LIDODERM® (Lidocaine Patch 5%)

Rx only

DESCRIPTION
LIDODERM (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm.

Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, propylparaben, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, lanolin, and water.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ion fluxes required for the initiation and conduction of impulses.

Pharmacokinetics
Absorption: The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three LIDODERM patches were applied over an area of 420 cm² of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in Table 1.

Table 1: Absorption of Lidocaine from LIDODERM

<table>
<thead>
<tr>
<th>Patch Size (cm²)</th>
<th>Area (cm²)</th>
<th>Mean Absorbed (mg)</th>
<th>Tmax (hr)</th>
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</thead>
<tbody>
<tr>
<td>3 patches (1200)</td>
<td>420</td>
<td>64.32</td>
<td>0.13</td>
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When LIDODERM is used according to the recommended dosing instructions, only 3% to 6% of the dose applied is expected to be absorbed. At least 90% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

Figure 1: Mean lidocaine blood concentration after three consecutive daily treatments of three LIDODERM patches simultaneously for 12 hours per day in healthy volunteers (n = 15).

Distribution: When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.5 L/kg). At concentrations produced by application of LIDODERM, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL), the plasma protein binding of lidocaine is concentration dependent. 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 to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacological activity. In the skin, lidocaine is metabolized to a minor extent but less extensively than that of lidocaine. A monoethyl metabolite, 2,6-Xylidine, has unknown pharmacological activity. Carcinogenicity in rats. The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion: Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22.0 min, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 L/min, n = 15).

CLINICAL STUDIES

Single-dose treatment with LIDODERM was compared to treatment with vehicle patch (without lidocaine), and to no treatment in a double-blind, crossover clinical trial with 35 post-herpetic neuralgia patients. Pain and pruritus scores were evaluated periodically for 12 hours. LIDODERM performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.

Multiple-dose, two-week treatment with LIDODERM was compared to vehicle patch (without lidocaine) in a double-blind, crossover clinical trial of withdrawal-type design conducted in 32 patients, who were considered as responders to the open-label use of LIDODERM prior to the study. The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia). Statistically significant differences favoring LIDODERM were observed in terms of time to exit from the trial (14 versus 9.8 days at peak vs. 0.001, daily average pain relief, and patient's preference of treatment. About half of the patients also used oral medications commonly used in the treatment of post-herpetic neuralgia. The extent of use of concomitant medication was similar in the two treatment groups.

INDICATIONS AND USAGE
LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.

CONTRAINDICATIONS
LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS

Accidental Exposure in Children

Even a used LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for parents to store and dispose of LIDODERM out of the reach of children and pets.

Excessive Dosing

Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Dose Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5.0 µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Lower duration of application, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

Hepatic Disease

Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally. Allergic Reactions: Patients allergic to para-aminobenzoic acid derivatives (procaine, imidocaine, benzocaine, etc.) have not shown cross sensitivities to lidocaine. However, LIDODERM should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Hypersensitivity: Application to broken or inflamed skin, although not studied, 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 vision returns.

Drug Interactions

Antihypertensive Drugs: LIDODERM should be used with caution in patients receiving Class I antihypertensive drugs (such as lidocaine and methyldopa) since the toxic effects are additive and potentially synergistic.

Local Anesthetics: LIDODERM may be used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM.

Mutagenesis: Lidocaine HCI has not been mutagenic in Salmonella/mammalian microsome test or clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility: The effect of LIDODERM on fertility has not been studied.

Pregnancy

Teratogenic Effects: Pregnancy Category B. LIDODERM (lidocaine patch 5%) has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due 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, LIDODERM should be used during pregnancy only if clearly needed.

Labor and Delivery

LIDODERM has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should LIDODERM be used concurrently with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers

LIDODERM has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk/plasma ratio of lidocaine is 0.4. Caution should be exercised when LIDODERM is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.
ADVERSE REACTIONS

Application Site Reactions

During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of application may develop erythema, edema, bruising, papules, vesicles, discoloration, depigmentation, burning sensation, pruritus, dermatitis, petechia, blistering, exfoliation, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by urticaria, angioedema, bronchospasm, laryngospasm, dermatitis, pruritus, dyspnea, and shock. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Events Observed During Postmarketing Surveillance of LIDODERM

Due to the nature and limitation of spontaneous reports, causality has not been established for the following reported adverse events with LIDODERM treatment.

Hypersensitivity reaction, skin irritation, asthenia, paresthesia, hyperesthesia, hypoesthesia, metallic taste, taste alteration, headache, dizziness, lightheadedness, nervousness, disorientation, confusion, visual disturbances such as blurred vision, tinnitus, tremor, and flushing.

Systemic (Dose-Related) Reactions

Systemic adverse reactions following appropriate use of LIDODERM are unlikely due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, disorientation, dizziness, lightheadedness, numbness, disorientation, confusion, visual disturbances, such as blurred vision, tinnitus, tremor, and flushing). Cardiovascular manifestations may include bradycardia, hypotension, and cardiovascular collapse leading to arrest.

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdosage includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD50 of lidocaine HCl is 459 (346-773) mg/kg (as the salt) in non-fast-food female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION

Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination. When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HANDLING AND DISPOSAL

Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. The used patch should be immediately disposed of in such a way as to prevent its access by children or pets.

HOW SUPPLIED

LIDODERM (lidocaine patch 5%) is available as the following:

- Can of 30 patches, packaged into individual child-resistant envelopes

NDC 63481-687-06

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). (See USP Controlled Room Temperature).