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:

\[
\begin{align*}
\text{H} & \quad \text{N} & \quad \text{O} \\
\text{N} & \quad \text{C} & \quad \text{H} & \quad \text{N} & \quad \text{O} \\
\end{align*}
\]

M.W. 222.24 C_4H_6N_4O_3 S_2

Acetazolamide is available for intravenous use and is supplied as a sterile powder requiring reconstitution. Each vial contains acetazolamide sodium equivalent to 500 mg of acetazolamide. The bulk solution is adjusted to pH 9.6 using sodium hydroxide and, if necessary, hydrochloric acid prior to lyophilization.

**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 nonbacterial conditions. Evidence seems to indicate that acetazolamide is effective in the treatment of certain dysfunctions of the central nervous system (e.g., epilepsy).

**DESCRIPTION**

Acetazolamide is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid.

The result is a loss of HCO_3^- ion, which carries out sodium, water, and potassium. Alkalization 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 alkalization.

**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.

**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 cases of marked kidle disease or dysfunction, in cases of marked kidney and liver disease or dysfunction.

**WARNINGS**

Fatality may occur, 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 anemia, tachycardia, lethargy, coma and death have been reported.

**ADVERSE REACTIONS**

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 derivations may occur: anaphylaxis, fever, rash (including vasculitis multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), crystalluria, renal calculi, 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.

Caution is advised for patients receiving concurrent high-dose aspirin and acetazolamide, as anemia, tachycardia, lethargy, coma and death have been reported (see WARNINGS).

**PRECAUTIONS**

**Pediatric Use**

The safety and effectiveness of acetazolamide in children have not been fully established. Periodic monitoring of serum electrolytes is recommended. 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.

**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.

**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 discontinuation 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 to 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.
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 dimunition or discontinuance of the medication.

Other occasional adverse reactions include urticaria, melena, fever, nausea, vomiting, dyspepsia, paresthesia, photosensitivity and convulsions. Also see PRECAUTIONS.

Information for Patients

PRECAUTIONS:

Other occasional adverse reactions include urticaria, melena, gastrointestinal disorders such as nausea, vomiting and diarrhea; polyuria, and occasional instances of drowsiness and confusion.

Serious adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, aplastic anemia and other blood dyscrasias (see WARNINGS).

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 acidic 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 acidic state can usually be corrected by the administration of bicarbonate.

Despite its high intracellular distribution and plasma protein binding properties, acetazolamide may be dialyzable. This may be of importance in the management of acetazolamide overdose when complicated by the presence of renal failure.

DOSAGE AND ADMINISTRATION

Preparation and Storage of Parenteral Solution

Each 500 mg vial containing sterile acetazolamide sodium should be reconstituted with at least 5 mL of Sterile Water for Injection prior to use. Store drug product at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Reconstituted solutions retain their physical and chemical properties for 3 days under refrigeration at 2° - 8°C (36° - 46°F), or 12 hours at room temperature 20° to 25°C (68° to 77°F). CONTAINS NO PRESERVATIVE. The direct intravenous route of administration is preferred.

Intramuscular administration is not recommended.

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 preparative 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 acetazolamide has been used in conjunction with mydriatics or myectomy 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 jerking 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.

Intravenous Therapy

Acetazolamide can be administered intravenously at a rate of 250 to 750 mg per hour. Overdosage may result in profound acidosis, especially in patients with renal failure, hypokalemia, or both. If severe acidosis develops, treatment should consist of alkalization of the blood with sodium bicarbonate.

Intravenous administration is not recommended.

Drug-Induced Edema

Other therapy such as digitalis, bed rest, and salt restriction. The use of acetazolamide does not eliminate the need for other therapy such as digitalis, bed rest, and salt restriction.

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

OVERDOSAGE

1-800-FDA-1088 or www.fda.gov/medwatch.

SAGENT Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

SAGENT Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

SAGENT Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.