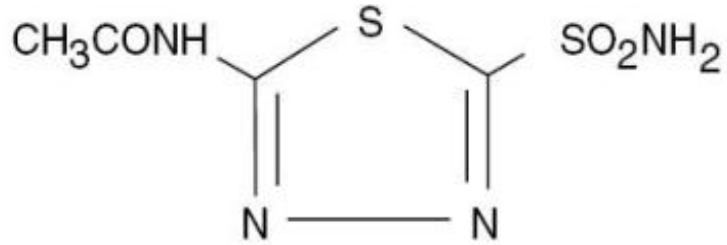
ACETAZOLAMIDE - acetazolamide tablet
Physicians Total Care, Inc.

DESCRIPTION

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 acetaZOLAMIDE is *N*-(5-Sulfamoyl-1,3,4-thiadiazol-2yl)-acetamide and has the following structural formula:



$C_4H_6N_4O_3S_2$ MW 222.24

Each tablet, for oral administration, contains 250 mg of acetaZOLAMIDE. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, sodium starch glycolate, corn starch, and calcium stearate.

CLINICAL PHARMACOLOGY

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

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

AcetaZOLAMIDE 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 acetaZOLAMIDE has utility as an adjuvant in the treatment of certain dysfunctions of the central nervous system (e.g., epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons. The diuretic effect of acetaZOLAMIDE is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result of renal loss of HCO_3 ion, which carries out sodium, water, and potassium. Alkalinization of the urine and promotion of diuresis are thus affected. 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 acetaZOLAMIDE 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 (e.g., minute ventilation, expired vital capacity and peak flow) is greater in the acetaZOLAMIDE treated group, both in subjects with AMS and asymptomatic subjects. The acetaZOLAMIDE 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. AcetaZOLAMIDE 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

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 hyperchloremia acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy.

Long-term administration of acetaZOLAMIDE is contraindicated in patients with chronic non-congestive 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 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) crystalluria, 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, 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 acetaZOLAMIDE 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. i.e., high altitude pulmonary edema (HAPE) or high-

altitude cerebral edema.

Caution is advised for patients receiving concomitant high-dose aspirin and 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 acetaZOLAMIDE 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 acetaZOLAMIDE have not been conducted. In a bacterial mutagenicity assay, acetaZOLAMIDE 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.

PregnancyTeratogenic EffectsPregnancy 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 reactions in nursing infants from acetaZOLAMIDE, 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 acetaZOLAMIDE in children have not been established.

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**).

OVERDOSAGE

No data are available regarding acetaZOLAMIDE overdose in humans as no cases of acute poisoning with this drug have been reported. Animal data suggest that acetaZOLAMIDE is remarkably nontoxic. 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, acetaZOLAMIDE may be dialyzable. This may be particularly important in the management of acetaZOLAMIDE overdosage when complicated by the presence of renal failure.

DOSAGE AND ADMINISTRATION

Glaucoma

AcetaZOLAMIDE 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 acetaZOLAMIDE 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 mg 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 acetaZOLAMIDE 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 children.

Good results, however, have been seen in patients, both children and adults, 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 acetaZOLAMIDE 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 acetaZOLAMIDE 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.

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 acetaZOLAMIDE 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 acetaZOLAMIDE 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 28 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.

HOW SUPPLIED

AcetaZOLAMIDE is available as white, convex, double-scored, 250 mg tablet, debossed with LAN/1050.

Bottle of 12	NDC 54868-1195-2
Bottle of 15	NDC 54868-1195-0
Bottle of 20	NDC 54868-1195-3
Bottle of 60	NDC 54868-1195-4

Store at controlled room temperature 15°-30° C (59°-86° F)[see USP]

Dispense in a well-closed container, as defined in the USP.

Rx only

FINAL DOSAGE FORM
MANUFACTURED BY
LANNETT CO. INC.
PHILADELPHIA, PA 19136

AcetaZOLAMIDE TABLETS, USP

Revised 2/08

Distributed and Repackaged by:
Physicians Total Care, Inc.
Tulsa, Oklahoma 74146

PRINCIPAL DISPLAY PANEL

AcetaZOLAMIDE TABLETS, USP

250 mg tablets

ACETAZOLAMIDE

acetazolamide tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:54868-1195(NDC:0527-1050)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ACETAZOLAMIDE (ACETAZOLAMIDE)	ACETAZOLAMIDE	250 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE	
SODIUM STARCH GLYCOLATE TYPE A POTATO	
STARCH, CORN	
CALCIUM STEARATE	

Product Characteristics

Color	white (white)	**Score**	4 pieces
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	LAN;1050
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-1195-0	15 in 1 BOTTLE		
2	NDC:54868-1195-2	12 in 1 BOTTLE		
3	NDC:54868-1195-3	20 in 1 BOTTLE		
4	NDC:54868-1195-4	60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA084840	02/09/2010	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations

Physicians Total Care, Inc.		194123980	relabel(54868-1195), repack(54868-1195)