

AUSTRALIAN PRODUCT INFORMATION – DIAMOX (ACETAZOLAMIDE) TABLETS

1 NAME OF THE MEDICINE

Acetazolamide.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DIAMOX tablets contain 250mg acetazolamide.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

DIAMOX tablets are white, round, convex tablet, one side plain, the other side scored into quarters.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For adjunctive treatment of: oedema due to congestive heart failure; drug-induced oedema; 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 per 24 hours, usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 2 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 4 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 4 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 children. Good results, however, have been seen in both adult and paediatric patients, in other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk pattern etc.

The recommended dose in paediatric patients is 8-30 mg/kg daily in divided doses not to exceed 750 mg/day. In adults the recommended dose is 250-1000 mg daily in divided doses. When DIAMOX is given in combination with any other anticonvulsant, it is suggested that the starting dose should be 250 mg once daily in addition to the existing medication. This can be increased to the levels indicated above. The change from other medication to DIAMOX should be gradual 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 oedema fluid, do not increase the dose but allow for kidney recovery by omitting medication for a day. DIAMOX yields best diuretic results when given on alternate days, or for 2 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 Oedema

Recommended dosage is 250 to 375 mg (5 mg/kg) once daily for 1 to 2 days, alternating with a day of rest.

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.

Use in Patients with Renal Impairment

Acetazolamide is contraindicated in patients with a glomerular filtration rate (GFR) of <10mL/min (see **Section 4.3 contraindications**). In patients with renal impairment, GFR of >10mL/min, the dose should be reduced by half or the dosage interval should be increased to every 12 hours.

4.3 CONTRAINDICATIONS

Acetazolamide is contraindicated in the presence of:

- hyperchloraemic acidosis
- hypokalaemia
- hyponatraemia
- suprarenal gland failure
- impairment of renal function, GFR < 10mL/min
- hypersensitivity to acetazolamide, sulfonamides, or sulfonamide derivatives, or any excipients in the formulation. Cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.
- marked liver disease or impairment of liver function, including cirrhosis because of the risk of development of hepatic encephalopathy. Acetazolamide decreases ammonia clearance.

Long-term administration 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. 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.

There have been reports of increased muscular weakness, occasionally severe, in patients with hyperkalaemic periodic paralysis who have taken acetazolamide.

Hypersensitivity

Fatalities have occurred, due to severe reactions to sulfonamides and sulphonamide derivatives, including acetazolamide. Adverse reactions common to all sulfonamide derivatives may occur: fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias, anaphylaxis, renal and ureteral colic and renal lesions (see also **Section 4.8 Adverse effects (undesirable effects)**).

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving acetazolamide.

Hypersensitivity reactions may recur if a sulfonamide or sulfonamide derivative is re-administered, irrespective of the route of administration. The drug should be discontinued and appropriate therapy instituted if such reactions are detected.

Haematological reactions

To monitor for haematological reactions common to all sulfonamides, it is recommended that a baseline complete blood count (CBC), platelet count and electrolyte levels be obtained on patients prior to initiating DIAMOX therapy and at regular intervals during therapy. If significant changes or

toxic skin manifestations occur, early discontinuation and institution of appropriate therapy are important.

Glucose metabolism

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

Acid/base and electrolyte balance

Acetazolamide treatment may cause electrolyte imbalances, including hyponatraemia and hypokalaemia, 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 predisposed to, electrolyte and acid/base imbalance, such as patients with impaired renal function, including elderly patients; (see **Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use – Use in the Elderly and Section 4.2 Dose and method of administration**), patients with diabetes mellitus, and patients with impaired alveolar ventilation (such as patients with pulmonary obstruction or emphysema).

Use in the elderly

Metabolic acidosis, which can be severe, may occur in the elderly with reduced renal function (see **Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use - Acid/base and Electrolyte balance and Section 4.2 Dose and method of administration**).

Paediatric use

The safety and effectiveness of acetazolamide in paediatric patients have not been established. Growth retardation has been reported in children receiving long-term therapy, believed secondary to chronic acidosis. (See **Section 4.2 Dose and method of administration**)

Effects on laboratory tests

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein nitrogen and for 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Amphetamines: By increasing the pH of renal tubular urine, acetazolamide reduces the urinary excretion of amphetamine and so may enhance the magnitude and duration of the effect of amphetamines.

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

Cyclosporin: When given concomitantly, acetazolamide may elevate cyclosporin blood levels. Caution is advised when administering acetazolamide in patients receiving cyclosporin.

Folic Acid Antagonists: Acetazolamide may potentiate the effects of other folic acid antagonists.

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

Lithium: Acetazolamide increases lithium excretion due to impaired reabsorption of lithium in the proximal tubule. The effect of lithium carbonate may be decreased.

Methenamine compounds: By increasing the pH of urine, acetazolamide may prevent the urinary antiseptic effect of methenamine compounds.

Phenytoin: When given concomitantly, acetazolamide modifies the metabolism of phenytoin, leading to increased serum levels of phenytoin. Acetazolamide may increase the occurrence, or accelerate the manifestation of osteomalacia in some patients receiving chronic phenytoin therapy. Caution is advised in patients receiving chronic concomitant therapy.

Primidone: 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.

Quinidine: By increasing the pH of renal tubular urine, acetazolamide reduces the urinary excretion of quinidine and so may enhance the effect of quinidine.

Salicylates: Caution is advised for patients receiving concomitant aspirin and acetazolamide, as severe toxicity has been reported. Severe metabolic acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates. Pharmacokinetic studies showed that the plasma protein binding and renal clearance of acetazolamide were significantly reduced during chronic salicylate therapy. Salicylate appears to competitively inhibit plasma protein binding of acetazolamide and simultaneously to inhibit acetazolamide renal secretion that may produce serious metabolic acidosis. Systemic acidosis produced by acetazolamide may increase salicylate toxicity by enhancing salicylate tissue penetration.

Precaution is advised for patients receiving concomitant high-dose aspirin and DIAMOX as anorexia, tachypnoea, lethargy and coma have been reported due to a possible drug interaction. (See **Section 4.4 Special warnings and precautions for use**). Concomitant administration with high-dose aspirin may potentiate the adverse reactions of DIAMOX.

Sodium Bicarbonate: The use of concurrent sodium bicarbonate therapy enhances the risk of renal calculus formation in patients taking acetazolamide.

Cardiovascular Agents: Potentiation of the effects of oral anticoagulants is possible when administered with Diamox, and may warrant a reduction in the dose of the anticoagulant. Adjustment of dose may be required when DIAMOX is given with cardiac glycosides or antihypertensive agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The potential adverse effects of acetazolamide on fertility and general reproductive performance have not been adequately assessed in animals.

Use in pregnancy – Pregnancy Category B3

Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters and rabbits, at oral or parenteral doses in excess of ten times those recommended in human beings. There are no adequate and well-controlled studies in pregnant women.

As there are no adequate and well-controlled studies in pregnant women, DIAMOX should not be used in pregnancy, especially during the first trimester.

Use in lactation.

DIAMOX has been detected in low levels in the milk of lactating women who have taken DIAMOX. Therefore the potential exists for adverse reactions in the infant. Extreme caution should be utilized when DIAMOX is administered to lactating women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Body as a whole

Headaches, malaise, fatigue, pain at injection site, fever, growth retardation in children, flaccid paralysis, flushing and anaphylactic/anaphylactoid reactions, including shock and fatalities

Digestive

Gastrointestinal disturbances such as nausea, vomiting and diarrhoea

Haematological/Lymphatic

Blood dyscrasias such as aplastic anaemia, agranulocytosis, leukopenia, thrombocytopenia, and thrombocytopenic purpura

Metabolic/Nutritional

Metabolic acidosis and electrolyte imbalance, including hypokalaemia, hyponatraemia, osteomalacia with long-term therapy, loss of appetite, taste alteration, hyper/hypoglycaemia

Nervous

Drowsiness, paraesthesia, involving numbness and tingling of extremities and face, depression, excitement, ataxia, confusion, convulsions, dizziness

Skin

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

Special Senses

Hearing disturbances, tinnitus, myopia

Urogenital

Crystalluria, increased risk of nephrolithiasis with long-term therapy, haematuria, abnormal liver function including cholestatic jaundice, glycosuria, renal failure

The following adverse events have also been reported: polyuria, polydipsia, thirst, melaena and hepatic insufficiency.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Acetazolamide is dialyzable.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

DIAMOX (acetazolamide) is a carbonic anhydrase inhibitor.

DIAMOX 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 catalyses 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 humour 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 (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 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_3^- ions, that carry 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 alkalinisation.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

No data available.

Distribution

No data available.

Metabolism

No data available.

Excretion

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of acetazolamide has not been adequately assessed, although in a bacterial mutagenicity assay, it was found to be negative.

Carcinogenicity

Long term animal studies have not been conducted to investigate the carcinogenic potential of acetazolamide.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

DIAMOX tablets contain the following excipients: sodium starch glycollate, povidone, calcium hydrogen phosphate dihydrate, maize starch and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

DIAMOX tablets are available in bottles (HDPE material) containing 100 tablets or 250* tablets.

* Not currently marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

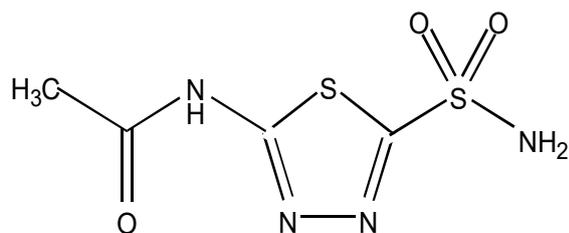
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Acetazolamide is a white to yellowish-white crystalline substance, sparingly soluble in cold water with a mp of 258-259°C, a weak acid and a pKa of 7.2, .

Chemical structure

Acetazolamide is N-(5-sulphamoyl-1,3,4-thiadiazole-2-yl) acetamide and its structural formula is:



$C_8H_9NO_2$

Molecular weight of 151.16

CAS number

CAS No. 103-90-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121
Australia

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

9 September 1991

10 DATE OF REVISION

16 November 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
n/a	Reformatting