Dirección: Cra. 53 N° 50-09
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TECHNICAL DATA SHEET: ANESTHETIC ARTHEEK® 4% E-100
PRFTPT-009

1. GENERAL PRODUCT INFORMATION

ARTHEEK® 4% - E100
Articaine Hydrochloride 4% with Epinephrine 1:100.000
Injectable anesthetic solutions used in dental treatments

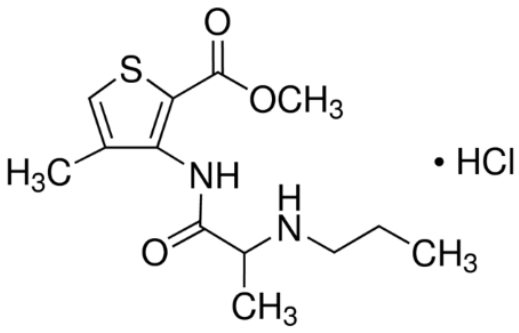
Artheek® 4% is an injectable solution (parenteral absorption, of small-volume) used as a dental anesthetic to produce local anesthesia when administered through infiltration or nerve block. This product must use by personnel whit professional certification and trained to perform dental procedures.

1.1. Commercial Name
ARTHEEK® 4% E-100

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

1.2.1. ARTICAINE HYDROCHLORIDE
- **Molecular Formula:** $C_{13}H_{20}N_2O_3S.HCl$
- **Molecular Mass:** 320.83 g/mol.
- **IUPAC Name:** - methyl 4–methyl - 3 -(2-propylaminopropanoylamino) thiophene - 2 - carboxylate hydrochloride

1.2.1.1 Structural Formula



1.2.2 EPINEPHRINE
- **Molecular Formula:** $C_9H_{13}NO_3$

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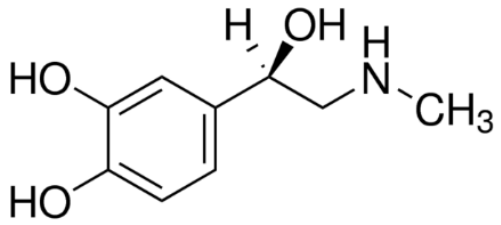
- **Molecular Mass:** 183.21 g/mol
- **IUPAC Name:** *(R)*-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol1,2-Benzenediol, 4-[1-Hydroxy-2-(methylamino) ethyl]-, (R) (-) - 3,4-Dihydroxy-a-[(methylamino) methyl] benzyl alcohol.

1.2.2.1 Structural Formula



2. INFORMATION ABOUT COMPOSITION ELEMENTS

Each dental carpule contains	
Articaine Hydrochloride	0.072 g
Epinephrine Base	0.000018 g
Excipients	q.s.a.d 1.8 mL

3. PROPERTIES OF THIS PRODUCT

3.1 ARTICAINE

Articaine is a short-acting local anesthetic of the amide type whose structure is similar to the other local anesthetics whereas Articaine is exceptional because it contains an additional ester group that is hydrolyzed very quickly in the blood.

Articaine causes a transient and completely reversible nerve block because it blocks the initiation and conduction of the nerve impulse by decreasing the neuronal membrane's permeability to sodium ions. This reduction causes a depolarization of membrane and increases the threshold that is necessary for electrical excitability.

To exert its anesthetic action, Articaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses.

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3.2 EPINEPHRINE

Epinephrine causes local vasoconstriction which restricts the absorption of the anesthetic, prolongs its action and diminishes its systemic toxicity.

4. INDICATION AND USES

Artheek® is a local anesthetic which contains epinephrine that indicated in simple and complex dental procedures for infiltration and nerve block anesthesia.

5. DOSE AND ADMINISTRATION

5.1 GENERAL DOSING INFORMATION

The dosage of the local anesthetic depends upon the following aspects: physical condition of patient, area of the oral cavity that will be anesthetized, vascularity of the oral tissues, and the technique of anesthesia that will be employed.

The lowest dose that results in effective anesthesia should be used to avoid high plasma levels and serious undesirable adverse effects. Patients should be carefully observed for any adverse reaction.

5.2 MAXIMUM RECOMMENDED DOSAGE

Adults: For normal healthy adults, the maximum dose of articaine administered should not exceed 7 mg/kg (0.175 mL/kg).

- Infiltration: 0.5 to 2.5 mL; total dose of articaine: 20 to 100 mg
- Nerve block: 0.5 to 3.4 mL; total dose of articaine: 20 to 136 mg
- Oral surgery: 1 to 5.1 mL; total dose of articaine: 40 to 204 mg

Pediatric patients ages 4 to 16 Years: The quantity of articaine should be determined by the age and weight of the child and the magnitude of the operation. the maximum dose of articaine HCL administered should not exceed 7 mg/kg (0.175 mL/kg). Safety and effectiveness of Artheek in pediatric patients below the age of 4 years have not been established.

- Simple procedures: Reported range: 0.76 to 5.65 mg/kg of articaine
- Complex procedures: 0.37 to 7 mg/kg of articaine

Adolescents ≥17 years: refer to adults' dose

The provided dosages are guides only; other dosages may be necessary; however, do not exceed the maximum recommended dose.
The actual volumes to be used depending upon a number of factors, such as type and extent of surgical procedure, depth of anesthesia, a degree of muscular relaxation, and condition of the patient. In all cases, the smallest dose that will produce the desired result should be used.

6. USE IN SPECIFIC POPULATIONS

6.1 PREGNANCY

Adverse events have been observed in some animal reproduction studies using this combination. Articaine crosses the placenta.

6.2 NURSING MOTHERS

It is not known if articaine or epinephrine are excreted in breast milk, nevertheless, it should be cautious when administering articaine/epinephrine to breastfeeding women; consideration may be given to pumping and discarding milk for 4 hours after the last dose. In general, women administered single dose local anesthesia for dental procedures may resume breast-feeding once they are awake and stable

7. WARNINGS

Accidental intravascular injection of Artheek may be associated with convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest.

Resuscitative equipment and drugs should be immediately available because an accidental intravascular injection of Artheek® may be associated with convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Also, Dental practitioners who employ local anesthetic agents should be well versed in the diagnosis and management of emergencies that may arise from their use.

Artheek® is injected, for this reason, the needle must reposition until no return blood can elicit by aspiration, however, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Small doses of local anesthetics injected in dental block may produce adverse reactions similar to the systemic toxicity seen with unintentional intravascular injections of larger

doses. Confusion, convulsions, respiratory depression or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should be observed constantly

Artheek® contains sodium metabisulfite, a sulfite may cause allergic type reaction including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people

In patients with acidosis or hypoxia, the risk and severity of toxic reactions may increase, such reactions involve the Nervous Central System (CNS) and the Cardiovascular System. Local anesthetics must be used with caution in patients with anemia, severe cardiovascular diseases or circulatory dysfunctions of any kind, as a consequence, the minimum possible amount of vasoconstrictor should be used, besides the effect of local anesthetics may reduce if the injection is made into an inflamed area.

8. PRECAUTIONS

8.1 Systemic conditions

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of Articaine may cause significant increases in blood levels because of possible accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient.

The dose for debilitated, elderly patients, acutely ill patients, and children should be calculate commensurate with their age and physical condition.

At blood concentrations achieved with therapeutic doses of Artheek, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations can depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, possibly resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilatation occurs, leading to decreased cardiac output and arterial blood pressure cardiovascular function also it should be used with caution in patients with heart block as well as those with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs

Cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be monitored after each local anesthetic injection. Restlessness, anxiety tinnitus, dizziness, blurred vision, tremors, depression or drowsiness should alert the practitioner to the possibility of central nervous system toxicity.

No studies have been performed in patients with liver dysfunction, and caution should be used in patients with severe hepatic disease.

8.2 Vasoconstrictor toxicity

Artheek® contains vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury (such as exfoliating or ulcerating lesions) or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

The American Heart Association has made the following recommendation regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection

8.3 Methemoglobinemia

Articaine, like other local anesthetics, can cause methemoglobinemia, particularly in conjunction with methemoglobin-inducing agents, therefore in patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, exposure to oxidizing agents or their metabolites, or infants <6 months of age are more susceptible and should be closely monitored for signs and symptoms of methemoglobinemia. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia include slate grey cyanosis seen in buccal mucous membranes, lips, and nail beds. In severe cases, symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrythmia, and shock.

Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if methemoglobin-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia.

The diagnosis can be confirmed by an elevated methemoglobin level of at least 10% is present. The development of methemoglobinemia is dose-related.

Management of methemoglobinemia: If methemoglobinemia does not respond to administration of oxygen, clinically significant symptoms of methemoglobinemia should be treated with administration of a slow intravenous injection (over 5 minutes) of methylene blue at a dosage of 1-2 mg/kg body weight.

9. CONTRAINDICATIONS

Artheek® is contraindicated in patients who are hypersensitivity to articaine or any component of the formulation. The product contains sodium metabisulfite may cause an allergic-type reaction, Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
It should not use in children <4 years of age.
Documentation of allergenic cross-reactivity for local anesthetics is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

10. ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are rare when Articaine 4% E100 is used. If some adverse reactions appear, they have similar characteristics to those produced by other local anesthetics.

Adverse reactions are generally produced by high blood plasma levels (which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation), injection technique, volume of injection, or hypersensitivity or they may be idiosyncratic.

Common

- Hypotension
- Pain (6.1% to 13%)

Serious

- Cardiac arrest, Negative inotropic effect on myocardium, Syncope (less than 1%), Ventricular arrhythmia
- Injection site necrosis
- Methemoglobinemia

- Hypersensitivity reaction

11. TREATMENT IN CASE OF OVERDOSAGE

The following will be the management of local anesthetic emergencies in case of overdose:

Lie the patient face up; lift the patient's legs up (30°- 45°) from his/her resting-position; if ventilation is not adequate, provide assisted or controlled ventilation with oxygen if possible.

If the pulse rate of patient is low (<40) or not shown, standard cardiopulmonary resuscitation procedures should be instituted, for example, an external cardiac massage. If the patient is unconscious and /or the ventilation is inadequate in spite of the afore-mentioned supportive measures, begin a treatment of convulsions and apply mechanic ventilation.

- **Convulsions:** 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. Efforts must be made in order to stop convulsions. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as. Sodium Thiopental (50-100 mg, increased) every 2 or 3 minutes) or a benzodiazepine (such as diazepam, 2.5 mg, increased) may be administered intravenously in order to stop convulsion, keeping in mind that barbiturates may also depress the circulation when injected intravenously. The clinician should be familiar, prior to use local anesthetics, with these 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). This treatment may also involve the risk of respiratory depression. Facilities for providing or controlling mechanical ventilation should be available.

- Neuromuscular blockers can also be used to decrease persistent convulsions. Artificial respiration is compulsory when using neuromuscular blockers.

  Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution [see Warnings and Precautions (5.1, 5.2)]. 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 anesthetic injection. At the first sign of

change, oxygen should be administered. The first step in the management of convulsions, as well as hypo-ventilation, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation as needed. The adequacy of the circulation should be assessed. Should convulsions persist despite adequate respiratory support, treatment with appropriate anticonvulsant therapy is indicated. The practitioner should be familiar with the use of anticonvulsant drugs, prior to the use of local anesthetics. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor. If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and/or cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

12. RELEVANT CLINICAL INTERACTIONS

12.1 DRUG INTERATIONS

12.1.1 Articaine

Drug group	Effect	Severity
Neuromuscular-Blocking Agents	Local Anesthetics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents	Moderate

12.1.2 Epinephrine

The risk of a significant systemic effect depends on the total dose administrated and the factors such as the administration site and the intravascular injection that affect the average vasoconstrictor absorption agent.

Drug group	Effect	Severity
Non selective beta blockers	May result in severe prolonged hypertension.	Major
IMAO		Major
Triciclyc antidepressant agent		Major Consider reductions in initial dosages
Ergot derivates	May enhance the hypertensive and vasoconstricting effect.	Contraindicated
		Excepcions: - Ergoloid Mesylates (No

		interactions) - Nicergoline (Moderate)
Atypical antipsychotic	May diminish the therapeutic effect	Moderate Excepcions: - Blonanserin (contraindicated)
Phenothiazines and butyrophenones	May result in decreased or reversal of epinephrine pressor response.	Major
Linezolid	May enhance the hypertensive effect **Note:** Reduce initial doses of Epinephrine, and closely monitor for enhanced pressor response.	Major

13. QUALITY ASSURANCE OF THE PRODUCT

ARTHEEK® 4% - E100 is manufactured under the strictest technical and quality controls. the manufacturing process is carried out in manufacture areas with environmental, microbiological and operational controls. Raw materials used are previously examined and approved according to requirements of available pharmacopeias. The control process includes the control of Blister Packing and secondary packaging materials. All raw materials are furnished by qualified providers.

ARTHEEK® 4% - E100 meets all requirements established for this product by current pharmacopeias and regulating agencies. These specifications include the appearance of the product, physical properties, contents of active ingredients, and microbiological controls. All these parameters are verifying during the different steps of the manufacturing process by using high technology equipment, standardized procedures, analytical areas, and trained employees.

14. OTHERS RECOMMENDATIONS

- Injections into infected Area

The buffer capacity of tissues may cause a pH stabilization but, injections into infected areas may result in incomplete anesthesia as a consequence, of residual acid produced, thus reduce the tissues buffer capacity

- Anatomic variations:

In some patients, injections may fail due to a deviated position of the nerve or to an exceptionally thick and compact bone that constitutes a barrier for the diffusion as a result anesthesia effect decrease.

- Intravenous Injections:

An intravascular injection may diminish local anesthetic effect, additional adverse reactions and toxicity of Artheek may enhance.

- Very rapid Injections:

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

- Disinfection of carpules:

Local anesthetic cartridges should not submerge in anticorrosive solutions or quaternary ammonium salts solutions such as benzalkonium chloride. Some metal ions (mercury, zinc, copper) are contained in disinfectant solutions and may be the cause of inflammations after anesthetic procedures.

For chemical disinfection of the cartridges, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. Many commercially available brands of isopropyl (rubbing) alcohol, as well as solutions of ethyl alcohol not of U.S.P. grade, contain denaturants that are injurious to rubber and therefore are not to be used.

Artheek should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Any amount of anesthetic solution remains must be discarded.

15. COMMERCIAL PACKAGING SPECIFICATIONS OF THIS PRODUCT

The anesthetic solution ARTHEEK® 4% - E100 is marketed in the following commercial packagings:

- Primary Packaging
  - Glass cartridges: Cylindrical cartridges made of type I- glass (Borosilicate glass).

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- This type of commercial primary packaging has a natural-rubber plug and metallic top cap with diaphragm (aluminium and natural rubber).

- Secondary Packaging
  - Blister x 10 carpules in cardboard box per 5 blister.
  - Plastic Box por 50 carpules

16. CONSERVATION AND STORAGE CONDITIONS

ARTHEEK® 4% - E100 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 30.0 °C.

17. EXPIRY DATE

Two (2) years.