeding

No breastfeeding mothers were included in clinical studies of this product. The only published data concerns the safe passage of lidocaine into breast milk. However, given the lack of data for mepivacaine, we cannot exclude risks for newborns and infants. It is therefore recommended that nursing mothers refrain from breastfeeding for 10 hours following anesthesia using this medicine.

Fertility

No relevant data on the toxic effects of mepivacaine on fertility have been reported in animals. So far, there is no information available in humans.

4.7. Effects on the ability to drive and use machines.

Mepivacaine combined with adrenaline may have a minor effect on the ability to drive and use machines. Dizziness (including vertigo, blurred vision, and fatigue) may occur following administration of mepivacaine/adrenaline (see section 4.8). Patients with these symptoms should not drive or operate machines until these symptoms have disappeared.

4.8. Side effects

Security Profile Summary

Side effects following mepivacaine/adrenaline administration are like those observed with other amide local anesthetics combined with vasoconstrictors. In general, these adverse effects are dose-dependent and may occur due to elevated plasma levels following overdose, more rapid absorption, or accidental intravascular injection. They may also occur because of a hypersensitivity reaction, idiosyncrasy, or reduced tolerance in a patient. Neurological, cardiac, or vascular disorders are the most common side effects.

Major adverse effects are generally systemic. The presence of adrenaline increases the safety profile of the product through its sympathomimetic effects.

Table of side effects

This list of adverse reactions comes from spontaneous reports, clinical studies, and scientific publications. By convention, the following frequency groups are used: very common (≥ 1/10), common (≥1/100 à <1/10), uncommon (≥1/1,000 à <1/100), rare (≥1/10,000 à <1/1,000), very rare (< 10,000) and « not known » (cannot be estimated from the available data).

MedDRA Systems Organ Class	Frequency	Adverse reactions
Infections and infestations	Not known	Gingivitis
Immune system disorders	Rare	Hypersensitivity Anaphylactic/anaphylactoid reactions
Psychiatric conditions	Not known	Confusion, disorientation Anxiety/Nervousness/impatience, restlessness, Euphoric mood, Logorrhea
Nervous system disorders	Common	Headache
	Rare	Neuropathy[3:] Neuralgia (neuropathic pain) Hypoesthesia/numbness Dysesthesia including Dysgeusia (e.g., metallic taste, taste disorder) Ageusia Horner syndrome (eyelid ptosis, enophthalmos, miosis) Tremors, Nystagmus, Dizziness
	Very rare	Paresthesia (burning, tingling, and tingling sensations on the skin with no apparent physical cause)

MedDRA Systems Organ Class	Frequency	Adverse reactions
	Not known	Severe CNS depression: Loss of consciousness Coma Seizures (including tonic-clonic seizures) Presyncope, syncope Loss of balance (imbalance) Speech difficulties (i.e., dysarthria) Drowsiness
Eye conditions	Not known	Amaurosis, temporary blindness Diplopia, mydriasis Myosis, Visual impairment Blurry vision Accommodation problem
Ear and labyrinth disorders	Not known	Hearing discomfort Tinnitus Hyperacusis Dizziness
Heart conditions	Common	Palpitations
	Rare	Conduction disorders, Atrioventricular blocks, Bradyarrhythmias, Tachycardia, Bradycardia
	Not known	Cardiac arrest, Myocardial depression, Tachyarrhythmia (including extrasystoles and ventricular fibrillations)[5] Angina pectoris[6]
Vascular conditions	Common	Hypertension, Hypotension (with risk of circulatory collapse) Pallor (local, regional, general)
	Not known	Vasoconstriction, Vasodilatation
Respiratory, thoracic, and mediastinal conditions	Rare	Dyspnea Bronchospasm / asthma[2]
	Not known	Respiratory depression Apnea (respiratory arrest), Hypoxia[7] (including cerebral), Tachypnea, Bradypnea, Hypercapnea[7], Yawning Dysphonia (hoarseness[1])
Gastrointestinal conditions	Rare	Vomiting, Nausea
	very rare	Oral (and perioral) paresthesia)
	Not known	Ulceration/necrosis [8] Swelling [9] of the tongue, lips or gums Dysphagia[1], Exfoliation / ulceration of the gingival / oral mucosa (desquamation) Stomatitis, glossitis Salivary hypersecretion Diarrhea
Skin and subcutaneous tissue conditions	Rare	Angioedema (face/tongue/lips/throat/larynx/peri-orbital edema)1 Urticaria, Rashes Pruritus, Erythema
	Not known	Swelling of the face Hyperhidrosis

Musculoskeletal and Connective Tissue Conditions	Not known	Trismus, Muscle contractions

MedDRA systems organ class	Frequency	Adverse reactions
General disorders and administration site diseases	Rare	Pain. Pain at the injection site Hematoma at the injection site
	Not known	Local tumor. Swelling at the injection site. Faintness Chills Tremors, Sensation of heat, Sensation of cold Asthenia, Discomfort
Injuries, poisonings, and procedural complications	Rare	Neurological Injuries Pain during the procedure Pain after the procedure

Detailed description of some side effects

[1] Angioedema including swelling of the face/tongue/lips/throat/larynx/periorbital edema. Laryngopharyngeal edema is typically accompanied by hoarseness and/or dysphagia.

[2] Bronchospasm (bronchoconstriction) typically occurs with dyspnea.

[3] These neurological disorders can occur with varying symptoms of abnormal sensations (i.e., paresthesia, hypoesthesia, dysesthesia, hyperesthesia, etc.) of the lips, tongue, and oral tissues.

[4] These effects on the nervous system are due to the presence of local anesthetic/vasoconstrictor in excessive concentrations regionally or in the systemic circulation.

[5] This mainly occurs in patients who have an underlying heart problem or are taking certain medications).

[6] In patients predisposed to or at high risk of ischemic heart disease.

[7]Hypoxia and hypercapnia are secondary to respiratory depression and/or epileptic seizures and continued muscular exhaustion.

[8] Ulceration and necrosis of soft tissues may occur following excessive local effect of the vasoconstrictor.

[9] This occurs through accidental biting or chewing of the lips or tongue while anesthesia persists.

Pediatric population

The safety profile is similar in children and adolescents aged 4 to 18 years and adults.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continuous monitoring of the benefit/risk ratio of the medicine. Healthcare professionals report any suspected adverse reactions via the national reporting system: National Center of Pharmacovigilance (NCPV).

4.9. Overdosage

Types of overdoses

Local anesthetic overdose in the broad sense is often used to describe:

- Absolute overdose,
- Relative overdose such as:
  - Accidental injection into a blood vessel, or
  - Abnormally rapid absorption into the systemic circulation, or
  - Delayed drug metabolism and elimination.

Symptomatology

Mepivacaine-Related Symptoms:

These symptoms are dose-dependent and have progressive severity in terms of neurological manifestations, followed by vascular, respiratory, and finally cardiac toxicity (see detailed description in section 4.8)

Adrenaline-related symptoms:

An overdose of adrenaline can lead to cardiovascular effects.

Treatment of overdose

The presence of resuscitation equipment must be confirmed before starting dental anesthesia with local anesthetics.

If signs of serious toxicity are suspected, the injection of this medication should be discontinued immediately.

Oxygen should be administered promptly, if necessary, through assisted ventilation.

Change the patient's position so that they are lying down if necessary.

In case of cardiac arrest, cardiopulmonary resuscitation should be started immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic Class: Local anesthetics, ATC code: N01BB53.

Mepivacaine hydrochloride is a local anesthetic with an amino-amide function, which interrupts the propagation of nerve impulses along the nerve fiber at the site of injection.

Mepivacaine reduces nerve conduction by inducing reversible blockage of calcium channels. Adrenaline (diluted 1/100,000) added to the mepivacaine solution slows down the passage of mepivacaine into the general circulation and makes it possible to extend the duration of anesthesia and delay systemic exposure to mepivacaine hydrochloride and achieve good local hemostasis at the surgical site.

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

5.2. Pharmacokinetic properties

Absorption:

Various clinical trials have made it possible to determine the peak plasma concentrations of mepivacaine hydrochloride at 20 mg/ml with adrenaline at 0.1 mg/ml, after perioral injections during dental procedures. C_{max} values reported for mepivacaine hydrochloride ranged from 0.62 to 1.3 µg/ml with one to two cartridges after intraoral injection.

Injected into the oral mucosa, mepivacaine reaches its peak blood concentration approximately 30 minutes after injection.

Distribution:

Mepivacaine is rapidly distributed into tissues and is approximately 75% bound to plasma proteins.

Metabolism:

Like all amide local anesthetics, mepivacaine is primarily metabolized by hepatic microsomes with extensive hepatic biotransformation. There is less than 5% of intact drug excreted in the urine.

Its metabolism occurs first by hydroxylation of the original compound to inactive mepivacaine 3-OH- and inactive mepivacaine 4-OH by the CYP1A2 enzyme. More than 50% is eliminated in the form of metabolites in the bile by the enterohepatic circulation because a very small dose appears in the stools.

Elimination:

Excretion occurs primarily via the kidneys and metabolites are excreted with less than 10% of unchanged mepivacaine in the urine. The plasma elimination half-life would be approximately 2 hours in adults.

5.3. Preclinical safety data

No teratogenic effects were observed for mepivacaine. Some effects regarding fertility and teratogenicity have been observed in animals treated with adrenaline at doses much higher than those recommended for humans.

Like other local anesthetics with an amide function, the active component, at high doses, can induce toxic reactions on the central nervous system and the cardiovascular system (see section 4.8).

6. PHARMACEUTICAL DATA

6.1. List of excipients

Sodium chloride, Sodium metabisulfite, water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicine should not be mixed with other medicines.

6.3. Shelf life

24 months.
After opening the cartridge, immediate use is recommended.

6.4. Special precautions for storage

Store at a temperature below 25°C and away from light.
Do not freeze.

6.5. Nature and contents of outer packaging

1.8 mL in cartridge (glass). Box of 50.

6.6. Special precautions for disposal and handling

As with any cartridge, the diaphragm will be disinfected just before use. It will be stamped carefully:

- Either with 70% ethyl alcohol,
- Or with 90% pure isopropyl alcohol, for pharmaceutical use.

Under no circumstances should cartridges be immersed in any solution.
A cartridge can only be used for one patient during a single session.
Do not use again an opened anesthetic solution cartridge. In case the solution has not been used in full, the residual must be discarded.
Any unused medicine or waste must be disposed of in accordance with the current regulations.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES MEDIS-S.A.
Road of Tunis - KM 7 - BP 206 - 8000 Nabeul - Tunisia
Tel: (216) 72 23 50 06
Fax: (216) 72 23 51 06
E-mail:marketing.ventes@medis.com.tn

8. MARKETING AUTHORISATION NUMBER(S)

MEDICAINE 2% with adrenaline, B/50/1.8 ml: 9233011

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorisation:
14/03/2000.
Date of latest renewal:
15/03/2020.

10. DATE OF TEXT UPDATE

12/2023

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.