FPO 20011-0

Physician's Prescribing Information

ISOCAINE 3%

1) Name of the medicinal product: ISOCAINE 3%

2) Qualitative and quantitative composition:

1 ml solution for injection contains 30 mg of mepivacaine hydrochloride.

Each cartridge of 1.8 ml of solution for injection contains 54 mg of mepivacaine hydrochloride.

For the full list of excipients, see section 6.1.

3) Pharmaceutical Form: Solution for Injection. Clear and colourless solution. The pH of the solution is adjusted between 4.5 and 6.8 with Sodium Hydroxide.

4) CLINICAL PARTICULARS:

4.1) Therapeutic indications: Production of local anaesthesia for dental procedures by infiltration or nerve block in adults and children.

4.2) Posology and method of administration:

THIS SOLUTION IS INTENDED FOR DENTAL USE ONLY.
DENTAL CARTRIDGES MAY NOT BE AUTOCLAVED. ISOCAINE 3% are sterile solutions for injection.

As with all local anesthetics, the dose varies and depends upon the area to be anesthetized, the vascularity of the tissues, individual tolerance and the technique of anesthesia. The lowest dose needed to provide effective anesthesia should be administered. For specific techniques and procedures refer to standard dental manuals and textbooks.

For infiltration and block injections in the upper or lower jaw, the average dose of 1 cartridge will usually suffice.

Each cartridge contains 1.8 mL (54 mg of 3%).

5 cartridges (270 mg of the 3% solution) are usually adequate to effect anesthesia of the entire oral cavity. Whenever a larger dose seems to be necessary for an extensive procedure, the maximum dose should be calculated according to the patient's weight. A dose of up to 3 mg per pound of body weight (equals 6.6 mg per kilogram of body weight) may be administered. At any single dental sitting the total dose for all injected sites should not exceed 400 mg in adults.

The maximum pediatric dose should be *carefully calculated*.

$$\text{Maximum dose for pediatric population} = \frac{\text{Child's Weight (kg)}}{68} \times \text{Maximum Recommended Dose for Adults (400 mg)}$$

$$\text{Maximum dose for pediatric population} = \frac{\text{Child's Weight (lbs.)}}{150} \times \text{Maximum Recommended Dose for Adults (400 mg)}$$

The following table, approximating these calculations, may also be used as a guide. This table is based upon a recommended maximum for larger pediatric population of 5 cartridges (the maximum recommended adult dose) during any single dental sitting, regardless of the child's weight:

Maximum Allowable Dosage*: 3% Mepivacaine HCl; 6.6 mg/kg or 3 mg/lb. (270 mg max.)

Weight (kg)	Mepivacaine HCl in mg	Number of Cartridges	Weight (kg)	Mepivacaine HCl in mg	Number of Cartridges
10	66	1.2	30	198	3.7
15	99	1.8	35	231	4.3
20	132	2.4	40	264	4.9
25	165	3.1	50	270	5.0

Weight (lb.)	Mepivacaine HCl in mg	Number of Cartridges	Weight (lb.)	Mepivacaine HCl in mg	Number of Cartridges
20	60	1.1	60	180	3.3
30	90	1.7	80	240	4.4
40	120	2.2	100	270	5
50	150	2.8	120	270	5

* Adapted from Malamed, Stanley F: Handbook of medical emergencies in the dental office, ed.2, St. Louis, 1982. The C.V. Mosby Co.

When using ISOCAINE 3% for infiltration or regional block anesthesia, injection should always be made slowly and with frequent aspiration.

Any unused portion of a cartridge should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DISINFECTION OF CARTRIDGES:

As in the case of any cartridge, the diaphragm should be disinfected before needle puncture. The diaphragm should be thoroughly swabbed with either pure 91% isopropyl alcohol or 70% ethyl alcohol, USP, just prior to use. Many commercially available alcohol solutions contain ingredients which are injurious to container components, and therefore, should not be used. Cartridges should not be immersed in any solution.

Pediatric Use: Great care must be exercised in adhering to safe concentrations and dosages for pedodontic administration.

4.3) Contraindications:

- Mepivacaine is contraindicated in patients with a known hypersensitivity to amide-type local anesthetics.

4.4) Special warnings and precautions for use:

WARNINGS:

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE. (See ADVERSE REACTIONS).

Reactions resulting in fatality have occurred on rare occasions with the use of local anesthetics, even in the absence of a history of hypersensitivity.

Fatalities may occur with use of local anesthetics in the head and neck region as the result of retrograde arterial flow to vital CNS areas even when maximum recommended doses are observed. The practitioner should be alert to early evidence of alteration in sensorium or vital signs.

Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use; Mepivacaine, along with other local anesthetics, is capable of producing this condition. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by cyanosis of the skin, nail beds and lips, and/or abnormal coloration of the blood, fatigue and weakness. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue mepivacaine and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. If methemoglobinemia does not respond to administration of oxygen, a more severe clinical presentation may require treatment with methylene blue exchange transfusion, or hyperbaric oxygen.

PRECAUTIONS:

The safety and effectiveness of mepivacaine depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dose that results in effective anesthesia should be used to avoid high plasma levels and possible adverse effects. Injection of repeated doses of mepivacaine may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites, or due to slower metabolic degradation than normal.

Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their weight and physical status. Mepivacaine should be used with caution in patients with a history of severe disturbances of cardiac rhythm or heart block.

INJECTIONS SHOULD ALWAYS BE MADE SLOWLY WITH ASPIRATION TO AVOID INTRAVASCULAR INJECTION AND THEREFORE SYSTEMIC REACTION TO LOCAL ANESTHETIC.

If sedatives are employed to reduce patient apprehension, use reduced doses, since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect. Young children should be given minimal doses of each agent.

Changes in sensorium such as excitation, disorientation or drowsiness may be early indications of a high blood level of the drug and may occur following inadvertent intravascular administration or rapid absorption of mepivacaine.

Local anesthetic procedures should be used with caution when there is inflammation and/or sepsis in the region of the proposed injection.

Information for Patients/Patient Counseling Information:

The patient should be cautioned against loss of sensation and possibility of biting trauma should the patient attempt to eat or chew gum prior to return of sensation. Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

4.5) Interaction with other medicinal products and other forms of interaction:

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

EXAMPLES OF DRUGS ASSOCIATED WITH METHEMOGLOBINEMIA:

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic Agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenobarbital, phenytoin, sodium valproate
Other drugs	Acetaminophen (paracetamol), metoclopramide, quinine, sulfasalazine

MEPIVACAINE SHOULD BE USED WITH CAUTION IN PATIENTS WITH KNOWN DRUG ALLERGIES AND SENSITIVITIES. A thorough history of the patient's prior experience with mepivacaine or other local anesthetics as well as concomitant or recent drug use should be taken (see CONTRAINDICATIONS). Patients allergic to methylparaben or para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide type such as mepivacaine. Since mepivacaine is metabolized in the liver and excreted by the kidneys, it should be used cautiously in patients with liver and renal disease.

4.6) Fertility, pregnancy and lactation:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of Mepivacaine HCl in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with this solution. It is also not known whether this solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. This solution should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this solution is administered to a nursing woman.

4.7) Effects on ability to drive and use machines:

ISOCAINE 3% may have a minor influence on the ability to drive and use machines.

Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of mepivacaine (see section 4.8). So, patients should not leave the dental office until they recover their abilities (generally within 30 minutes) following the dental procedure.

4.8) Undesirable effects:

Reactions to mepivacaine are characteristic of those associated with other amide-type local anesthetics. Systemic adverse reactions involving the central nervous system and the cardiovascular system usually result from high plasma levels (which may be due to excessive dosage, rapid absorption, inadvertent intravascular injection, or slow metabolic degradation), injection technique, or volume of injection.

A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance to normal dosage on the part of the patient.

Persistent paresthesias of the lips, tongue, and oral tissues have been reported with the use of mepivacaine, with slow, incomplete, or no recovery. These post-marketing events have been reported chiefly following nerve blocks in the mandible and have involved the trigeminal nerve and its branches.

Reactions involving the central nervous system are characterized by excitation and/or depression. Nervousness, dizziness, blurred vision, or tremors may occur followed by drowsiness, convulsions, unconsciousness, and possible respiratory arrest.

Since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular reactions are depressant. They may be the result of direct drug effect or more commonly in dental practice, the result of vasovagal reaction, particularly if the patient is in the sitting position. Failure to recognize premonitory signs such as sweating, 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 administration of oxygen. Vasoactive drugs such as Ephedrine or Methoxamine may be administered intravenously.

Allergic reactions are rare and may occur as a result of sensitivity to the local anesthetic and are characterized by cutaneous lesions of delayed onset or urticaria, edema and other manifestations of allergy. The detection of sensitivity by skin testing is of limited value. As with other local anesthetics, anaphylactoid reactions to Mepivacaine have occurred rarely. The reaction may be abrupt and severe and is not usually dose related. Localized puffiness and swelling may occur.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il /

4.9 Overdose:

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway and supporting ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilatory therapy, small increments of anticonvulsive agents may be given intravenously, such as benzodiazephine (e.g., diazepam) or ultrashort-acting barbiturates (e.g., thiopental or thiamylal) or short-acting barbiturates (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressor (e.g., Ephedrine) as dictated by the clinical situation. Allergic reactions should be managed by conventional means.

IV and SC LD50's in mice for Mepivacaine Hydrochloride 3% are 33 and 258 mg/kg, respectively.

5) PHARMACOLOGICAL PROPERTIES

5.1) Pharmacodynamic properties:

Pharmacotherapeutic group: Nervous System / Anaesthetics / Local anaesthetics / Amides / Mepivacaine.

ATC code: N01 BB 03

Mepivacaine stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting local anesthesia.

Mepivacaine is rapidly metabolized, with only a small percentage of the anesthetic (5 to 10 percent) being excreted unchanged in the urine. Mepivacaine because of its amide structure, is not detoxified by the circulating plasma esterases. The liver is the principal site of metabolism, with over 50 percent of the administered dose being excreted into the bile as metabolites. Most of the metabolized Mepivacaine is probably resorbed in the intestine and then excreted into the urine since only a small percentage is found in the feces. The principal route of excretion is via the kidney. Most of the anesthetic and its metabolites are eliminated within 30 hours. It has been shown that hydroxylation and N-demethylation, which are detoxification reactions, play important roles in the metabolism of the anesthetic. Three metabolites of Mepivacaine have been identified from adult humans: two phenols, which are excreted almost exclusively as their glucuronide conjugates, and the N-demethylated compound (2', 6' - pipecoloxylidide).

The onset of action is rapid (30 to 120 seconds in the upper jaw; 1 to 4 minutes in the lower jaw) and Mepivacaine HCl 3% (30 mg/mL) will ordinarily provide operating anesthesia of 20 minutes in the upper jaw and 40 minutes in the lower jaw.

Mepivacaine does not ordinarily produce irritation or tissue damage.

Mechanism of action: Mepivacaine is an amide local anaesthetic. Mepivacaine reversibly inhibits the conduction of nerve impulses by decreasing or blocking sodium (Na+) flow during propagation of the nerve action potential. As the anaesthetic action progressively develops in the nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines and impulse conduction slows. Mepivacaine has a rapid onset, a high potency of anaesthesia and a low toxicity.

The mepivacaine displays slight vasoconstrictive properties leading to a longer duration of action than with most other local anesthetics when administered without a vasoconstrictor. Studies revealed, that mepivacaine has vasoconstrictive properties. This property could be beneficial when the use of vasoconstrictor is contraindicated. Several factors such as pH of tissue, pKa, lipid solubility, local anaesthetic concentration, diffusion in the nerve of local anaesthetic, etc., may influence the onset and the duration of the local anaesthetic.

Onset of action: When a dental peripheral nerve block is performed, mepivacaine effect occurs rapidly (generally within 3 to 5 minutes).

Analgesia duration: Pulp anaesthesia generally lasts approximately 25 minutes after maxillary infiltration and around 40 minutes after inferior alveolar block, whereas anaesthesia of soft tissue was maintained around up to 90 minutes after maxillary infiltration and approximatively 165 minutes after inferior alveolar nerve block.

Bioavailability: The bioavailability is 100% at the action site.

5.2) Pharmacokinetic properties

Absorption: Peak plasma levels of mepivacaine 30 mg/ml solution following peri-oral injections during dental usual procedures were determined in various clinical studies. The maximum plasma level of mepivacaine is achieved approximately after 30-60 minutes. Mepivacaine maximum concentrations were reported to be between 0.4 – 1.2 µg/ml at around 30 minutes post-intraoral injection with one cartridge and between 0.95-1.70 µg/ml with two cartridges. The ratio of the average plasma levels following one and two cartridges were approximately 50%, evidencing a dose proportionality at these dose levels. These plasmatic concentrations are well below the threshold of CNS and CVS toxicity, respectively 10 to 25 fold lower.

Distribution: Mepivacaine distribution covers all body tissues. Higher concentrations are found in highly perfused tissues such as liver, lungs, heart and brain. Mepivacaine binds to plasmatic proteins up to around 75% and can cross placental barrier by simple diffusion.

Metabolism: As all amide-type local anaesthetics, mepivacaine is largely metabolised in the liver by microsomal enzymes (cytochrome P450 1A2 (CYP1A2)). Given this fact, inhibitors of P450 isoenzymes may decrease its metabolism and increase the risk of adverse effects (see section 4.5.). Over 50% of a dose is excreted as metabolites into the bile but these probably undergo entero-hepatic circulation as only small amounts appear in the faeces.

Elimination: The plasma elimination half-life is 2 hours for adults. Clearance of amides is dependent on hepatic blood flow. The plasma half-life is prolonged if the patient is suffering from liver and renal insufficiency. The duration of the local anaesthetic is unrelated to the half-life as its action is terminated when the drug is removed from the receptor. Metabolites are excreted in the urine with less than 10% of unchanged mepivacaine.

Elimination can be accelerated by acidifying the urine (See section 4.9).

5.3) Preclinical safety data:

General toxicity studies (Single dose toxicity, Repeat-dose toxicity) were performed with mepivacaine demonstrating a good safety margin. *In vitro* and *in vivo* testing carried out on mepivacaine hydrochloride did not reveal any genotoxic effect of this product.

No relevant reproductive and development toxicity study demonstrated teratogenic effects with mepivacaine.

No specific carcinogenicity studies were performed.

6) PHARMACEUTICAL PARTICULARS

6.1) List of excipients: Sodium Chloride, Hydrochloric Acid (for pH-adjustment), Sodium Hydroxide (for pH-adjustment) and Water for injection.

6.2 Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with any other medicinal products.

6.3) Shelf life: The expiry date of the product is indicated on the label and packaging. Do not use after the expiry date.
Shelf life after first opening: Use immediately after opening.

6.4) Special precautions for storage: Store at controlled room temperature, below 25°C. Protect from light. Do not permit to freeze.
For protection from light, retain in box until time of use. Once opened, the box should be reclosed by closing the top flap.

Cartridge warmers should not be used with ISOCAINE 3%.

6.5) Nature and contents of container: Single use type I glass cartridge, sealed at its base by a mobile synthetic rubber and at the top by a synthetic rubber seal kept in place by an aluminium cap.
ISOCAINE 3% is available in cardboard boxes containing 5 blisters of 10 × 1.8 mL single-dose dental cartridges, 50 per carton.

6.6) Special precautions for disposal and other handling: The cartridges are intended for single use. The drug administration to the patient should take place immediately after the opening of the cartridge.
As for any cartridge, the diaphragm should be disinfected prior to use. It should be carefully swabbed either with 70% ethyl alcohol or with 90% pure isopropyl alcohol for pharmaceutical use.

The cartridges should under no circumstance be dipped into any solution whatsoever.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7) Israeli drug registration number: 126-77-28970-00

8) Manufacturer: Novocol Pharmaceutical of Canada, Inc., Cambridge, Ontario, Canada.

9) Israeli marketing authorization holder: Dentorient Fuss Ltd., P.O.B. 2232, Tel Aviv 6102101.

10) REVISED ON: 07/2021 according to MOH guidelines
[Internal code: ISCN-3%-DCTR-07/21 dated 28/07/2021]

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