

## IONTOCAINE® Package Insert

### **Clinical Pharmacology**

**Mechanism of Action:** Iontophoresis is a drug delivery method that uses a small external electric current to deliver water-soluble, charged drugs into the skin. Since lidocaine HCl and epinephrine are both positively charged in the pH 4.5 Iontocaine solution, both drugs are delivered simultaneously by the Phoresor System from the positive electrode to provide dermal anesthesia.



Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action. Epinephrine increases the depth and duration of anesthesia, presumably because of its vasoconstrictor activity, which decreases the rate of removal of lidocaine from the site of administration.

Iontophoresis of Iontocaine causes a transient, local blanching followed by a transient, local redness, or erythema.

**Hemodynamics:** Excessive blood levels of lidocaine may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. However, doses delivered directly to the skin by iontophoresis do not result in blood levels high enough to cause these hemodynamic effects (See [Pharmacokinetics and Metabolism](#)).

**Pharmacokinetics and Metabolism:** The Phoresor Iontophoretic Drug Delivery System consists of a microprocessor-controlled battery-powered DC current generator and electrodes. The IOMED® Iontophoretic Drug Delivery electrodes are composed of a hydrogel material that is hydrated before use. (Refer to the directions for use supplied with the IOMED Iontophoretic Drug Delivery electrodes for further information.)

The amount of lidocaine and epinephrine delivered by iontophoresis is directly proportional to the total electric charge applied, ie, current (mA) x time (min) expressed in milliamper minute (mAmin). Seven, normal healthy human volunteers received a single 40 mAmin iontophoretic administration of Iontocaine. No lidocaine plasma concentrations were detected immediately following administration or after two hours post-administration using FPIA (fluorescence-polarization immunoassay) with an assay sensitivity of  $>0.1 \mu\text{g/mL}$ .

In another study in rabbits, plasma lidocaine levels were determined following 14 daily 40 mAmin iontophoretic treatments of Iontocaine. No detectable levels were found using FPIA.

Iontophoresis of Iontocaine in hairless mouse skin and full thickness human cadaver skin in vitro showed that total lidocaine delivered into and through the skin and other body tissues was directly proportional to the applied charge and that delivery was significantly higher (2:1) in human cadaver skin than in hairless mouse skin.

Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration. Its rate of absorption is dependent upon various factors such as the site and route administration and the presence or absence of a vasoconstrictor agent.

Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after iontophoretic administration. Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys.

Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide.

The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline (4-hydroxy-2,6-xylidine).

The metabolite 2,6-xylidine has unknown pharmacological activity but is carcinogenic in rats (See Carcinogenesis subsection of Precautions).

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours.

Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

### **Clinical Studies**

Iontophoresis of lontocaine to determine the depth and duration of dermal anesthesia was studied in 13 normal, healthy human volunteers using a variety of treatment times with the Phoresor System. Both depth and duration were dependent on total charge dose (mAmin). Median needle pain depth thresholds were 6.8 mm (20 mAmin), 8.4 mm (30 mAmin), and 8.6 mm (40 mAmin). Duration of anesthesia varied between 42 minutes (20 mAmin) to 110 minutes (40 mAmin).

Iontophoresis of lontocaine using the Phoresor and IOMED Iontophoretic Drug Delivery electrodes to induce dermal anesthesia in adults was studied in five clinical studies (243 subjects). In these studies a 40 mAmin treatment was utilized which provided effective superficial dermal analgesia which reduced and frequently eliminated the pain associated with pulsed dye laser therapy, shave biopsies, and curettage. The pain associated with the establishment of peripheral vascular access with small (20 gauge) catheters was reduced (p=0.06).

Iontophoresis of lontocaine to induce dermal anesthesia in children was studied in 60 subjects. A 40 mAmin treatment provided effective dermal analgesia for shave biopsies, and for curettage.

Local dermal effects associated with the iontophoresis of lontocaine or placebo in a total of 359 adult and pediatric subjects (399 treatments) on intact skin included blanching, erythema and urticarial reactions that were transient in nature (See [Adverse Reactions](#)).

### **Indications and Usage**

Iontocaine is indicated for production of local dermal analgesia by iontophoresis using procedures described in the directions for use with the Phoresor Iontophoretic Drug Delivery System and IOMED Iontophoretic Drug Delivery electrodes (IOMED, Inc. Salt Lake City, Utah).

### **Contraindications**

Iontocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any other component of the product.

The Phoresor Iontophoretic Drug Delivery System is contraindicated for use on electrically sensitive patients and patients with electrically sensitive support systems (e.g., pacemakers).

It is also contraindicated for use over damaged or denuded skin; across the right and left temporal regions; and for treatment of the orbital region.

### **Warnings**

Iontocaine contains sodium metabisulfite, a sulfite that may cause allergic-type reactions 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.

### **Precautions**

**General:** The safety and effectiveness of Iontocaine depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use (See [Warnings](#) and [Adverse Reactions](#)).

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities 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 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.

Since amide type local anesthetics are metabolized by the liver, lidocaine iontophoresis should be used with caution in patients with hepatic disease. Patients with severe hepatic disease because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution in patients 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.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-amino-benzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

**Information For Patients:** Because of dermal anesthesia, patients should avoid inadvertent trauma to the treated area until complete sensation has returned.

**Clinically Significant Drug Interactions:** The administration of local anesthetic solutions containing epinephrine or norepinephrine to subjects receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine, which may shorten the duration of anesthesia.

Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

**Carcinogenesis:** A metabolite of lidocaine has been shown to be carcinogenic in laboratory animals. A two-year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine, has shown that in both male and female rats, 2,6-xylidine daily doses of 900 mg/m<sup>2</sup> (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. With daily doses of 300 mg/m<sup>2</sup> (50 mg/kg) the increase of incidence of nasal carcinomas and/or adenomas in each sex of the rat were not statistically greater than the control group. In the low dose and control groups, no nasal tumors were observed. A rhabdomyosarcoma, a rare tumor, was observed in the nasal cavity of both male and female rats at the high dose of 900 mg/m<sup>2</sup> (150 mg/kg). In addition, the metabolite caused subcutaneous fibromas and/or fibrosarcomas in both male and female rats and neoplastic nodules of the liver in the female rats with a significantly positive trend test; pairwise comparisons using Fishers Exact Test showed significance only at the high dose of 900 mg/m<sup>2</sup> (150 mg/kg). The animal studies were conducted at oral doses of 15, 50, and 150 mg/kg/day.

**Mutagenesis:** The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome Test, by analysis of structural chromosome aberrations in human lymphocytes in vitro, and by the mouse micronucleus test in vivo. There was no indication in these three tests of any mutagenic effects.

2,6-xylidine, a metabolite of lidocaine, has been shown to be weakly mutagenic at the thymidine kinase locus, with or without activation, and included chromosome aberrations and sister chromatid exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/mL). No evidence of genotoxicity was found in the in vivo assays measuring unscheduled synthesis in rat hepatocytes, chromosome damage in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts from mice. However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions in vivo.

**Impairment of Fertility:** See [Use in Pregnancy](#).

**Use In Pregnancy:** Teratogenic Effects: Pregnancy Category B.

Reproduction studies have been performed in rats at doses up to 6.6 times the human injected dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

**Nursing Mothers:** Lidocaine is excreted in human milk. Therefore, caution should be exercised when lidocaine is administered to a nursing mother since the milk: plasma ratio of lidocaine is 0.4.

**Pediatric Use:** Children may receive the same 40mAmin treatment (4mA of current for 10 minutes) that is used in adult subjects. If the child experiences any skin discomfort during treatment, treat with a lower current level and lengthen the treatment time so a total dose of 40 mAmin is given.

Example:

Time (min) X	Current (mA) =	Total Dose (mAmin)
10 Min	4.0 mA	= 40 mAmin
13.3 Min	3.0 mA	= 40 mAmin
20 Min	2.0 mA	= 40 mAmin

(See [Dosage and Administration](#))

### **Adverse Reactions**

#### **Localized Reactions:**

The incidence of adverse reactions for the iontophoretic dermal delivery of Iontocaine is based on clinical trials involving 359 adult and pediatric subjects (399 treatments). The most frequent side effect reported (approximately 6%) was an urticarial reaction predominately under the dispersive electrode, mild in severity and resolved spontaneously. There were occasional reports of paresthesia (3%) and taste perversion (1%). Rash (1%) under the dispersive electrode and burning sensation under the dispersive electrode (5%) was reported. Abrasion, application site reaction, ecchymosis, petechia, hypesthesia, dizziness, pain, postural dyspnea, and redness lasting greater than 24 hours occurred in <1% of the subjects. In all but one instance these reactions did not interfere with the iontophoresis treatments.

Animal studies showed that a single application of the product can cause erythema and edema; furthermore multiple applications could cause acanthosis, hyperkeratosis, inflammatory response, hemorrhage and/or necrosis involving only epidermis and papillary dermis. These lesions resolved after one week.

#### **Systemic (Dose Related) Reactions:**

Systemic adverse reactions following the iontophoresis of Iontocaine using the Phoresor Iontophoretic Drug Delivery System and IOMED Iontophoretic Drug Delivery electrodes according to the directions for use are unlikely due to the negligible dose absorbed (See [Pharmacokinetics and Metabolism](#) subsection of [Clinical Pharmacology](#)). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide type local anesthetics including CNS manifestations either excitatory and/or depressant (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or may not occur at all, in which case the first manifestation may be drowsiness leading into unconsciousness. Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, cardiovascular collapse, which may lead to cardiac arrest.

**Allergic:** Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents, to bisulfites or to the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

#### **Overdosage**

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 [Adverse Reactions](#), [Warnings](#) and [Precautions](#).) High lidocaine plasma levels can not occur from iontophoretic administration when used as directed.

### **Dosage and Administration**

For iontophoretic administration use the Phoresor Iontophoretic Drug Delivery System (IOMED)

Fill the IOMED Iontophoretic Drug Delivery electrode with the appropriate amount of Lontocaine as indicated in the directions for use supplied with the electrodes. Please refer to the directions for use for further instructions. Due to lack of clinical experience, administration of doses greater than 40 mAmin is not recommended.

**Sterilization, Storage and Technical Procedures:** Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.), should not be used for skin or mucous membrane disinfection as they have been related to incidence of swelling and edema. When chemical disinfection of multi-dose vials is desired, either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of USP grade, contain denaturants that are injurious to rubber and, therefore, are not to be used. It is recommended that chemical disinfection be accomplished by wiping the vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

**Do not autoclave.**

**How Supplied**

Lontocaine is supplied in a multiple-unit container as shown below:

<b>Drug Concentration</b>				
<b>List No.</b>	<b>Container</b>	<b>Size</b>	<b>Lidocaine HCl</b>	<b>Epinephrine</b>
018-71	Fliptop Vial	30 ml	2%	1:100,000

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Lontocaine is for iontophoretic dermal delivery using only the Phoresor Iontophoretic Drug Delivery System models for which the device labeling carries specific indications for Lontocaine use.

**Protect from light.**

Caution: Federal (USA) law prohibits dispensing without prescription.  
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**Manufactured for:**

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**By:**

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