ACETAZOLAMIDE EXTENDED-RELEASE- acetazolamide extended-release capsule
AvPAK

Acetazolamide Extended-Release Capsules

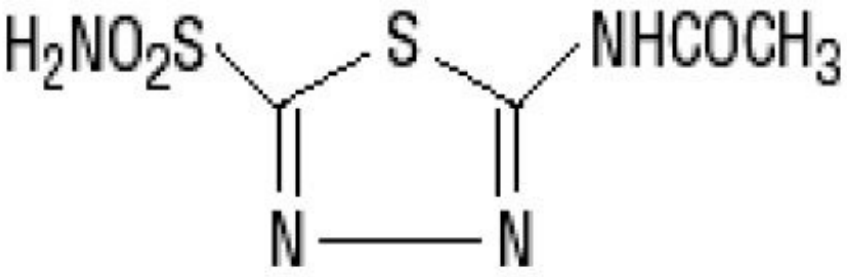
Rx only

Revised: 05/2022

DESCRIPTION:

Acetazolamide extended-release capsules are an inhibitor of the enzyme carbonic anhydrase.

Acetazolamide USP is a white to faintly yellowish-white, crystalline, odorless powder. Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water. The chemical name for acetazolamide is N-(5-Sulfamoyl-1,3, 4-thiadiazol-2-yl) acetamide and has the following chemical structure:



Molecular Weight 222.24

Chemical Formula $C_4H_6N_4O_3S_2$

Acetazolamide extended-release capsules are, for oral administration, each containing 500 mg of acetazolamide and the following inactive ingredients: hydroxypropyl cellulose, microcrystalline cellulose, sodium lauryl sulfate and talc.

The ingredients in the capsule shell are D&C RED no. 28, D&C YELLOW no. 10, FD&C RED no. 40, gelatin and titanium dioxide.

The ingredients in the imprinting ink are shellac (24 to 27%), dehydrated alcohol (23 to 26%), isopropyl alcohol (1 to 3%), butyl alcohol (1 to 3%), propylene glycol (3 to 7%), strong ammonia solution (1 to 2%), black iron oxide (24 to 28%), potassium hydroxide (0.05 to 0.1%) and purified water (15 to 18%).

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 non-bacteriostatic 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 non-glaucomatous conditions. Evidence seems to indicate that acetazolamide has utility as an adjuvant in 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 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.

Acetazolamide extended-release capsules provide prolonged action to inhibit aqueous humor secretion for 18 to 24 hours after each dose, whereas tablets act for only eight to 12 hours. The prolonged continuous effect of acetazolamide extended-release capsules permits a reduction in dosage frequency.

Plasma concentrations of acetazolamide peak from three to six hours after administration of acetazolamide extended-release capsules, compared to one to four

hours with tablets. Food does not affect bioavailability of acetazolamide extended-release capsules.

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 of acute mountain sickness (AMS) such as headache, nausea, shortness of breath, dizziness, drowsiness, and fatigue. 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: chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angleclosure glaucoma where delay of surgery is desired in order to lower intraocular pressure. Acetazolamide extended-release capsules are also indicated for the prevention or amelioration of symptoms associated with acute mountain sickness despite gradual ascent.

CONTRAINDICATIONS:

Hypersensitivity to acetazolamide or any excipients in the formulation. Since acetazolamide is a sulfonamide derivative, cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.

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, anaphylaxis, 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, metabolic acidosis, 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. Caution 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, metabolic acidosis, coma, and death have been reported (see **WARNINGS**).

Both increases and decreases in blood glucose have been described in patients treated with acetazolamide. This should be taken into consideration in patients with impaired glucose tolerance or diabetes mellitus.

Acetazolamide treatment may cause electrolyte imbalances, including hyponatremia and hypokalemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution is recommended in patients with conditions that are associated with, or predispose a patient to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients; see **PRECAUTIONS, Geriatric Use**), patients with diabetes mellitus, and patients with impaired alveolar ventilation.

Some adverse reactions to acetazolamide, such as drowsiness, fatigue, and myopia, may impair the ability to drive and operate machinery.

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.

Drug Interactions

Aspirin - See **WARNINGS**

Acetazolamide modifies phenytoin metabolism with increased serum levels of phenytoin. This 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, acetazolamide 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 acetazolamide in patients receiving primidone.

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

Acetazolamide may increase the effects of other folic acid antagonists.

Acetazolamide decreases urinary excretion of amphetamine and may enhance the magnitude and duration of their effect.

Acetazolamide reduces urinary excretion of quinidine and may enhance its effect.

Acetazolamide may prevent the urinary antiseptic effect of methenamine. Acetazolamide increases lithium excretion and the lithium may be decreased.

Acetazolamide and sodium bicarbonate used concurrently increase the risk of renal calculus formation.

Acetazolamide may elevate cyclosporine levels.

Drug/laboratory Test Interactions

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein, and serum uric acid. Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

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:

Teratogenic effects

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. Acetazolamide should only be used by nursing women if the potential benefit justifies the potential risk to the child.

Pediatric Use

The safety and effectiveness of acetazolamide extended-release capsules in pediatric patients below the age of 12 years have not been established. Growth retardation has been reported in children receiving long-term therapy, believed secondary to chronic acidosis.

Geriatric Use

Metabolic acidosis, which can be severe, may occur in the elderly with reduced renal function.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

ADVERSE REACTIONS:

Body as a whole:

Headache, malaise, fatigue, fever, pain at injection site, flushing, growth retardation in children, flaccid paralysis, anaphylaxis.

Digestive:

Gastrointestinal disturbances such as nausea, vomiting, diarrhea.

Hematological/Lymphatic:

Blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia,

thrombocytopenic purpura, melena.

Hepato-biliary disorders:

Abnormal liver function, cholestatic jaundice, hepatic insufficiency, fulminant hepatic necrosis.

Metabolic/Nutritional:

Metabolic acidosis, electrolyte imbalance, including hypokalemia, hyponatremia, osteomalacia with long-term phenytoin therapy, loss of appetite, taste alteration, hyper/hypoglycemia.

Nervous:

Drowsiness, paresthesia (including numbness and tingling of extremities and face), depression, excitement, ataxia, confusion, convulsions, dizziness.

Skin:

Allergic skin reactions including urticaria, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Special senses:

Hearing disturbances, tinnitus, transient myopia. Transient myopia is the result of forward movement of the ciliary body leading to a narrowing of the angle.

Urogenital:

Crystalluria, increased risk of nephrolithiasis with long-term therapy, hematuria, glycosuria, renal failure, polyuria.

To report SUSPECTED ADVERSE REACTIONS, contact AvKARE at 1-855-361-3993 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

OVERDOSAGE:

No specific antidote is known. Treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and central nervous system 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

The recommended dosage is 1 capsule (500 mg) two times a day. Usually 1 capsule is administered in the morning and 1 capsule in the evening. It may be necessary to adjust

the dose, but it has usually been found that dosage in excess of 2 capsules (1 g) does not produce an increased effect. The dosage should be adjusted with careful individual attention both to symptomatology and intraocular tension. In all cases, continuous supervision by a physician is advisable.

In those unusual instances where adequate control is not obtained by the twice-a-day administration of acetazolamide extended-release capsules, the desired control may be established by means of acetazolamide (tablets or parenteral). Use tablets or parenteral in accordance with the more frequent dosage schedules recommended for these dosage forms, such as 250 mg every four hours, or an initial dose of 500 mg followed by 250 mg or 125 mg every four hours, depending on the case in question.

Acute Mountain Sickness

Dosage is 500 mg to 1000 mg daily, in divided doses using tablets or extended-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.

HOW SUPPLIED:

Acetazolamide Extended-Release Capsules are available as 500 mg:

Opaque orange / Opaque orange, hard gelatin capsule imprinted with 'M' on cap and '26' on body contains white to off white pellets.

NDC 50268-042-12 (10 capsules per card, 2 cards per carton).

Dispersed in Unit Dose Package. For Institutional Use Only.

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

Dispense in well-closed containers.

Manufactured for:
AvKARE
Pulaski, TN 38478

Mfg. Rev. 05/22
AV 06/22 (P)
AvPAK

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

ACETAZOLAMIDE EXTENDED-RELEASE

acetazolamide extended-release capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50268-042(NDC:42571-243)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ACETAZOLAMIDE (UNII: O3FX965V0I) (ACETAZOLAMIDE - UNII:O3FX965V0I)	ACETAZOLAMIDE	500 mg

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
TALC (UNII: 7SEV7J4R1U)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	

Product Characteristics

Color	orange (Opaque orange)	**Score**	no score
Shape	CAPSULE	**Size**	23mm
Flavor		**Imprint Code**	M;26
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-042-12	20 in 1 BOX	07/20/2022	
1	NDC:50268-042-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207401	07/20/2022	

Labeler - AvPAK (832926666)

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