CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-486

LABELING

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System)

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How Supplied

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System)

[For use with Empi Dupel® Iontophoretic Bi-Layer Ultra Electrodes and Dupel Iontophoretic Controller]

NOT FOR INJECTION

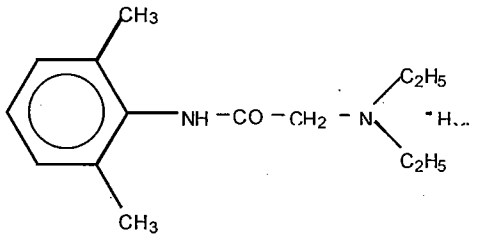
1.8 mL Cartridges

Protect from light.

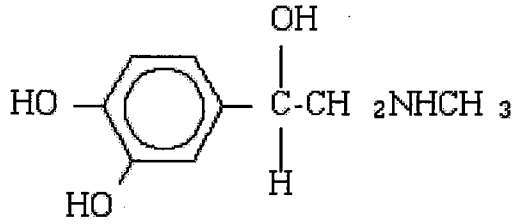
Description: Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is a sterile nonpyrogenic solution of lidocaine hydrochloride and epinephrine in water. Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is for iontophoretic dermal delivery using only the Dupel® Iontophoresis System models for which the device labeling carries specific indications for its use.

Each milliliter contains lidocaine HCl 20 mg/mL, epinephrine 10 µg/mL, sodium chloride 6 mg/mL, and sodium bisulfite 0.55 mg/mL. It may contain sodium hydroxide and/or hydrochloric acid for adjusting the pH to 3.8 to 5.5 (USP limits).

Lidocaine is a local anesthetic of the amide type. Lidocaine Hydrochloride, chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-monohydrochloride, is a white powder freely soluble in water with a molecular weight of 270.80. Its molecular formula $C_{14}H_{22}N_2O.HCl$ and its structural formula is:



Epinephrine, a sympathomimetic (adrenergic) agent designated chemically as (-)-3,4-dihydroxy-α-[(methylamino) methyl] benzyl alcohol, is a white, microcrystalline powder with a molecular weight of 183.20. Its molecular formula is $C_9H_{13}NO_3$ and its structural formula is:



Clinical Pharmacology

Mechanism of Action: Lidocaine blocks sodium ion channels required for the initiation and conduction of nerve impulses, resulting in local anesthesia.

Epinephrine contributes to the analgesic effect of lidocaine HCl 2% and epinephrine 1:100,000 solution for topical iontophoresis, presumably because of its vasoconstrictor activity, which is thought to decrease the rate of removal of lidocaine from the site of administration.

Hemodynamics: Epinephrine or 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 when Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is used as directed would not be expected to result in blood levels high enough to cause these hemodynamic effects (See Pharmacokinetics and Metabolism).

Pharmacokinetics:

Absorption

Nine, healthy human volunteers received iontophoretic administration of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System). Plasma levels of lidocaine up to 21 ng/mL were measured following an 80 mA·min (milliampere minutes) iontophoretic dose (4 mA delivery current applied to the skin for 20 minutes) to six hours post-iontophoresis. Epinephrine plasma levels were not measured.

CNS toxicity may occur over a range of plasma concentrations of local anesthetics. CNS toxicity may typically be found around 5000 ng/mL of lidocaine. However a small number of patients reportedly may show signs of toxicity at approximately 1000 ng/mL.

Distribution

Lidocaine is 70% protein bound in plasma, mainly to a-1-acid glycoprotein. When administered intravenously, the mean volume of distribution for lidocaine (for a 60-kg person) was 90 L at steady state. Lidocaine crosses the placental and blood-brain barriers, presumably by passive diffusion.

Metabolism

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.

The predominant metabolism of lidocaine is through N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), and is mainly mediated by CYP3A4. These metabolites are hydrolyzed to 2,6-xylidine, which is converted to 4-hydroxy-2, 6-xylidine (mediated by CYP2A6), the major urinary metabolite in man. Following intravenous administration of lidocaine, MEGX and GX concentrations in serum range from 11 to 36 % and from 5 to 11 % of lidocaine concentrations, respectively. MEGX has an antiarrhythmic and pro-convulsant activity similar to that of lidocaine and a somewhat longer half-life. GX has a weak antiarrhythmic effect but lacks convulsant activity and has a half-life of about 10 hours.

Elimination

Lidocaine and its metabolites are mainly excreted by the kidneys. The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. 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. When administered intravenously, the elimination half-life of lidocaine is longer in elderly subjects (2.5 hours) than in younger subjects (1.5 hours).

Pediatrics: The pharmacokinetics of lidocaine have not been studied in pediatric subjects with Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System).

Geriatrics : The pharmacokinetics of lidocaine have not been specifically studied in elderly subjects with Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System). However, when administered intravenously, the elimination half-life of lidocaine is longer in elderly subjects (2.5 hours) than in younger subjects (1.5 hours).

Special populations: No pharmacokinetic studies were conducted with Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) to specifically address special populations.

Renal Impairment: Lidocaine and its metabolites are known to be excreted by the kidney, and metabolites may accumulate in patients with impaired renal function.

Hepatic Impairment: The half-life of lidocaine may be prolonged two-fold or more in patients with liver dysfunction. Because of their inability to metabolize local anesthetics normally, patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations of lidocaine.

Clinical Studies

Clinical trials assessing efficacy of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) used, as a comparator, Tradename without lidocaine, i.e., a solution containing epinephrine 1:100,000 and inactive ingredients. An 8.1 cm^2 delivery electrode was used throughout these trials.

Reduction in the discomfort associated with peripheral venipuncture was assessed in a randomized, crossover study of 40 adult subjects. Following a 20-mA·min iontophoretic dose of Tradename administered to one arm and a 20-mA·min dose of the comparator treatment administered to the contralateral arm, 100-mm visual analogue scale (VAS) pain scores, with zero indicating no discomfort and 100 indicating the worst pain imaginable, were used to compare the pain of venipuncture for each of the two treatments. The 95% confidence interval for the difference in VAS pain scores between Tradename and placebo groups was (-20, -7); the mean (S.D.) VAS score was 11 (14) mm for Tradename and 24 (24) mm for placebo.

Efficacy for providing analgesia for superficial dermatological procedures was evaluated in two studies. One study established the efficacy of an 80-mA·min iontophoretic dose of Tradename versus the comparator when used for punch biopsies. A second trial established the efficacy of 60 and 80-mA·min doses of Tradename versus the same doses of comparator when used for shave removals of superficial skin lesions.

Indications and Usage

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is indicated for the iontophoretic production of local analgesia for superficial dermatological procedures such as venipuncture, shave removals and punch biopsies.

Contraindications

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type, sulfites or to any other component of the product.

The Dupel® Iontophoresis System is contraindicated for use on patients with known adverse reactions to the application of electrical current, and patients with cardiac pacemakers or other electrically sensitive implanted devices.

Warnings

Explosive Hazard

Iontophoretic delivery devices can serve as ignition sources and should not be used in the presence of supplemental oxygen administration or certain anesthetics that are flammable.

Accidental Exposure in Children

Even a used Dupel patch contains a large amount of lidocaine (up to 40 mg). The potential exists for a small child to suffer serious adverse effects from chewing or ingesting a Dupel patch filled with Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System). Tradename should be stored out of the reach of children, and used Dupel patches should be disposed of properly.

Sulfite Allergy

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) contains sodium bisulfite, 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. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Vasoconstriction Related to Epinephrine

Since Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) contains a vasoconstrictor, it should not be used on areas of the body supplied by end arteries or having otherwise compromised blood supply. Repeated applications of the Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should not be made to the same site. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit an exaggerated vasoconstrictor response. Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be used with caution in patients with severe coronary artery disease, hypertension or cardiac dysrhythmias or in patients who are currently taking monoamine oxidase (MAO) inhibitors or tricyclic antidepressants. 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.

Precautions

General: The safety and effectiveness of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

Since amide type local anesthetics are metabolized by the liver, Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) 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.

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be used with caution in persons with known drug sensitivities. Patients allergic to para-amino-benzoic acid derivatives, e.g., procaine, tetracaine, and benzocaine, have not shown cross sensitivity to lidocaine. Nevertheless, Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Lidocaine and epinephrine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes in cardiac conduction, contractility, and oxygen demand that may be caused by systemic exposure to these drugs.

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be applied only by a health care practitioner in a health care setting. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use when Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is administered (See Warnings and Adverse Reactions).

Lidocaine has been shown to inhibit viral and bacterial growth. The effect of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) on intradermal injections of live vaccines has not been determined.

Repeated application of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) at the same site may increase blood levels of lidocaine and is not recommended. Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine, including acutely ill, debilitated, or elderly patients.

Eye Exposure

The contact of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) with eyes should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If contact with the eye occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Skin Reactions

Iontophoresis can cause skin irritation, burning sensation and/or burns. Patients should be warned of the possibilities and alerted to early signs such as itching or warmth. Patients should be instructed to notify appropriate personnel as soon as symptoms are detected. Longer than recommended durations of application with or without administration of current, repeat applications or continued application after the occurrence of symptoms may increase the risk of

local skin irritation or injury. Delivery and return electrodes should both be removed immediately after completion of the iontophoretic dose.

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) causes a transient, local blanching at the site of the delivery electrode followed by a transient, local redness, or erythema.

The Empi Dupel® Iontophoretic Bi-Layer Ultra Electrodes must remain in complete contact with the skin during treatment. Incomplete electrode contact may result in burns or other local tissue injury. Therefore, restricting motion is recommended for those application sites where movement could release the electrodes from the skin.

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) has not been tested for safety or effectiveness in the head and neck areas, over damaged or denuded skin, or on mucous membranes.

The safety of the Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) has not been tested in patients who have received long-term treatment with corticosteroids. Clinical judgment should be exercised when considering the use of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) in these patients, as they may be more susceptible to skin injury from the Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System).

Non-intact skin: Application to broken or inflamed skin may result in local tissue injury or higher blood concentrations of lidocaine from increased absorption. Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is only recommended for use on intact skin.

If excessive hair is present at the intended treatment site, the hair may be clipped prior to electrode application, and iontophoresis should only be applied if complete skin adhesion is achieved. Excessive hair should not be shaved, as this may increase the risks of systemic absorption of lidocaine and local tissue injury.

Information For Patients: When Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is used, the patient should be aware that block of all sensations in the treated skin may occur. For this reason, the patient should avoid trauma to the treated area by scratching, rubbing or exposure to extreme hot or cold temperatures until complete sensation has returned. Diminished sensation may persist for 30 minutes or more after iontophoretic treatment. (See PHARMACODYNAMICS). Patients should be advised to monitor the treated area for the return of sensation.

The treated area may have a blanched or red appearance which usually resolves without treatment. Patients should be instructed to monitor the site and report persistent pain, redness and other skin abnormalities based upon directions provided by the health care professional.

Clinically Significant Drug Interactions:

Monoamine Oxidase Inhibitors: The administration of local anesthetic solutions containing epinephrine or norepinephrine to subjects receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Antiarrhythmic Drugs: Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the systemic toxic effects are thought to be additive and potentially synergistic.

Local Anesthetics: When Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is used concomitantly with other products containing local anesthetic agents, the systemic exposure from all formulations must be considered.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine, which may impact on the clinical effect of Tradename.

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

Carcinogenesis: Long-term studies to evaluate the carcinogenic potential of lidocaine in animals have not been conducted.

Mutagenesis The mutagenic potential of lidocaine HCl has been tested in a bacterial reverse mutation (Ames) assay in Salmonella, an in vitro chromosomal aberration assay using human lymphocytes, and an in vivo micronucleus test in mice. There was no indication of mutagenicity or structural damage to chromosomes in these tests.

Impairment of Fertility: Studies to evaluate the effects of Lidocaine on fertility in animals have not been conducted.

Use In Pregnancy: Teratogenic Effects: Pregnancy Category B.
Reproduction studies have been performed in rats at doses up to 500 mg/kg/day via mini-osmotic pumps and have revealed no significant adverse reproductive or teratogenic effects attributable to lidocaine. Converting this rat dose into a human equivalent dose (HED) based on body surface area results in a HED of 4,800 mg. In vitro testing which utilized the 8.1 cm^2 delivery electrode and an 80 mA•min current demonstrated a maximal theoretical delivery of 0.2 mg of lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Lidocaine is excreted in human milk. The milk to plasma ratio of systemically administered lidocaine is 0.4. Therefore, caution should be exercised when Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In published studies of intravenously administered lidocaine, the elimination half-life of lidocaine was longer in elderly patients (2.5 hours) than in younger patients (1.5 hours) (See CLINICAL PHARMACOLOGY). Therefore, elderly patients may be at greater risk of developing toxic plasma concentrations of lidocaine.

Clinical studies of Lidopel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Labor and Delivery: The effects of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) on the mother and fetus, on the duration of labor or delivery, and on neonatal outcome and maturation have not been studied.

Adverse Reactions

Systemic (Dose Related) Reactions: Systemic adverse reactions following the iontophoresis of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) using the Empi Dupel® Iontophoresis System and Empi Dupel® Iontophoresis Electrodes according to the Instructions For Use are unlikely due to the dose absorbed (See Pharmacokinetics and Metabolism subsection of Clinical Pharmacology).

Systemic adverse effects of lidocaine are similar to those observed with other 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, and/or cardiovascular collapse, which may lead to cardiac arrest.

Systemic adverse effects of epinephrine may include palpitations, tachycardia, hypertension, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety. Cardiac arrhythmias may follow the administration of epinephrine.

Allergic Reactions: Allergic reactions, including anaphylactoid and anaphylactic, may occur as a result of sensitivity either to the local anesthetic agents or to the preservatives, such as sodium bisulfite. They may be characterized by cutaneous lesions, urticaria, angioedema, bronchospasm, tachycardia, hypotension or shock. 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 dubious value.

Localized Reactions: The incidence of adverse reactions associated with Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is based on clinical trials involving 361 iontophoretic treatments administering Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) using the Dupel® Iontophoresis System and Empi Dupel® Iontophoresis Electrodes. The most commonly reported localized adverse reactions included: blanching (79%), petechiae (4%), burning or stinging sensation during treatment (2%), moderate erythema (3%), itching (1%), and pain (3%). Ecchymosis, aching, hives, telangiectases, and tingling occurred in <1% of the subjects. Seven percent of patients required discontinuation of iontophoretic delivery due to pain or discomfort from the iontophoretic treatment. The incidence of adverse events was similar in the control and treated groups. However, because of the nature of the control group, it is impossible to determine if adverse events were attributable to epinephrine, inactive ingredients, patch components, and/or iontophoretic treatment.

One clinical study assessed the dermal irritation and safety profile associated with repeat and multiple dosing. Two simultaneous 80 mA·min iontophoretic doses of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System), one on an arm and the other on the contralateral thigh, were followed by (15 minutes after the end of the first treatment) a second treatment to the same skin sites. A total of twelve subjects (48 treatments) were enrolled. Treatment sites were evaluated for adverse events; blood levels were not assessed. Most subjects experienced blanching. All subjects had erythema graded as mild or less. Erythema noted at both delivery and return electrodes generally resolved within 2-3 days, although there was one report of a recovery time of 1 week.

Other clinical studies conducted on the iontophoretic delivery of lidocaine HCl 2% and epinephrine 1:100,000 have also reported adverse reactions such as an urticarial reaction,

paresthesia, taste perversion, abrasion, application site reaction, hypesthesia, dizziness, scabbing, postural dyspnea, and redness lasting greater than 24 hours.

Where patients received either Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) or comparator (Tradename without lidocaine), the respective adverse events are summarized in the table below.

Adverse Reactions	Tradename	Tradename without lidocaine
Erythema	6/69 (9%)	7/25(28%)
Petechiae	16/69 (23%)	
Itching	5/69 (7%)	4/25 (16%)
Burning/stinging/scratching sensation	9/69 (13%)	5 (20%)
Headache	1/69 (1%)	1/25 (4%)
Tingling of the hand	1/69 (1%)	
Hives	1/69 (1%)	
Edema secondary to difficult phlebotomy	1/69 (1%)	
Pain/tenderness at dermatologic or iontophoresis site	9/69 (13%)	2/25 (8%)
Prolonged bleeding at procedure site	2/69 (3%)	
Local reaction to bandage	2/69 (3%)	
Inflammation at Dermatologic procedure site	1/69 (1%)	
Telangiectasis	1/69 (1%)	
Allergic reaction to polysporin	1/69 (1%)	
Lightheadedness	4/69 (6%)	
Cold sweats	1/69 (1%)	
Bruise at venipuncture site	5/69 (7%)	
Upset stomach	1/69 (1%)	
Arm numbness	1/69 (1%)	
Scab under return electrode	1/69 (1%)	
Vaginal bleeding		
Muscle cramp	1/69 (1%)	
Injured wrist		1/25 (4%)
Rash		1/25 (4%)
Fainting		
Emotional distress		1/25 (4%)

Systemic (Dose Related) Reactions:

Overdosage

High lidocaine and epinephrine plasma levels are unlikely to occur from iontophoretic administration of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) when used as directed.

Repeated applications, multiple simultaneous applications, application to smaller patients or to patients with impaired elimination may all contribute to increased blood concentrations of lidocaine. In addition, if other local anesthetics are administered at the same time, e.g. topically or by injection, the toxic effects are thought to be additive and could result in an overdose with systemic toxic reactions. There is generally an increase in severity of symptoms with increasing plasma concentrations of lidocaine. Systemic central nervous system (CNS) toxicity may occur over a range of plasma concentrations of local anesthetics. CNS toxicity may typically be found around 5000 ng/mL of lidocaine; however a small number of patients reportedly may show signs

of toxicity at approximately 1000 ng/mL. CNS symptoms usually precede cardiovascular manifestations of toxicity.

Plasma levels of lidocaine up to 21 ng/mL were measured in healthy adult subjects after a single application of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System). Toxic levels of lidocaine may cause seizures, decreases in cardiac output, total peripheral resistance and mean arterial pressure, as well as life-threatening dysrhythmias and cardiac arrest. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine. In the absence of massive topical overdose or oral ingestion, evaluation should include assessment for other etiologies of these clinical effects and overdosage from other sources of lidocaine (consult package insert for parenteral lidocaine for further information on the management of overdose).

Epinephrine plasma levels were not measured in clinical trials of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System). Overdosage of epinephrine can cause hypertension, tachycardia, cardiac dysrhythmias, cerebral hemorrhage and pulmonary edema. It is unlikely that overdosage would be caused by use of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) as labeled and patients with symptoms or signs of overdose should be evaluated for other etiologies of these clinical effects or overdosage from other sources of epinephrine (consult package insert for epinephrine injection).

Local skin reactions: Application of multiple doses of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) to the same site or failure to promptly remove electrodes after iontophoretic treatment could result in increased risk of local skin reactions.

Dosage and Administration

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should be administered using procedures described in the Instructions For Use with the Dupel® Iontophoresis System and utilizing the Empi Dupel® B.L.U.E.™ (Bi-Layer Ultra Electrode) Iontophoresis Electrodes (Empi, Inc. St. Paul, MN).

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) should only be applied by a health care practitioner.

Set Up Instructions:

The DUPEL Dual Channel Iontophoresis System is used to set and deliver the iontophoretic dose. The user sets the dosage and current levels. The length of treatment (time) is dependent on the dosage and current selected by the user. (See DUPEL Dual Channel Iontophoresis System instructions for further details.)

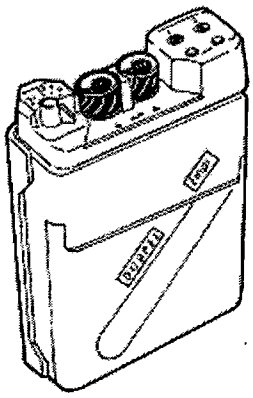


Figure 1. DUPEL Iontophoresis Device

The Dupel Iontophoresis Device is connected by a lead wire to a set of iontophoresis electrodes. The Empi Iontophoresis Electrode Set consists of one bi-layer buffering drug delivery electrode and one buffering self-adhering return electrode (Figure 3). The Dupel B.L.U.E. (Bi-Layer Ultra Electrode) Iontophoresis Electrodes come in three shapes and sizes (see Figure 2) for conformability, adhesion, and site coverage. Based on the dermatological procedure to be performed and the anatomic site to which the treatment electrode is to be applied, select the clinically appropriate amount of Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System).

Figure 2. Delivery Electrodes

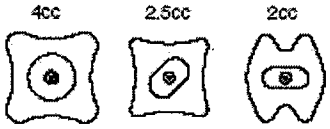


Figure 3. Return Electrode

To administer the Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System):

1. Inspect the skin area where the electrodes are to be placed and ensure the skin is intact. Excessive hair at the application site for either electrode may be clipped but not shaved to ensure complete contact of the electrode with the skin surface. Clean the skin with the alcohol wipe provided prior to application of the electrodes.

2. Using a syringe, draw up the amount of solution marked on the electrode's backer. More than one drug cartridge will be required. Based on the available clinical data, the 10. cm^2 and 16.0 cm^2 electrodes are expected to be less effective in providing analgesia than the 8.1 cm^2 electrode.

	Medium	Medium Standard	Large
Active area (cm^2)	8.1	10.1	16.0
Drug Fill Volume	2.0 cc	2.5 cc	4.0 cc

3. The backer of the delivery electrode has an opening for filling (see Figure 4). Using a circular motion, completely saturate the entire surface of the reservoir pad (Figure 4 below). If solution is spilled on the adhesive border of the electrode, the electrode should be discarded.

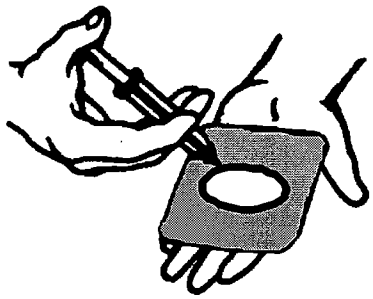


Figure 4. Filling the Delivery Electrode

4. Remove the backer from the delivery electrode.

5. Center and affix the filled delivery electrode directly over the treatment area.

6. Secure the electrode by pressing around the edge of the blue foam tape until a good seal is obtained all around the electrode. The blue foam tape may be stretched slightly to assist placement. DO NOT press on the reservoir pad or the solution may leak.

7. Before affixing the return electrode, slightly dampen the sticky side of the return electrode with 1 or 2 drops of water before applying to the skin. Excess water decreases adhesion. Apply over a major muscle, at least four inches from the treatment electrode site, on the same side of the body. Avoid placing the return electrode over bony areas.

8. Read and follow the instructions that accompany the Dupel® Iontophoresis System. Perform the following steps to operate the DUPEL Iontophoresis System:

   Step 1. Connect the lead wire to the electrodes. Connect the positive lead to the delivery electrode, and the negative lead to the return electrode.

   Step 2. After ensuring that the POWER Switch is OFF, connect the lead wire to the Channel 1 Outlet Jack.

   Step 3. To begin a treatment, turn the POWER Switch under the front cover to ON.

   Step 4. Turn the Treatment Control Switch on top of the device to the set-up position for Channel 1 (S1). The LCD Window will now display the dosage to be delivered by Channel 1 and Channel 2 (not in use). The DUPEL device is automatically set at a 40mA•min dosage for Channel 1.

   Step 5. To adjust the dosage for Channel 1, press the up or down Dosage Control Button until the correct number is displayed in the LCD Window. A dose of 20 mA•min should be used for venipuncture, and a dose of 80 mA•min should be used for superficial dermatological procedures.

Step 6. Set the current for Channel 1 to 4 mA. To do this, move the Treatment Control Switch to P (Pause). Current for the programmed channel(s) now appears in the LCD Window. To set the desired current for each channel, rotate the appropriate Current Control Knob located on top of device.

Note: Do not operate the DUPEL device while the flip cover is open. Close the flip cover before initiating or resuming treatment.

Step 7. To start the treatment, turn the Treatment Control Switch to R (Run).

The green LED indicator for Channel 1 will light, indicating that current is being output. Current will automatically ramp up to set level over a period of 30 seconds. During ramping, current is displayed in the LCD Window and corresponding channel indicator (CH 1 or CH 2) blinks. Once current reaches set level, the display in the LCD Window will switch to Dose and show dose delivered as it steps up to the target dosage.

Step 8. After treatment has been completed the current will ramp down to zero over a period of 30 seconds. A continuous beep will sound for up to 10 seconds. Wait until the current has ramped down and the green LED indicator goes off before removing the lead wire and electrodes.

For more information on the operation of the Dupel® Iontophoresis System, consult the instructions that accompany the Dupel® Iontophoresis System.

Iontophoresis dose:
The iontophoresis dose is expressed in milliampere•minutes (mA·min) and is determined as follows:

Current (mA) X Time (min) = Total Dose (mA•min)

For example, to achieve a dose of 20 mA•min, a 4 mA current should be applied for 5 minutes. Safety and efficacy have been evaluated only for the 4 mA current, therefore, adjustment of the duration of the iontophoretic treatment should be relied upon to adjust the iontophoretic dose.

Discontinue iontophoretic treatment if the patient complains of burning or discomfort at either electrode site.

Both electrodes should be removed immediately after completion of the iontophoretic dose. Prolonged electrode application times may increase the risk of local tissue irritation or injury. The treatment site should then be examined for burns or skin injury and then cleansed according to standard practice prior to initiating venipuncture or dermatological procedure.

Repeated or simultaneous applications of Tradename at the same site are not recommended, as this has not been fully evaluated for safety and may increase the risk of local and systemic toxicities.

Disinfection, Storage and Technical Procedures: The Empi cartridges containing Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) consist of a 1.8 mL tube-shaped glass cartridge with a rubber septum and aluminum outer cap seal at the top and a slightly compressed rubber plunger/stopper at the bottom. The drug product is withdrawn from the cartridge through the rubber septum. If chemical disinfection of the Empi cartridges is desired after customer storage, 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 rubber septum

thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

Quaternary ammonium salts, such as benzalkonium chloride, are electrolytically incompatible with aluminum. Cartridges of 2% Lidocaine HCl and Epinephrine 1:100,000 are sealed at the top with aluminum caps and, therefore, should not be immersed in solutions containing these salts.

Cracking of glass cartridges is most often the result of an attempt to use a cartridge with an extruded plunger. An extruded plunger loses its lubrication and can be forced back into the cartridge only with difficulty. Cartridges with extruded plungers should not be used and should be returned to the manufacturer.

If using a syringe to remove the drug from the cartridge, be sure to penetrate the center of the rubber septum to avoid leakage of solution. An off-center penetration produces an oval shaped puncture that allows leakage around the needle.

Do not autoclave.

How Supplied
Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is supplied in 1.8 mL cartridges, 50 cartridges per carton.

Drug Concentration

List No.: XXX-XX
Container: Cartridge
Size: 1.8 mL
Lidocaine HCl: 2%
Epinephrine: 1:100,000

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

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System) is for iontophoretic dermal delivery using only the Empi Dupel® Iontophoresis System model for which the device labeling carries specific indications for its use.

Protect from light.

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

P/N 360295, Rev 01

Manufactured for:
Empi, Inc., St. Paul, MN 55126 USA

By:
Novocol Pharmaceutical of Canada Inc.
Cambridge, Ontario N1R 6X3
Rx only

Tradename

Empi's Brand of Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System
For Dermal Iontophoresis with the Dupel® Iontophoresis System

- To be sold only as unbroken package.
- Usual Dosage: See package insert. Read directions enclosed concerning possible side effects, precautions and contraindications.
- Warning: Contains sulfites.
- Do not inject.
- Store at controlled room temperature 15° - 30°C (59° - 86°F).
- Any unused portion of a cartridge should be discarded.
- Protect from light. Keep in carton until ready to use.
- Do not permit to freeze.

Manufactured for EMPI, Inc., St. Paul, MN 55216
By: Novocol Pharmaceutical of Canada, Inc.
Cambridge, Ontario N1R 6X3

CAUTION: Federal law prohibits dispensing without prescription

Tradename

Empi's Brand of Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System

For Dermal Iontophoresis with the Dupel® Iontophoresis System

CAUTION: Federal law prohibits dispensing without prescription
50 Cartridges containing minimum content of 1.8 mL

Lot No. XXXX
Exp. X/XX

Tradename(Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System)
Mfg. for Empi, Inc., St. Paul, MN By:
Novocol Pharmaceutical of Canada

Lot: XXXX Exp. X/XX1.8 mL