LIDOCAINE HYDROCHLORIDE - lidocaine hydrochloride solution
Morton Grove Pharmaceuticals, Inc.

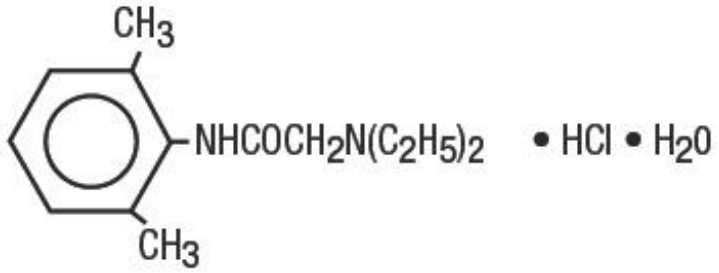
LIDOCAINE HYDROCHLORIDE TOPICAL SOLUTION, USP 4%

Rx only

DESCRIPTION

Lidocaine Hydrochloride Topical Solution, USP 4% contains a local anesthetic agent and is administered topically. See INDICATIONS for specific uses.

Lidocaine Hydrochloride Topical Solution USP 4% contains lidocaine hydrochloride monohydrate, which is chemically designated as 2-(Diethylamino)-2',6'-acetoxylidide monohydrochloride monohydrate and has the following structural formula:



$C_{14}H_{22}N_2O \cdot HCl \cdot H_20$
M.W. 288.81

Each mL contains:

Lidocaine Hydrochloride Monohydrate, USP	40 mg

Inactive Ingredients: methylparaben, propylene glycol and purified water. **It may also contain** sodium hydroxide for pH adjustment. The pH range is between 5.0 and 7.0.

An aqueous solution for topical use only. NOT FOR INJECTION.

CLINICAL PHARMACOLOGY

Mechanism of Action

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

Hemodynamics

Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. These changes may be attributable to a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

Pharmacokinetics and Metabolism

Information derived from other formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon such factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Lidocaine may be absorbed following topical administration to mucous membranes, its rate of absorption and percent of dose absorbed depending upon concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application occurs most rapidly after intratracheal administration. Lidocaine is also well-absorbed from the gastrointestinal tract, but little intact drug appears in the circulation because of biotransformation by the liver.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline. Studies have shown that peak blood levels of lidocaine may occur as early as 5 and as late as 30 minutes after endotracheal administration of a 4% lidocaine HCl solution.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Studies of lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey arterial blood levels of 18 to 21

mcg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE

Lidocaine Hydrochloride Topical Solution is indicated for the production of topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract.

CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type, or to other components of Lidocaine Hydrochloride Topical Solution.

WARNINGS

IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS, RESUSCITATIVE EQUIPMENT, OXYGEN AND OTHER RESUSCITATIVE DRUGS MUST BE IMMEDIATELY AVAILABLE WHEN LOCAL ANESTHETIC AGENTS, SUCH AS LIDOCAINE, ARE ADMINISTERED TO MUCOUS MEMBRANES.

Lidocaine Hydrochloride Topical Solution USP 4% should be used with extreme caution if there is sepsis or severely traumatized mucosa in the area of application, since under such conditions there is the potential for rapid systemic absorption.

Methemoglobinemia

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

Signs and symptoms of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue Lidocaine and any other oxidizing agents. Depending on the severity of the symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

PRECAUTIONS

General

The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See **WARNINGS** and **ADVERSE REACTIONS.**) The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine should also be used with caution in patients with severe shock or heart block.

Although it has been shown that the rate of absorption of lidocaine after spraying the laryngotracheal mucosa with a solution of the local anesthetic agent is normally relatively slow, there is the attendant risk that occasionally some of the solution may gravitate into the lower respiratory tract where surface area for absorption and tissue blood flow are markedly greater. This can result in unexpectedly rapid and high blood levels, and this possibility must be kept in mind whenever Lidocaine Hydrochloride Topical Solution is administered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Lidocaine Hydrochloride Topical Solution, USP 4% should be used with caution in patients with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Information for Patients

When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. For this reason, food should not be ingested for 60 minutes following use of local anesthetic preparations in the mouth or throat area. This is particularly important in children because of their frequency of eating.

Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food and chewing gum should not be taken while the mouth or throat area is anesthetized.

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Use in Pregnancy

Pregnancy Category B

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

Labor and Delivery

Lidocaine is not contraindicated in labor and delivery. Should Lidocaine Hydrochloride Topical Solution, USP 4% be used concomitantly with other products containing lidocaine, the total dose being administered must be kept in mind.

Nursing Mothers

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

Pediatric Use

Dosages in pediatric patients should be reduced, commensurate with age, body weight and physical condition. See **DOSAGE AND ADMINISTRATION**.

Drug Interactions:

Drug Interactions: Patients that are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following oxidizing agents:

Class	Examples
Nitrates/Nitrites	nitroglycerin, nitroprusside, nitric oxide, nitrous oxide
Local anesthetics	benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine
Antineoplastic agents	cyclophosphamide, flutamide, rasburicase, isofamide, hydroxyurea
Antibiotics	dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenytoin, sodium valproate, phenobarbital

Other drugs	acetaminophen, metoclopramide, sulfa drugs (i.e., sulfasalazine), quinine
Nitrates/Nitrites	nitroglycerin, nitroprusside, nitric oxide, nitrous oxide

ADVERSE REACTIONS

Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central Nervous System

CNS manifestations are excitatory and/or depressant and may be characterized by 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. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular System

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic

Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics. (see **ADVERSE REACTIONS**, **WARNINGS,** and **PRECAUTIONS**).

Management of Local Anesthetic Emergencies

The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic administration. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The intravenous LD_{50} of lidocaine hydrochloride in female mice is 26 (21 to 31) mg/kg and the subcutaneous LD_{50} is 264 (203 to 304) mg/kg.

DOSAGE AND ADMINISTRATION

When Lidocaine Hydrochloride Topical Solution, USP 4% is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

The dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. Dosages should be reduced for children and for elderly and debilitated patients. Although the incidence of adverse effects with Lidocaine Hydrochloride is quite low, caution should be exercised, particularly when employing large volumes, since the incidence of adverse effects is directly proportional to the total dose of local anesthetic agent administered.

The dosages recommended below are for normal, healthy adults:

When used as a spray, or when applied by means of cotton applicators or packs, as when instilled into a cavity, the suggested dosage of Lidocaine Hydrochloride Topical Solution is 1 to 5 mL (40 to 200 mg lidocaine hydrochloride), i.e., 0.6 to 3.0 mg/kg or 0.3 to 1.5 mg/lb body weight.

NOTE: The solution may be applied with a sterile swab which is discarded after a single use and never reused under any circumstances. When spraying, transfer the solution from the original container to an atomizer.

MAXIMUM RECOMMENDED DOSAGES

Normal Healthy Adults

The maximum recommended dose of Lidocaine Hydrochloride Topical Solution, USP 4%

should be such that the dose of lidocaine hydrochloride is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) body weight.

Children

It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children of less than ten years who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (e.g., Clark's rule). For example, in a child of five years weighing 50 lbs., the dose of lidocaine hydrochloride should not exceed 75 to 100 mg when calculated according to Clark's rule. In any case, the maximum dose of Lidocaine Hydrochloride with epinephrine should not exceed 7 mg/kg (3.2 mg/lb) of body weight. When used without epinephrine, the amount of Lidocaine Hydrochloride administered should be such that the dose of lidocaine is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) of body weight.

HOW SUPPLIED

Lidocaine Hydrochloride Topical Solution, USP 4% is supplied in 50 mL bottle (NDC 60432-465-50) and packaged in a carton (NDC 60432-465-51). An aqueous solution for topical application. NOT FOR INJECTION.

RECOMMENDED STORAGE

Store at 20 ° to 25 °C (68 ° to 77 °F) [see USP Controlled Room Temperature].

AVOID FREEZING

Rx Only

Product No.: 8465

Manufactured By:

Morton Grove Pharmaceuticals, Inc.

Morton Grove, IL 60053

Manufactured For:

Wockhardt USA, LLC

Parsippany, NJ 07054

28465

REV. 06-20

PRINCIPAL DISPLAY PANEL

MGP

NDC 60432-465-51

LIDOCAINE

HYDROCHLORIDE

TOPICAL

SOLUTION, USP

4%

NOT FOR INJECTION

TOPICAL USE ONLY

Rx Only

NET: 1 ⅔ fl oz (50 mL)

carton-r1222

LIDOCAINE HYDROCHLORIDE

lidocaine hydrochloride solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:60432-465
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LIDOCAINE HYDROCHLORIDE (UNII: V13007Z41A) (LIDOCAINE - UNII:98PI200987)	LIDOCAINE HYDROCHLORIDE ANHYDROUS	40 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:60432-465-51	1 in 1 CARTON	11/18/1982	
1	NDC:60432-465-50	50 mL in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA087881	11/18/1982	

Labeler - Morton Grove Pharmaceuticals, Inc. (801897505)

Registrant - Morton Grove Pharmaceuticals, Inc. (801897505)

Establishment

Name	Address	ID/FEI	Business Operations
Morton Grove Pharmaceuticals, Inc.		801897505	ANALYSIS(60432-465) , MANUFACTURE(60432-465) , PACK(60432-465)

Establishment

Name	Address	ID/FEI	Business Operations

Societa Italiana Medicinali Scandicci S.I.M.S. SrL - Italy		428994180	API MANUFACTURE(60432-465)