1. NAME OF THE MEDICINAL PRODUCT

Alphacaine 20 mg/mL + 12.5 µg/mL; Alphacaine 20 mg/mL + 10 µg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ALPHACAINE 1:80,000 injection contains:

Lidocaine hydrochloride.....20.0 mg

Epinephrine 12.5µg

Excipients e.f.....1.0 mL

Excipients: Sodium Bisulfite, Sodium Chloride and Water for Injection.

Each mL of ALPHACAINE 1:100,000 injection contains:

Lidocaine hydrochloride.....20.0 mg

Epinephrine 10.0µg

Excipients e.f.....1.0 mL

3. PHARMACEUTICAL FORM

INJECTABLE SOLUTION

4. Clinical particulars

4.1 Therapeutic indications

The product is indicated for local anesthesia by nerve block or infiltration, for general dental interventions, multiple extractions, immediate dentures and endodontic and periodontal procedures simple and complex. The product is indicated for pediatric and adult use.

4.2 Posology and method of administration

As occurs with all local anesthetics, dosages vary and depend on the area to be anesthetized, the vascularity of tissues, the number of nerve segments to be blocked, the individual tolerance and the technique of anesthesia. The least volume of injection that results in effective local anesthesia should be administered. The necessary dosage must be determined on an individual basis. The maximum dosage suggested by the Council on Dental Therapeutics of the American Dental Association and the USP

Convention is 4.4 mg/kg for lidocaine with or without a vasoconstrictor additive. This dose still allows for a significant volume of drug to be used to achieve profound clinical anesthesia with a somewhat diminished risk of development of toxic (overdose) reactions. For children of less than ten years who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (e.g., Clark's rule). The maximum recommended dosage of epinephrine is 0.2 mg (8.8 cartridges of ALPHACAINE 80 or 11 cartridges of ALPHACAINE 100) for healthy adult patients. The maximum recommended dosage for epinephrine-sensitive patients, such as ASA III and ASA IV and clinically hyperthyroid patients, is 0.04 mg of epinephrine (1and ½ cartridge of ALPHACAINE 80 or 2 cartridges of ALPHACAINE 100) per appointment. In oral infiltration and/or mandibular block, initial dosages of 1.0-5.0 ml of lidocaine (1/2 to 21/2 cartridges of ALPHACAINE) are usually effective. In children under 10 years of age it is rarely necessary to administer more than one-half cartridge of ALPHACAINE (0.9 to 1.0 ml of lidocaine) per procedure, to achieve local anesthesia for a procedure involving a single tooth. During administration, it is recommended to perform a slight aspiration in order to avoid the risks of intravenous injection.

Maximum dose: 4.4 mg of lidocaine hydrochloride/kg and

0.2 mg of epinephrine/kg

(Each 1.8 ml cartridge contains 36 mg of lidocaine hydrochloride)

Weight (Kg)	Number of **ALPHACAINE 80** Cartridges	Number of **ALPHACAINE 100** Cartridges
10	1 (44 mg)	1 (44 mg)
20	2 (88 mg)	2 (88 mg)
30	3,5 (132 mg)	3,5 (132 mg)
40	4,5 (176 mg)	4,5 (176 mg)
50	6 (220 mg)	6 (220 mg)
60	7 (264 mg)	7 (264 mg)
70	8 (300 mg)	8 (300 mg)
80	8 (300 mg)	8 (300 mg)
90	8 (300 mg)	8 (300 mg)
100	8 (300 mg)	8 (300 mg)

Doses indicated are the maximum suggested for normal healthy individuals: they should be decreased for debilitated or elderly patients.

It is recommended that chemical disinfection of the cartridge cap be accomplished by wiping it thoroughly with a pledget of cotton that has been moistened with 70% ethyl alcohol just prior to use. Immersion is not recommended. During administration, it is recommended to perform a slight aspiration in order to avoid the risks of an undesirable intra-vascular injection. However, it should be noted that the absence of blood in the syringe does not guarantee that intravascular injection was avoided and a

double aspiration is always recommended. Cartridges partially used should not be reused.

4.3 Contraindications

ALPHACAINE is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any other substance present in formula and in patients receiving drugs known to produce blood pressure alterations, as MAO inhibitors, tricyclic antidepressants and phenothiazines.

4.4 Special warnings and precautions for use

The safety and efficacy of local anesthetics depend on the recommended dosage, the correct technique employed, the previous anamnesis, the appropriate precautions taken and the fastness and qualification of the health care professional during emergencies. It should be used the lowest doses that are able to provide efficient anesthesia.

The administration of frequent doses of lidocaine may cause a sharp increase of levels in the blood with each additional dose, due to the increase of the drug, its metabolites or to slow metabolic breakdown. Tolerance may vary depending on the patient's state, those debilitated by old age or serious illnesses or children should be given reduced doses, calculated in accordance with their age and physical condition.

Special care is recommended in frequent application in patients with serious kidney or liver problems due to their inability to normally metabolize the anesthetic drug, thereby being subject to the risk of toxic concentrations in the plasma. Special care should be taken in the administration of local anesthetics in patients with known drug sensitivities or allergies to any of the substances in the formula.

Patients with hypertension, coronary or cardiovascular problems (particularly related to sequela of acute rheumatic fever), must avoid the use of anesthetics containing vasoconstrictors as ALPHACAINE. In patients with peripheral vascular disease, there is a little potential risk that vasoconstrictors cause ischemic injury or local necrosis. The presence of Sodium Bisulfite in the formula must be taken into account when treating patients who are susceptible to asthma. Parents should be advised, as well as people liable for patients with mental disturbance, to observe them, in order to avoid possible inadvertent trauma to the lips. This product is not to be used if the solution is yellowish or with particles.

In elderly patients, in who the metabolic, renal and hepatic functions are usually diminished, care must be taken in terms of administering the smallest necessary dose that is enough for providing a specific kind of anesthesia. Care should be taken in the use of ALPHACAINE in patients with liver or kidney problems and in patients susceptible to asthma.

The use in children under 10 years old should follow the recommendations described in Dosage.

There aren't available adequate and well-controlled studies in pregnant and breastfeeding women so ALPHACAINE must be used, in this risk group, carefully and under professional supervision.

There is no data available on the possible excretion of lidocaine in human milk and as many drugs are excreted in this way, it is recommended special caution when this product is administered to mothers during the breastfeeding period.

4.5 Interaction with other medicinal products and other forms of interaction

According to studies undertaken by P. Henry and J. Van der Driessche of the pharmacology laboratory of the Rennes University Hospital Center, the use of local anesthetic associated with the consumption of alcohol and/or tranquilizing medication directly interferes in the efficiency of the anesthetic, potentially

increasing or decreasing its time of action and potency.

ALPHACAINE should not be used in patients in treatment with drugs known to affect blood pressure, as monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines. Serious cardiac arrhythmia may occur if preparations containing vasoconstrictors are used in patients during or after the administration of halotane, trichloroethylene, cyclopropane or chloroform. Concurrent administration of vasopressor drugs and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

4.6 Pregnancy and Lactation

There aren't available adequate and well-controlled studies in pregnant and breastfeeding women so ALPHACAINE must be used, in this risk group, carefully and under professional supervision.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Side effects following lidocaine administration are similar to those observed in other amide-based anesthetics. Adverse reactions are normally the result of high plasma levels caused by excessive dosage, rapid absorption or unintentional intravascular injection, or may result from hypersensitivity, idiosyncrasy, or reduced tolerance on the part of the patient. Effects involving cardiovascular and central nervous systems may occur. Reactions in the CNS are exciting and/or depressing and may be characterized by photo-phobia, irritability, apprehension, euphoria, confusion, dizziness, drowsiness, ringing in the ears, blurred vision, vomiting, burning sensation, cold or numbness, loss of consciousness, respiratory depression and arrest. Cardiovascular reactions are normally depressive and characterized by bradycardia, hypertension and cardiovascular collapse, which may lead to cardiac arrest. Signs and symptoms of a depressed cardiovascular system are commonly the result of a vasovagal reaction but may also be the result of a direct effect of the drug. The health care professional should have support treatments for these reactions available within easy reach so as to effect a rapid response if, and when, necessary. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Allergy to amide local anesthetics is virtually nonexistent; true, documented and reproducible allergic reactions are extremely rare, though possible. Mild allergic reactions may include cutaneous lesions, itchiness and edema. Anaphylactic reactions are extremely rare. Neurological reactions, as persistent neurological deficiency, associated with the use of local anesthetics may be related to the technique used, the total dose of anesthetic administered, the route of administration and the patient's physical condition. Paresthesia may occur using ALPHACAINE.

4.9 Overdose

Generalized reactions in the central nervous system or cardiovascular reactions are generally related to high plasmatic levels due to accidental intravenous injection or overdose (See Warnings and Adverse Reactions). The first signs and symptoms of lidocaine overdose may be drowsiness, leading to a loss of consciousness and respiratory arrest. In such cases, the following procedure should be followed:

- Place the patient in the supine position. Raise the legs 30-45 above horizontal level.

- The passage of air must be ensured. If the ventilation is inadequate, ventilate the patient with oxygen if possible.

- If the pulse is weak (<40) or non-determinable, initiate external cardiac massage.

- Support treatment of circulatory deficiency may require the intravenous administration of parenteral solutions (saline).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Primary Pharmacodynamics

Lidocaine Hydrochloride is the hydrochloride salt from of lidocaine, an aminoethylamide and a prototypical member of the amide class anesthetics. Lidocaine interacts with voltage-gated Na+ channels in the nerve cell membrane and blocks the transient increase in permeability of excitable membranes to Na+. This prevents the generation and conduction of nerve impulses and produces a reversible loss of sensation. Lidocaine hydrochloride also exhibits class IB antiarrhythmic effects. The agent decreases the flow of sodium ions into myocardial tissue, especially on the Purkinje network, during phase 0 of the action potential, thereby decreasing depolarization, automaticity, and excitability.

Local anesthetics (LA) are compounds that produce reversible loss of sensation by preventing or diminishing the conduction of sensory nerve impulses near to the site of their application or injection. Also, their mode of action is to decrease permeability of the nerve cell membrane to sodium ions, they are considered because to have a membrane stabilizing effect. Clinically useful local anesthetics have the same general chemical configuration of an amine portion joined to an aromatic residue by an ester or amide link. The type of linkage is important in determining the properties of the drug.

The use of local anesthetic agents is standard practice in dentistry. Some of the LA formulations in delivery systems intended for use in oral healthcare settings (i.e., cartridges) include epinephrine or levonordefrin for vasoconstriction**.** These adjuvants decrease the rate of LAs' systemic absorption; prolong LAs' duration of action; reduce the risk of LAs' systemic toxicity; and with infiltration anesthesia, they may reduce bleeding in the operative field.

5.2 Pharmacokinetic properties

Lidocaine Hydrochloride

Classification: Amide Other names: Xylocaine

Chemical formula: 2-Diethylamino 2',6-acetoxylidide hydrochloride.

Potency: 2 (procaine = 1)

Toxicity: 2 (in comparison with procaine)

Mechanism of action: Promotes local anesthesia through the stabilization of neuronal membranes, inhibiting the ionic flux required for the onset and conduction of impulses.

Absorption: Lidocaine is completely absorbed following parenteral administration and its margin of absorption depends on the site of administration and the presence or otherwise of vasoconstrictors. The link between plasma and lidocaine depends on the concentration of the drug and the linked fraction decreases in accordance with the increase of concentration. It crosses the blood-brain and placentary barriers, presumably via passive diffusion.

Metabolism: It is metabolized in the liver by the microsomal fixed-functions oxidases, to monoethylglyceine and xylidide; xylidide is a local anesthetic and potentially toxic.

Excretion: Via the kidneys; less than 10% unchanged, more than 80% various metabolites.

Vasodilating properties: Considerably less than those of procaine; however, more than those of prilocaine or mepivacaine. Onset of action: Rapid (2 to 3 minutes).

Anesthetic half-life: 1.6 hours.

Topical anesthetic action: Yes (in clinically acceptable concentrations).

Epinephrine

Other chemical names: Adrenaline

It is a sympathomimetic amine, being chemically recognized as 3,4-dihydroxi (methylamino) methyl benzilic alcohol. It acts on both α- and β-adrenergic receptors, where β effects predominate. It has been used in minimal concentrations which permit a prolonged anaesthetic effect, necessary for lengthy surgical interventions or where major bleeding occurs.

5.3 Preclinical safety data

According methods and results of "*Oshikiri and colleagues (2020) assessed whether combined administration of landiolol with adrenaline and lidocaine would induce local anesthesia without causing hemodynamic changes".*

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients used in the manufacturing process of Lidocaine hydrochloride + Epinephrine (20 mg/mL + 12,5µg/mL | 20 mg/mL + 10µg/mL) injectable solution are given in the table below:

Name of excipients	Function	Reference to Standards
Sodium chloride	Excipient (isotonic agent)	USP 39
Sodium bisulfite	Excipient (antioxidant)	Japanese Pharmacopoeia 15th ed., p. 1094-1095

Water for Injection	Excipient (vehicle)	European Pharmacopoeia 8° edition

6.2 Incompatibilities

The glass cartridge used is a borosilicate glass, which has a high hydrolytic resistance due to the chemical composition of the glass itself. It is classified as Type I, USP. And according to stability study, the product is compatibility with primary package.

6.3 Shelf life

The shelf life of this product is equivalent to 24 months after manufacturing date.

6.4 Special precautions for storage

This product should be kept in its original package, at room temperature (between 15°C and 30ºC). Protect from light.
Batch number and manufacturing and expiry date: see product box. Do not use medicine with expire date. Store in its original package. Before use, observe the medicine aspect.
Every drugs should be kept out of the reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Lidocaine hydrochloride + Epinephrine injectable solution is packaged in a 1.8mL glass tube with a label, with a piston and seal, packaged in a card cartridge with a leaflet.

Summary of container closure system

Table - Summary of container closure system

Container closure system	Description	Justification
Primary packaging	Transparent glass tube of 1.8 mL with a piston and a seal, protected by a blister pack.	Used extensively for the packaging of dental parenteral dosage forms. Compatibility of the packaging material with the dosage form is verified by the stability studies provided in section 3.2.P.8 of this dossier.
Intermediate packaging	Blister	Protect the glass tube from breaking
Secondary packaging	Card cartridge, containing blister pack with the glass tube and patient information leaflet.	Industry standard for non-functional secondary packaging

Primary packaging
Lidocaine hydrochloride + Epinephrine (20 mg/mL + 12.5µg/mL) injectable solution is packaged in a 1.8mL

glass tube, with a piston red and a golden aluminium seal.
Lidocaine hydrochloride + Epinephrine (20 mg/mL + 10µg/mL) injectable is packaged in a 1.8mL glass tube, with a piston red and a gray seal.

Intermediate packaging
The glass tube is labeled and then inserted into a blister to protect breaking.

Secondary packaging
The blister with the glass tubes is inserted in a cartridge made of triplex Nobrecel card with varnish finish, zipper seal, reactive ink and text according to artwork.

6.6 Special precautions for disposal <and other handling>

Partially used cartridges should not be reused.

7. <APPLICANT/MANUFACTURER>

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