

ACETAZOLAMIDE- acetazolamide tablet
Advagen Pharma Ltd

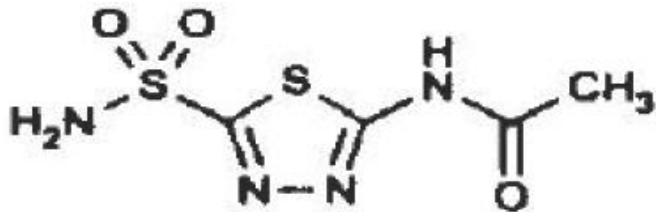
AcetaZOLAMIDE

Tablets USP

Rx only

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-2-yl)-acetamide and has the following chemical structure:



Molecular Weight: 222.25

Molecular Formula: C₄H₆N₄O₃S₂

Acetazolamide is available as oral tablets containing 125 mg and 250 mg of acetazolamide, respectively, and the following inactive ingredients: maize starch, gelatin, glycerin, lactose monohydrate, magnesium stearate, sodium starch glycolate and talc.

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 is renal loss of HCO₃ 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 Tablets are 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 hyperchloremic 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 tablets are 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 tablet 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.

Pregnancy

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 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 pediatric patients has 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 overdosage 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. 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 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 acetazolamide tablets are 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 tablets yield 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. 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.

HOW SUPPLIED

Acetazolamide Tablets USP are supplied as follows:

125 mg - White to off white, round, uncoated tablets, scored in half on one side and debossed with 'A' on other side.

42

NDC 72888-047-01 - Bottle of 100

250 mg - White to off white, round, uncoated tablets, scored in quarters on one side and debossed with 'A' on other side.

043

NDC 72888-048-01 - Bottle of 100

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

Distributed By:

Advagen Pharma Ltd.,
666 Plainsboro Road,
Suite 605
Plainsboro, NJ 08536, USA.

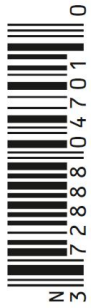

Manufactured by:

Rubicon Research Private Limited
 Ambernath, Dist: Thane, 421506 India.



Rev. 05/2021

PRINCIPAL DISPLAY PANEL

**AcetaZOLAMIDE Tablets USP, 125 mg - NDC 72888-047-01 - 100 Tablets
 Bottle Label**

<p>Each tablet contains: Acetazolamide, USP.....125 mg</p>	<p>NDC 72888-047-01</p>	<p>Distributed by: Advagen Pharma Limited, 666 Plainsboro Road Suite 605, Plainsboro, NJ, 08536, USA</p>	
<p>Usual Dosage: See package insert for full prescribing information.</p>	<p>AcetaZOLAMIDE Tablets USP, 125 mg</p>	<p>Manufactured by: Rubicon Research Private Limited Ambernath, Dist. Thane, 421506 India</p>	
<p>Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.]</p>		<p>Mfg. Lic. No.: KD-682 Rev 01, 11/20</p>	
<p>Dispense in a well-closed containers as defined in the USP.</p>	<p>Rx Only 100 Tablets</p>	<p style="text-align: center; color: magenta;">Overprinting Area 45 X 15 mm</p>	
<p>Keep this and all medication out of the reach of children.</p>			

**AcetaZOLAMIDE Tablets USP, 250 mg - NDC 72888-048-01 - 100 Tablets
 Bottle Label**

<p>Each tablet contains: Acetazolamide, USP.....250 mg</p>	<p>NDC 72888-048-01</p>	<p>Distributed by: Advagen Pharma Limited, 666 Plainsboro Road Suite 605, Plainsboro, NJ, 08536, USA</p>	
<p>Usual Dosage: See package insert for full prescribing information.</p>	<p>AcetaZOLAMIDE Tablets USP, 250 mg</p>	<p>Manufactured by: Rubicon Research Private Limited Ambernath, Dist. Thane, 421506 India</p>	
<p>Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.]</p>		<p>Mfg. Lic. No.: KD-682 Rev 01, 11/20</p>	
<p>Dispense in a well-closed containers as defined in the USP.</p>	<p>Rx Only 100 Tablets</p>	<p style="text-align: center; color: magenta;">Overprinting Area 50 X 15 mm</p>	
<p>Keep this and all medication out of the reach of children.</p>			

ACETAZOLAMIDE			
acetazolamide tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72888-047
Route of Administration	ORAL		

Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
ACETAZOLAMIDE (UNII: O3FX965V0I) (ACETAZOLAMIDE - UNII:O3FX965V0I)			ACETAZOLAMIDE	125 mg
Inactive Ingredients				
Ingredient Name			Strength	
STARCH, CORN (UNII: O8232NY3SJ)				
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)				
GLYCERIN (UNII: PDC6A3C00X)				
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
SODIUM STARCH GLYCOLATE TYPE A (UNII: H8AV0SQX4D)				
TALC (UNII: 7SEV7J4R1U)				
Product Characteristics				
Color	white (White to off white)	Score	2 pieces	
Shape	ROUND	Size	9mm	
Flavor		Imprint Code	UpArrowhead42	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72888-047-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	08/19/2021	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA215101	08/19/2021		

ACETAZOLAMIDE				
acetazolamide tablet				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72888-048	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
ACETAZOLAMIDE (UNII: O3FX965V0I) (ACETAZOLAMIDE - UNII:O3FX965V0I)			ACETAZOLAMIDE	250 mg
Inactive Ingredients				
Ingredient Name			Strength	
STARCH, CORN (UNII: O8232NY3SJ)				
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)				
GLYCERIN (UNII: PDC6A3C00X)				

LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
SODIUM STARCH GLYCOLATE TYPE A (UNII: H8AV0SQX4D)				
TALC (UNII: 7SEV7J4R1U)				
Product Characteristics				
Color	white (White to off white)	Score	4 pieces	
Shape	ROUND	Size	11mm	
Flavor		Imprint Code	UpArrowhead043	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72888-048-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	08/19/2021	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA215101	08/19/2021		

Labeler - Advagen Pharma Ltd (051627256)

Establishment			
Name	Address	ID/FEI	Business Operations
Rubicon Research Private Limited		677604197	manufacture(72888-047, 72888-048) , analysis(72888-047, 72888-048) , pack(72888-047, 72888-048)

Revised: 8/2021

Advagen Pharma Ltd