Local Anesthetic for Topical Use

LidoSite™ Topical System

comprised of the

LidoSite™ Patch

(Lidocaine HCl / Epinephrine topical iontophoretic patch) 10%/0.1%

and the

LidoSite™ Controller

Rx only

CAUTION: Contains sodium metabisulfite (See WARNINGS Section)

DESCRIPTION:

The LidoSite™ Topical System (LidoSite™ System) consists of a LidoSite™ Patch (LidoSite™ Patch) and a LidoSite™ Controller, a portable microprocessor-controlled battery-powered DC current source. The LidoSite™ System delivers lidocaine and epinephrine simultaneously by topical iontophoresis to achieve dermal analgesia on intact skin.

Iontophoresis is based on the principle that a soluble salt or drug can be transported across the skin barrier as a part of an electric current induced in the skin. The quantity and distribution of delivered drug(s) is dependent on the ion charge, molecular weight, intensity of the electric current, concentration of the drug(s), contact surface area of the delivery electrode, and duration of current. In most iontophoretic systems, iontophoresis is measured as total charge delivered in milliampere-minutes (mA-min) units. At the patch electrode pH (4.5), lidocaine HCl and epinephrine are both positively charged.

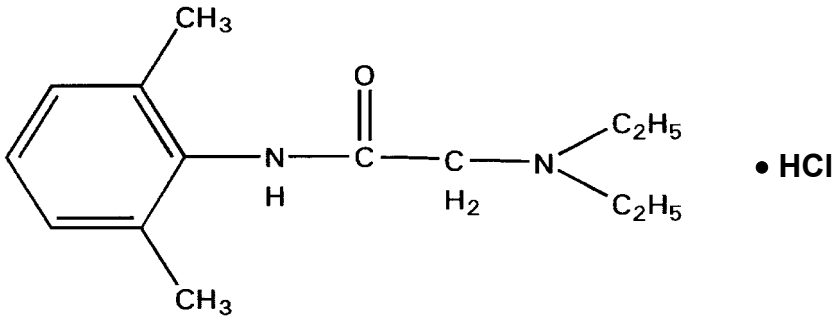
The LidoSite™ Controller is designed with a non-replaceable battery that provides up to 99 drug applications at 1.77 mA for 10 minutes (17.7 mA-min). Refer to the "LidoSite™ Topical System Instructions" for proper system operation.

The LidoSite™ Patch is for single use only and is disposable. The patch contains a 5-cm^2 circular drug reservoir that delivers lidocaine and epinephrine to the skin and an elongated return reservoir containing electrolytes to complete the electrical circuit.

The drug reservoir contains 100-mg lidocaine HCl, 1.05 mg of epinephrine (equivalent to 1.91 mg of epinephrine bitartrate) and excipients consisting of sodium chloride, glycerin, preservatives (2-phenoxyethanol, methyl-, ethyl-, propyl-, butyl-, and isobutyl-p-hydroxybenzoate), citric acid as a buffer and chelator, edetate disodium as a chelator, and sodium metabisulfite as an antioxidant, in a non-sterile hydrogel. The elongated return reservoir contains glycerin, sodium chloride, preservatives (2-phenoxyethanol, methyl-, ethyl-, propyl-, butyl-, and isobutyl-p-hydroxybenzoate), and monobasic sodium phosphate as an acidulating agent. The drug and return reservoirs are made from a polyvinylpyrrolidone (PVP) hydrogel.

Lidocaine is a local anesthetic of the amide type. Lidocaine hydrochloride is chemically designated as:

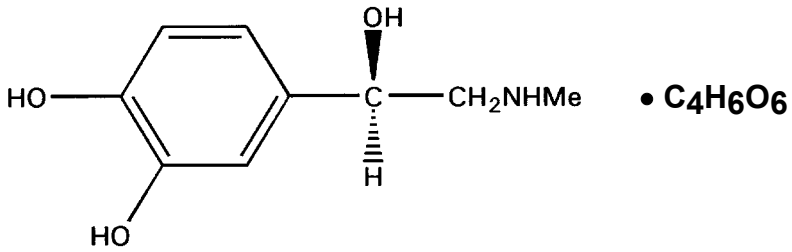
> 2-(Diethylamino)-2′, 6′-acetoxylidide mono-hydrochloride, monohydrate, is a white crystalline powder freely soluble in water, with a molecular weight of 288.81. Its molecular formula is $C_{14}H_{22}N_2O•HCl$ and its structural formula is:



$C_{14}H_{22}N_2O•HCl$

Epinephrine is a sympathomimetic (adrenergic) agent. Epinephrine bitartrate is designated chemically as:

> 1,2 Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-,(R)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt) is a white, crystalline powder with a molecular weight of 333.29. Its molecular formula is $C_9H_{13}NO_3•C_4H_6O_6$ and its structural formula is:



$C_9H_{13}NO_3•C_4H_6O_6$

CLINICAL PHARMACOLOGY:

MECHANISM OF ACTION:
Lidocaine belongs to the amide class of local anesthetics. 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 the LidoSite™ system, 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 LidoSite™ System is used as directed are not expected to result in blood levels high enough to cause these hemodynamic effects. (See PHARMACOKINETICS).

Pharmacodynamics:
In a single-center, prospective, placebo-controlled double-blind study, 20 adult subjects were evaluated to quantify the depth of the anesthetic effect over time from both pain and sensory perspectives following treatment with the LidoSite™ System. The placebo was a LidoSite™ System utilizing a patch containing epinephrine only, but with application of current. An 18-gauge needle with constant 200-grams pressure was used to penetrate the skin at a rate of 0.2 mm/sec. Subjects indicated the points at which they felt pressure and pain, identified as the sensory penetration depth (SD) and the pain threshold depth (PD), respectively. Immediately following completion of a 10-minute iontophoretic treatment with LidoSite™ System, the average SD and the PD were 3.9 mm and 6.4 mm, respectively, compared to 1.4 mm and 3.0 mm, respectively, after placebo treatment. Sixty minutes after removal of the LidoSite™ System, the average SD and PD increased to 5.6 mm and 10.7 mm, respectively, compared to 1.4 mm and 3.4 mm, respectively, with placebo treatment.

Pharmacokinetics:

Absorption
Plasma levels of lidocaine were below the minimum level of quantitation, 5 ng/ml, in healthy adult or pediatric subjects after three sequential LidoSite™ System applications at different sites over a 3.5 hour period. Epinephrine levels did not exceed the normal physiologic range (10 - 50 pg/mL) in healthy adult subjects after a single standard LidoSite™ System application.

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 α-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 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 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 hour.

Elimination
Lidocaine and its metabolites are excreted by the kidneys. Following an intravenous bolus injection, the elimination half-life of lidocaine is typically 1.5 to 2.0 hours. Approximately 90% of administered lidocaine 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. During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly subjects (2.5 hours) than in younger subjects (1.5 hours).

Pediatrics: Plasma levels of lidocaine in pediatric subjects between 6 and 15 years of age were below the minimum level of quantitation, <5 ng/ml, after three sequential LidoSite™ System applications on different sites over a 3.5-hour period.

Geriatrics : The pharmacokinetics of lidocaine have not been specifically studied in geriatric subjects. However, during intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly subjects (2.5 hours) than in younger subjects (1.5 hours).

Special populations: No pharmacokinetic studies were conducted 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

In one randomized, double-blind, placebo-controlled, parallel-group, single-center study, 48 adult subjects were evaluated for the degree of dermal analgesia upon venipuncture or IV cannulation, typically within 10 minutes following treatment with LidoSite™ System or placebo (LidoSite™ Patch, no current) treatment. Less pain was reported following LidoSite™ System treatment compared to placebo at both sites, the antecubital fossa and the dorsum of the hand, as measured by a 10-cm visual analog scale (VAS). All subjects received treatment on each of their antecubital fossae prior to venipuncture, and on the dorsum of each hand prior to cannulation. Three of the treatments were with LidoSite™ System and one was with placebo. VAS scores for active and placebo treatments were 0.7 and 3.2, respectively, at the antecubital fossa, and 1.6 and 4.0, respectively, on the dorsum of the hand.

In a randomized, double-blind, placebo-controlled, single-center study, 48 pediatric patients were stratified by age group (5 to 7 years, 8 to 11 years, and 12 to 18 years) to compare the efficacy of LidoSite™ System with placebo (LidoSite™ Patch, no current) in the reduction of pain associated with venipuncture in the antecubital fossa. Venipuncture occurred within 10 minutes of patch removal. Based on the Nine Face Integrated Scale (NFIS) scores ("A through I" scale, with an "A" face indicating a laughing child and an "I" face indicating a child crying vigorously), patients treated with LidoSite™ System experienced less pain during venipuncture than subjects treated with the placebo patch. The mean NFIS scores, calculated by equating "A" through "I" with "1" through "9," respectively, for all age groups were 2.8 and 4.3 for LidoSite™ System and placebo, respectively.

Two prospective, randomized, double-blind, placebo-controlled (a patch with only epinephrine and with current applied) trials were conducted to assess the analgesia provided within 10 minutes following treatment during venipuncture or intravenous cannulation. The first trial used a 10-cm Visual Analog Scale (VAS) score to assess pain experienced by 270 subjects ≥ 18 years of age. The mean (SD) VAS score was significantly lower in the LidoSite™ System group, 0.8 (1.5) compared to the placebo group, 2.5 (2.3). The second trial utilized the NFIS to evaluate the pain experienced by 256 pediatric subjects ages 5 to 17 years. The median NFIS scores for all subjects in the LidoSite™ System and placebo treatment groups were C and E, respectively.

Pain reported during laser removal of superficial skin lesions such as port wine stain, telangiectasia, lipoma, keloid scar, or tattoo was evaluated in one controlled study with the LidoSite™ System. Sixty-six subjects (ages 9 to 79 years) were randomized to LidoSite™ System or placebo, (LidoSite™ System, a patch with only epinephrine and with current applied) prior to laser treatment. The dermatological procedures were performed within 20 minutes following treatment. At the end of the procedure, subjects rated their pain using the Ordered Category Anesthesia Scale (OCAS) (with 0 indicating no sensation and 6 indicating intolerable pain). In the LidoSite™ System group, 91% of subjects reported no pain or mild discomfort (OCAS scores of 0 to 3) compared to 53% of subjects in the placebo group. Among LidoSite™ System subjects, 4% of adults and 14% of children required supplemental anesthetic during the procedure compared to 21% of adults and 33% of children who received placebo treatments.

INDICATIONS AND USAGE

LidoSite™ System is a topical local anesthetic delivery system indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions.

LidoSite™ System is indicated for use on patients 5 years of age and older.

CONTRAINDICATIONS

LidoSite™ 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 (See also WARNINGS and PRECAUTIONS sections).

LidoSite™ System is contraindicated for use in patients with electrically-sensitive devices (e.g., pacemakers).

WARNINGS

Rx Only

DANGER-EXPLOSIVE HAZARD: This product could serve as an ignition source and should not be used in the presence of flammable anesthetics.

Accidental Exposure in Children
Even a used LidoSite™ patch contains a large amount of lidocaine (up to 100 mg). The potential exists for a small child to suffer serious adverse effects from chewing or ingesting a new or used LidoSite™ patch. Children should be closely observed when treated with the LidoSite™ System, and Lidosite patches should be stored and and disposed of in the proper manner.

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, repeat applications or continued application after the occurrence of symptoms may increase the risk of local skin irritation or injury.

Iontophoresis with the LidoSite™ Patch may cause transient, local blanching or erythema in the dermis under the patch. The redness under the elongated reservoir is normally uniform in color, while under the circular reservoir the color may be mottled.

Sulfite Allergy
LidoSite™ Patch 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. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Vasoconstriction Related to Epinephrine
Since the LidoSite™ Patch 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 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. LidoSite™ System should be used with caution in patients with severe coronary artery disease, hypertension or cardiac disrhythmias or in patients who are currently taking monoamine oxidase (MAO) inhibitors or tricyclic antidepressants.

PRECAUTIONS

General:
Since amide-type local anesthetics are metabolized by the liver, LidoSite™ system should be used with caution in patients with hepatic disease. Patients with severe hepatic disease normally are at a greater risk of developing toxic plasma concentrations.

LidoSite™System 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. Nevertheless, LidoSite™ 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 be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for changes in cardiac conduction, contractility, and oxygen demand that may be caused by systemic exposure to these drugs.

LidoSite 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 LidoSite™ System is administered. (See WARNINGS and ADVERSE REACTIONS).

The intended treatment site should not be covered with excessive hair, as that may affect patch adhesion. The LidoSite™ 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 LidoSite™ 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 LidoSite™ System in these patients, as they may be more susceptible to skin injury from LidoSite™ System.

The LidoSite™ Patch reservoirs must remain in complete contact with the skin during treatment. Therefore, restricting motion is recommended for those application sites where movement could release the patch from the skin.

Following iontophoresis and patch removal, the treatment site should be cleansed according to standard practice prior to starting the medical procedure.

Non-intact skin: Application to broken or inflamed skin, may result in local tissue injury or higher blood concentrations of lidocaine from increased absorption. LidoSite™ System is only recommended for use on intact skin.

Eye exposure: The contact of LidoSite™ Patch with eyes, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Repeated application of LidoSite™ System may increase blood levels of lidocaine. LidoSite™ 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.

Lidocaine has been shown to inhibit viral and bacterial growth. The effect of LidoSite™ Patch on intradermal injections of live vaccines has not been determined.

Information For Patients:
When LidoSite™ 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 inadvertent 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 an hour or more (See PHARMACODYNAMICS). Patients should be advised to monitor the treated area for the return of sensation.

The appearance of the treated area may appear to be blanched or red which are normal reactions and usually disappear within 24 hours. 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 anesthetics containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Antiarrhythmic Drugs: LidoSite™ 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 LidoSite™ System is used concomitantly with other products containing local anesthetic agents, the systemic exposure from all formulations must be considered.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

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

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 of any mutagenic effects 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, s.c. (6.6 times the human injected dose) via mini-osmotic pumps and have revealed no significant adverse reproductive or teratogenic effects attributable to 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. Caution should be exercised when LidoSite™ System is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of the LidoSite™ System have been established in pediatric patients five years and older based on adequate and well-controlled studies (see CLINICAL STUDIES). The recommended dose for pediatric patients five years and older is the same as for adults.

Safety and effectiveness in pediatric patients below the age of five years have not been established.

Geriatric Use: In the clinical studies, there were sixty patients over 65 years of age and thirty-one patients over 75 years of age. No overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between elderly and younger patients. However, greater sensitivity of individual patients greater than 65 years of age cannot be ruled out. In clinical studies of intravenously administered

lidocaine, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours) (See CLINICAL PHARMACOLOGY)

Labor and Delivery: The effects of LidoSite™ System on the mother and fetus, on the duration of labor or delivery, and on neonatal outcome and maturation have not been studied. Should LidoSite™ System be used concomitantly with other products containing lidocaine and/or epinephrine, total doses contributed by all formulations must be considered.
(See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS:

Systemic (Dose Related) Reactions: Systemic adverse reactions following the iontophoresis of lidocaine and epinephrine using the LidoSite™ System according to the directions for use are unlikely due to the absorbed dose (See PHARMACOKINETICS section).

Systemic adverse effects of lidocaine are similar in nature to those observed with other amide-type local anesthetics including either excitatory and/or depressant (lightheadedness, 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) CNS manifestations. Excitatory CNS reactions may be brief or may not occur at all, in which case the first manifestation may be drowsiness leading to unconsciousness. Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, conduction abnormalities, dysrhythmias 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: 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 metabisulfite. 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 doubtful value.

Most Common Adverse Events

In placebo-controlled studies with LidoSite™ System, 4.5% of patients on placebo (N=333) and 4.5% of patients on LidoSite™ System (N=330) reported an adverse event. Because the placebo groups were not "no treatment" groups, but instead generally utilized an unaltered LidoSite™ Patch or an epinephrine only-containing patch with application of current, comparing the incidence of adverse events between the placebo and LidoSite™ System groups may not fully elucidate the incidence of adverse events that are attributable to iontophoresis, epinephrine or local irritation from patch application. In these studies, adverse events that occurred at a higher incidence in LidoSite™ System treated subjects compared to placebo treated subjects included subcutaneous hematoma (0.9% vs. 0.3%) and vasoconstriction (0.9% vs. 0.3%). In one study, the incidence of application site papules

was reported to be as high as 12% and in another study the incidence of burns was reported to be as high as 8%. There were no serious adverse events attributed to LidoSite™ System treatment. In the overall safety database (812 patients administered LidoSite™ System) 0.8% of patients discontinued due to an adverse event. The most common reasons for discontinuation were: application site pain, N=4 (0.5%), application site burning, N=3 (0.4%), and pruritus, N=1 (0.1%).

The most frequently observed adverse events from all studies are presented below:

Summary of most frequently observed adverse events from all studies involving LidoSite™

Adverse Event	LidoSite™ System (N_s = 827, N_t=925)[1]	Placebo	
	n (%)	LidoSite™ System without lidocaine (N_s = 308,N_t=308)[1] n (%)	LidoSite™Patch without application of current (N_s=25, N_t=25)[1] n (%)
Pain/burning sensation with iontophoresis	22 (2.4)	18 (5.8)	0
Rash (includes macular & papular)	45 (4.9)	0	0
Burns	13 (1.4)	1 (0.3)	0
Subcutaneous hematoma	3 (0.3)	1 (0.3)	0
Marked vasoconstriction	3 (0.3)	2 (0.6)	0
Erythema	1 (0.1)	0	0
Urticaria	1 (0.1)	0	0

[1]N_s=Number of Subjects, N_t=Number of Treatments; % computed based on the number of treatments (N_t); In three Pharmacokinetic studies each subject received three treatments during the study.

OVERDOSAGE:

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use. (See ADVERSE REACTIONS, WARNINGS and PRECAUTIONS.) High lidocaine plasma levels are unlikely to occur from administration of LidoSite™ System when used as directed.

Repeated applications, multiple simultaneous applications, application in smaller patients, or in 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.

Plasma levels of lidocaine were below the minimum level of quantitation, 5 ng/ml, in healthy adult or pediatric subjects after three sequential LidoSite™ System applications on different sites over a 3.5-hour period. 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 blood levels did not exceed the normal physiological range (<50 pg/ml), after a single LidoSite™ System application. 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 LidoSite™ System as labeled and patients with symptoms or sign 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 patches to the same site or failure to promptly remove patches after iontophoretic treatment could result in increased risk of local skin reactions.

Over Current Condition: If the controller detects a current in excess of the normal range of current, the current

(and delivery) is stopped, the flashing YELLOW indicator is illuminated and the device beeps three times.

DOSAGE AND ADMINISTRATION

LidoSite™ Controller can only be used with the LidoSite™ Patch as the complete LidoSite™ System, and LidoSite™ Patches should only be used with a LidoSite™ Controller.

LidoSite System should be applied only by a health care practitioner in a health care setting.

One LidoSite™ Patch is to be used with one LidoSite™ Controller. Do not use a damaged or altered patch. To administer, see the "LidoSite™ Topical System Instructions" contained in this package insert. Following iontophoresis and patch removal, the treatment site should be cleansed according to standard practice prior to the medical procedure. Disinfecting agents containing heavy metal ions (mercury, zinc, copper, etc.) should not be used for skin disinfection prior to iontophoresis as they have been associated with swelling and edema.

LidoSite™ Controller should not be subjected to any sterilization procedure.

LidoSite™ Controller should be disposed of in a trash receptacle.

Recommended Dose:	Each iontophoretic treatment delivers lidocaine and epinephrine at the 5-cm^2 site below the circular reservoir. Only one LidoSite™ Patch should be used at a time.
Application:	• See "LidoSite™ Topical System Instructions" • Apply patch immediately after opening pouch. • The LidoSite™ Patch reservoirs must remain in complete contact with the skin during treatment to ensure maximal safety and efficacy. • A new patch may be applied to a different skin site after 30 minutes. • The LidoSite™ Patch is for single use only.
Treatment Duration:	Current delivery lasts for 10 minutes following actuation of the LidoSite™ Controller. In clinical studies the medical procedure was initiated within 10 minutes of patch removal.
Patch Disposal:	LidoSite™ Patch should be disposed of as medical waste.
Storage Conditions:	Store LidoSite™ patches at controlled room temperature (20°C-25°C; 68°F-77°F).

LidoSite™ IONTOPHORETIC CONTROLLER FEATURES:

General description:

The LidoSite™ Topical System utilizes a solid-state electronic controller and a pre-filled patch to form an iontophoretic drug delivery system. The LidoSite™ Controller requires only an ON button actuation to start the treatment. Two light emitting diode (LED) indicators inform the user of the delivery status. The LidoSite™ Controller is designed with a non-replaceable battery that provides up to 99 drug applications at 1.77 mA for 10 minutes (17.7 mA-min).

Displays and Indicators:

The LidoSite™ Controller is provided with both visual and auditory indicators to assist the user in monitoring the function of the device.

There are two LED indicators on the controller, one green and the other yellow. The green indicator is used to indicate normal operating conditions while the yellow indicator informs the user of an abnormal condition.

Table of LED Indicators, LCD and Beeper

CONDITION	GREEN	YELLOW	LCD	Beeper	COMMENT
Controller without patch connected. ON pressed.	Flashes rapidly	Flashes rapidly	Doses Remain Displayed	Single	Self-Check completed successfully. Green and Yellow indicators alternate for 2 seconds. Display shows Doses Remain for 5 seconds Unit automatically shuts off. No current delivered.
Controller with patch detected, but not connected to skin. ON pressed.	Flashes rapidly	Flashes rapidly	No display	3 beeps	Self-Check completed successfully. Green and Yellow indicators alternate for 2 seconds. If No skin detected after 2 minutes, flashing YELLOW continues after 2 minutes for 30 minutes then turns OFF. Both indicators turn OFF. No current is delivered. If skin detected within 2 minutes, controller goes to delivery in progress. If skin not detected within initial 2 minutes (i.e. during period of alternate blinking of green and yellow indicators), remove the patch from the controller and discard the patch.
Controller with patch connected & patch placed on the skin ON pressed	Flashes rapidly	Flashes rapidly	No display	-	Self Check completed successfully Green and Yellow indicators alternate for 2 seconds.
Delivery in progress	Flashes slowly	OFF	No display	-	Green indicator continues flashing at a rate of once per second until delivery profile completed (10 minutes duration)
Delivery Profile complete and target delivery achieved	Flashes rapidly	OFF	No display	3 beeps	Flashing of green indicator continues at a rate of four times per second for 30 minutes or until patch is disconnected After initial 3 beeps, beeper sounds every second for 3 seconds, which repeats every 30 seconds for 30 minutes or until patch is disconnected
Delivery Profile complete but target delivery not achieved	OFF	Flashes rapidly	No display	3 beeps	Flashing of yellow indicator continues at 4 times per second for 30 minutes or until patch is disconnected After initial 3 beeps, beeper sounds every second for 3 seconds, which repeats every 30 seconds for 30 minutes or until patch is disconnected
Shutdown during delivery (over current or under current condition detected)	OFF	Flashes rapidly	No display	3 beeps	Flashing of yellow indicator continues at 4 times per second for 30 minutes or until patch is disconnected After initial 3 beeps, beeper sounds every second for 3 seconds, which repeats every 30 seconds for 30 minutes or until patch is disconnected
End of Life (99 doses delivered) or Low Battery	OFF	Steady	No display	-	Remains ON after patch is removed
Patch disconnected	OFF	OFF	-	-	Remains OFF after patch is removed

The LidoSite™ Controller has an internal beeper that sounds at the end of every delivery and at the end of the self-check function.

At the end of a delivery, there is a beep every second for three seconds which repeats every thirty seconds. The sequence continues for thirty minutes or until the patch is removed from the controller. It should be noted that this signal is present at the termination of a delivery, whether successful or not.

At the end of the self-check function, the unit provides one quick beep.

Delivery Profile:

The LidoSite™ System has a fixed delivery profile that cannot be altered by the user. The entire delivery is accomplished in approximately 10 minutes. Delivery is initiated upon pressing the ON button and the subsequent detection of skin at the patch site. Once started, the profile proceeds through three stages.

Ramp-Up: When the controller detects the presence of skin, it begins the delivery. To minimize patient discomfort the current is slowly ramped up from zero to 1.77 milliamperes. This ramp up requires approximately 0.5 minutes to complete.

Main Delivery: When the controller has reached the 1.77 mA current, it holds this current constant for approximately the next 9 minutes.

Ramp-Down: Upon completion of the main delivery, the current is slowly ramped down to zero. This ramp-down takes about 0.5 minutes.

Delivery Monitor:

The LidoSite™ Controller monitors the actual current delivered throughout the entire delivery profile. During this time, the controller checks for the following delivery conditions:

Over Current: If the controller detects a current in excess of the normal range (1.77 ± 0.09 mA) the current (and delivery) is stopped, the steady YELLOW indicator is illuminated and the device beeps three times.

Under Current: If the controller detects a current below the normal range of current, the delivery is stopped, the flashing YELLOW indicator is illuminated, and the device beeps three times.

Under Delivery: If the controller detects that the total delivered charge was less than 90% at the end of the delivery profile, the flashing YELLOW indicator is illuminated and the device beeps three times.

If the YELLOW light flashes at 4 times per second, the medication may not have been fully delivered to the application site. This may be caused by a higher than normal skin resistance of the patient, improper patch application, poor patch adhesion or by a malfunction of the patch or controller. In this case drug delivery may or may not have been sufficient to produce the desired effect. A second application using a new LidoSite™ Patch may be applied after 30 minutes to a different skin site.

LidoSite™ Patches should not be reapplied to a skin site that has previously been treated with a LidoSite™ Patch. Only one LidoSite™ Patch should be used at a time.

Automatic Shutoff:

To maximize battery life, the controller operates with a number of automatic shutoffs.

No Patch: The controller goes through a Self-Check whenever the ON button is pushed. If the controller does not detect the presence of a patch, it will shut itself down. Both indicators turn OFF.

No Skin: After the controller detects the presence of the patch, it looks for the presence of skin. If it does not detect the presence of skin within 2 minutes of detecting the patch, the YELLOW LED continues to flash for 30 minutes then turns itself OFF. Both indicators turn OFF. If skin is not detected within the initial 2 minutes following controller activation (i.e. during alternating blinking of yellow and green LED indicators), remove the patch from the controller and discard the patch.

After Delivery: Upon completion of the delivery profile, the GREEN indicator continues to flash for 30 minutes or until the patch is removed.

Cleaning and Care:

The LidoSite™ Controller is a sealed unit requiring no calibration and no maintenance service except for periodic cleaning. Cleaning should be performed with a cloth dampened with an isopropyl alcohol solution. *LidoSite™ Controller should not be immersed in any liquid***.**

TROUBLESHOOTING:

The LidoSite™ Controller is not designed to be serviced or repaired. The unit is sealed, contains a non-replaceable battery, and requires no calibration.

No Flashing GREEN and YELLOW During Self Check

If the controller does not go through the alternating GREEN and YELLOW flashing indicators when the ON button is first pressed, discard the unit.

Constant YELLOW indicator

The battery is below operational limits and the unit should be discarded.

No Flashing GREEN indicator With Patch Connected

- The patch is improperly connected to the controller, or
- The patch was previously used, or
- The patch was improperly placed on the patient or no skin was detected.

CONTACT INFORMATION:

B. Braun Clinical and Technical Support
824 Twelfth Avenue
Bethlehem, PA 18018
Phone: 800-854-6851

PATENTS:

The LidoSite™ Topical System is protected by U.S. patents: 5,246,418; 5,873,850; 6,377,847; 6,385,488; 6,402,732; 6,522,419; 6,629,968, 6,635,045. Additional patents pending.

HOW SUPPLIED:

LidoSite™ Patches are supplied as individually pouched, single-use, iontophoretic patches containing 10% Lidocaine and 0.1% Epinephrine, and are to be used only in conjunction with the LidoSite™ Controller. LidoSite™ Patches and LidoSite™ Controllers are available as follows:

LidoSite™ Topical System	
Reorder Number	**Description**
333901	One (1) LidoSite™ Controller
333925	Twenty five (25) LidoSite™ Patches

Rx only. Store LidoSite™ patches at controlled room temperature (20°C-25°C; 68°F-77°F). Excursions permitted between 15°-30° C (see USP Controlled Room Temperature).

Warning: Do not subject the patches to freezing temperatures.

Manufactured by:
Vyteris, Inc. Fair Lawn, NJ 07410, USA

Part # 20082 Rev. April 2004 Printed in USA

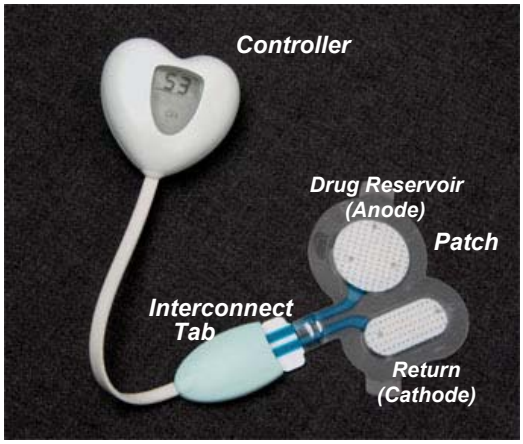


Figure 1. Picture of LidoSite™ Topical System

LidoSite™ Topical System Instructions*

1. Preparation of the Application Site

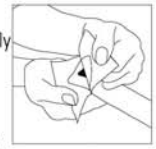
a) Examine the treatment site, ensuring that the application area is free of scars, scratches, wounds, bruises and not covered with excessive hair that could affect patch adherence to the skin.

b) Briskly rub the area with an isopropyl alcohol swab to remove dry skin, oils, and other surface matter.

c) Allow the area to dry thoroughly.

2. Application of LidoSite™ Patch to Skin

a) Open pouch from the V-shaped seal by peeling back the sealed sides approximately half way to expose the white tab of the patch.



b) Grasp the white tab and remove the patch from the pouch. Visually inspect the patch for creases or other apparent damage. Do not use if damaged.

c) Hold the patch by the white tab with the transparent, protective plastic cover side up. Remove the plastic cover and discard.

d) Using the handling tabs on opposite sides of the patch, position the center of the circular reservoir on the area to be treated and apply to the skin. If the patch folds upon itself or adhesive sections stick to each other, discard the patch and apply another.

e) Starting from the center of the circular reservoir, apply light pressure and move outwards to the edges of the patch to secure uniformly. Repeat for the oblong reservoir.

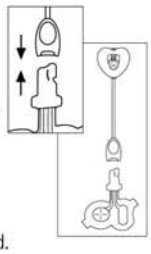
3. LidoSite™ Controller Operation

a) Prior to connecting the controller, an optional self-check can be performed to verify the treatments remaining. Depress the "ON" button, located in the middle of the controller, for one (1) second. The controller is ready to use after the GREEN and YELLOW indicators blink alternately for two (2) seconds and the unit beeps once. LCD will display "doses remain".

b) The **LidoSite**™ controller can be clipped to the patient's clothing or held in place using the supplied strap. Place the controller such that the interconnect can reach the patch with some slack remaining in the cable.

c) Connect the patch to the controller by inserting the tab into the interconnect.

d) Ensure the patch is in full contact with the skin (See step 2e).



e) During treatment, advise the patient to minimize movement.

f) After the patch is connected to the controller, depress the "ON" button for one (1) second to initiate delivery. A self-check will be performed.

After the self-check, the GREEN indicator should begin flashing at a rate of once per second, indicating that the delivery is in progress. The GREEN light will continue to flash slowly during the 10 minute treatment.

IF THE GREEN LIGHT DOES NOT START FLASHING, CHECK THAT (1) THE PATCH TAB IS FULLY INSERTED IN THE INTERCONNECT AND (2) THE PATCH IS COMPLETELY ADHERED TO THE PATIENT'S SKIN.

g) When the treatment is complete, the controller will beep three times and increase the flashing rate of the GREEN light to four times per second.

h) If the YELLOW light flashes at 4 times per second, the application site may not be fully anesthetized. This may be caused by a higher than normal skin resistance of the patient and may not necessarily be a malfunction of the patch or controller. Be aware that sufficient medication may or may not be present to produce the desired effect. A tactile check of the skin site may be performed at the application site to help determine a subjective level of medication effect. A second application using a new **LidoSite**™ Patch may be applied after 30 minutes to a different skin site. **LidoSite**™ Patches should not be reapplied to a skin site that had previously been treated with a patch. Only one (1) patch should be used at a time.

4. Removal and Disposal

a) Grasp the interconnect tab and disconnect the patch from the controller. The lights will go OFF and the controller will automatically turn OFF. The patch tab is slit when removed from the interconnect. preventing reuse of the patch.

b) **LidoSite**™ Patch should be disposed of as medical waste.

c) Remove the controller.

5. Preparation of the Treatment Site

a) Following patch removal, clean the treatment site prior to starting the medical procedure, according to standard practice.

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* For use with **LidoSite**™ Patch and **LidoSite**™ Controller

Each patch contains Lidocaine HCl (10%), Epinephrine (0.1%)