

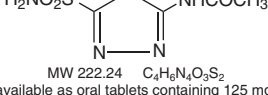
**DIAMOX®**  
Acetazolamide Tablets USP  
and  
**DIAMOX®**  
Sterile Acetazolamide Sodium USP  
Intravenous

CI 4995-5

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## DESCRIPTION

DIAMOX acetazolamide, an inhibitor of the enzyme carbonic anhydrase is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for DIAMOX is *N*-(5-Sulfamoyl-1,3,4-thiadiazol-2yl)-acetamide and has the following chemical structure:



MW 222.24    C<sub>4</sub>H<sub>6</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>

DIAMOX is available as oral tablets containing 125 mg and 250 mg of acetazolamide respectively and the following inactive ingredients: Corn Starch, Dibasic Calcium Phosphate, Magnesium Stearate, Povidone, and Sodium Starch Glycolate.

DIAMOX is also available for intravenous use, and is supplied as a sterile powder requiring reconstitution. Each vial contains an amount of acetazolamide sodium equivalent to 500 mg of acetazolamide. The bulk solution is adjusted to pH 9.2 using sodium hydroxide and, if necessary, hydrochloric acid prior to lyophilization.

## CLINICAL PHARMACOLOGY

DIAMOX acetazolamide is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion (eg, some types of glaucoma), in the treatment of certain convulsive disorders (eg, epilepsy) and in the promotion of diuresis in instances of abnormal fluid retention (eg, cardiac edema).

DIAMOX is not a mercurial diuretic. Rather, it is a nonbacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides.

DIAMOX is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye, this inhibitory action of acetazolamide decreases the secretion of aqueous humor and results in a drop in intraocular pressure, a reaction considered desirable in cases of glaucoma and even in certain nonglaucomatous conditions. Evidence seems to indicate that DIAMOX has utility as an adjuvant in the treatment of certain dysfunctions of the central nervous system (eg, epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons. The diuretic effect of DIAMOX is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result is renal loss of HCO<sub>3</sub> ion, which carries out sodium, water, and potassium.

Alkalinization of the urine and promotion of diuresis are thus effected. Alteration in ammonia metabolism occurs due to increased reabsorption of ammonia by the renal tubules as a result of urinary alkalinization.

Placebo-controlled clinical trials have shown that prophylactic administration of DIAMOX at a dose of 250 mg every eight to 12 hours (or a 500 mg controlled-release capsule once daily) before and during rapid ascent to altitude results in fewer and/or less severe symptoms (such as headache, nausea, shortness of breath, dizziness, drowsiness, and fatigue) of acute mountain sickness (AMS).

Pulmonary function (eg, minute ventilation, expired vital capacity, and peak flow) is greater in the DIAMOX treated group, both in subjects with AMS and asymptomatic subjects. The DIAMOX treated climbers also had less difficulty in sleeping.

## INDICATIONS AND USAGE

For adjunctive treatment of: edema due to congestive heart failure; drug-induced edema; centrencephalic epilepsies (petit mal, unlocalized seizures); chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure. DIAMOX is also indicated for the prevention or amelioration of symptoms associated with acute mountain sickness in climbers attempting rapid ascent and in those who are very susceptible to acute mountain sickness despite gradual ascent.

## CONTRAINDICATIONS

DIAMOX acetazolamide therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloremic acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy.

Long-term administration of DIAMOX is contraindicated in patients with chronic noncongestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intraocular pressure.

## WARNINGS

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitizations may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue use of this drug.

Caution is advised for patients receiving concomitant high-dose aspirin and DIAMOX acetazolamide, as anorexia, tachypnea, lethargy, coma and death have been reported.

## PRECAUTIONS

### General

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paresthesia. Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

### Information for Patients

Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), crystaluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia and agranulocytosis. Precaution is advised for early detection of such reactions and the drug should be discontinued and appropriate therapy instituted.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, DIAMOX acetazolamide which may precipitate or aggravate acidosis, should be used with caution.

Gradual ascent is desirable to try to avoid acute mountain sickness. If rapid ascent is undertaken and DIAMOX is used, it should be noted that such use does not obviate the need for prompt descent if severe forms of high altitude sickness occur, ie, high altitude pulmonary edema (HAPE) or high altitude cerebral edema.

Caution is advised for patients receiving concomitant high-dose aspirin and DIAMOX acetazolamide, as anorexia, tachypnea, lethargy, coma and death have been reported (see **WARNINGS**).

### Laboratory Tests

To monitor for hematologic reactions common to all sulfonamides, it is recommended that a baseline CBC and platelet count be obtained on patients prior to initiating DIAMOX therapy and at regular intervals during therapy. If significant changes occur, early discontinuance and institution of appropriate therapy are important. Periodic monitoring of serum electrolytes is recommended.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of DIAMOX acetazolamide have not been conducted. In a bacterial mutagenicity assay, DIAMOX was not mutagenic when evaluated with and without metabolic activation.

The drug had no effect on fertility when administered in the diet to male and female rats at a daily intake of up to 4 times the recommended human dose of 1000 mg in a 50 kg individual.

### Pregnancy

#### Pregnancy Category C

Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters and rabbits. There are no adequate and well-controlled studies in pregnant women. Acetazolamide should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nursing Mothers

Because of the potential for serious adverse reaction in nursing infants from DIAMOX, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

### Pediatric Use

The safety and effectiveness of DIAMOX in pediatric patients have not been established.

INSERT PHARMACODE

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## ADVERSE REACTIONS

Adverse reactions, occurring most often early in therapy, include paresthesias, particularly a "tingling" feeling in the extremities, hearing dysfunction or tinnitus, loss of appetite, taste alteration and gastrointestinal disturbances such as nausea, vomiting and diarrhea; polyuria, and occasional instances of drowsiness and confusion.

Metabolic acidosis and electrolyte imbalance may occur.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuance of the medication.

Other occasional adverse reactions include urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, photosensitivity and convulsions. Also see **PRECAUTIONS:**

**Information for Patients** for possible reactions common to sulfonamide derivatives. Fatalities have occurred although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias (see **WARNINGS**).

## DRUG INTERACTIONS

Aspirin - See **WARNINGS**.

DIAMOX® acetazolamide may increase or enhance the occurrence of osteomalacia in some patients receiving chronic phenytoin therapy. Caution is advised in patients receiving chronic concomitant therapy.

By decreasing the gastrointestinal absorption of primidone, DIAMOX may decrease serum concentrations of primidone and its metabolites, with a consequent possible decrease in anticonvulsant effect. Caution is advised when beginning, discontinuing, or changing the dose of DIAMOX in patients receiving primidone.

Because of possible additive effects with other carbonic anhydrase inhibitors, concomitant use is not advisable.

## OVERDOSAGE

No specific antidote is known. Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state, and central nervous effects might be expected to occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Supportive measures are required to restore electrolyte and pH balance. The acidotic state can usually be corrected by the administration of bicarbonate.

Despite its high intraerythrocytic distribution and plasma protein binding properties, DIAMOX may be dialyzable. This may be particularly important in the management of DIAMOX overdosage when complicated by the presence of renal failure.

## DOSAGE AND ADMINISTRATION

### Preparation and Storage of Parenteral Solution

Each 500 mg vial containing DIAMOX sterile acetazolamide sodium parenteral should be reconstituted with at least 5 mL of Sterile Water for Injection prior to use.

Reconstituted solutions retain their physical and chemical properties for 3 days under refrigeration at 2° to 8°C (36° to 46°F), or 12 hours at room temperature 15° to 30°C (59° to 86°F). CONTAINS NO PRESERVATIVE. The direct intravenous route of administration is preferred.

Intramuscular administration is not recommended.

**Glaucoma:** DIAMOX should be used as an adjunct to the usual therapy. The dosage employed in the treatment of *chronic simple (open-angle) glaucoma* ranges from 250 mg to 1 g of DIAMOX per 24 hours, usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 1 g per 24 hours does not produce an increased effect. In all cases, the dosage should be adjusted with careful individual attention both to symptomatology and ocular tension. Continuous supervision by a physician is advisable.

In treatment of secondary glaucoma and in the preoperative treatment of some cases of *acute congestive (closed-angle) glaucoma*, the preferred dosage is 250 mg every four hours, although some cases have responded to 250 mg twice daily on short-term therapy. In some acute cases, it may be more satisfactory to administer an initial dose of 500 mg followed by 125 or 250 mg every four hours depending on the individual case. Intravenous therapy may be used for rapid relief of ocular tension in acute cases. A complementary effect has been noted when DIAMOX has been used in conjunction with miotics or mydriatics as the case demanded.

**Epilepsy:** It is not clearly known whether the beneficial effects observed in epilepsy are due to direct inhibition of carbonic anhydrase in the central nervous system or whether they are due to the slight degree of acidosis produced by the divided dosage. The best results to date have been seen in petit mal in pediatric patients. Good results, however, have been seen in patients, both pediatric patients and adult, in other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk patterns, etc. The suggested total daily dose is 8 to 30 mg per kg in divided doses. Although some patients respond to a low dose, the optimum range appears to be from 375 to 1000 mg daily. However, some investigators feel that daily doses in excess of 1 g do not produce any better results

than a 1 g dose. When DIAMOX is given in combination with other anticonvulsants, it is suggested that the starting dose should be 250 mg once daily in addition to the existing medications. This can be increased to levels as indicated above.

The change from other medications to DIAMOX should be gradual and in accordance with usual practice in epilepsy therapy.

**Congestive Heart Failure:** For diuresis in congestive heart failure, the starting dose is usually 250 to 375 mg once daily in the morning (5 mg/kg). If, after an initial response, the patient fails to continue to lose edema fluid, do not increase the dose but allow for kidney recovery by skipping medication for a day. DIAMOX acetazolamide yields best diuretic results when given on alternate days, or for two days alternating with a day of rest.

Failures in therapy may be due to overdosage or too frequent dosage. The use of DIAMOX does not eliminate the need for other therapy such as digitalis, bed rest, and salt restriction.

**Drug-Induced Edema:** Recommended dosage is 250 to 375 mg of DIAMOX once a day for one or two days, alternating with a day of rest.

**Acute Mountain Sickness:** Dosage is 500 mg to 1000 mg daily, in divided doses using tablets or sustained-release capsules as appropriate. In circumstances of rapid ascent, such as in rescue or military operations, the higher dose level of 1000 mg is recommended. It is preferable to initiate dosing 24 to 48 hours before ascent and to continue for 48 hours while at high altitude, or longer as necessary to control symptoms.

Note: The dosage recommendations for glaucoma and epilepsy differ considerably from those for congestive heart failure, since the first two conditions are not dependent upon carbonic anhydrase inhibition in the kidney which requires intermittent dosage if it is to recover from the inhibitory effect of the therapeutic agent.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## HOW SUPPLIED

### DIAMOX® Acetazolamide Tablets

125 mg - Round, flat-faced, beveled, white tablets engraved with DIAMOX and 125 on one side and scored in half on the other side. Engraved with LL on the right of the score and D1 on the left, are supplied as follows:

NDC 0005-4398-23 - Bottle of 100

250 mg - Round, convex, white tablets engraved with DIAMOX and 250 on one side and scored in quarters on the other side. Engraved with LL in the upper right quadrant and D2 in the lower left quadrant, are supplied as follows:

NDC 0005-4469-23 - Bottle of 100

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



LEDERLE PHARMACEUTICAL DIVISION  
of American Cyanamid Company, Pearl River, NY 10965

### DIAMOX® Sterile Acetazolamide Sodium, Intravenous

Sterile intravenous (lyophilized) powder.

NDC 0205-4466-96 - 500 mg Vial

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



LEDERLE PARENTERALS, INC.  
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