NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DIAMOX acetazolamide 250 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DIAMOX tablets contain 250 mg of acetazolamide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

DIAMOX tablets are round, convex, white, cross scored, diameter 11mm.

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 of DIAMOX 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 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.

4.3 Contraindications

Situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, suprarenal gland failure, hyperchloraemic acidosis and hypersensitivity to acetazolamide, sulfonamides, or sulfonamide derivatives, or any excipients in the formulation. Cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.

Acetazolamide is contraindicated in patients with marked liver disease or impairment of liver function, including cirrhosis because of the risk of development of hepatic encephalopathy. Acetazolamide decreases ammonia clearance.

Acetazolamide is contraindicated in patients with severe glaucoma due to peripheral anterior synechias or in haemorrhagic glaucoma. Long-term administration 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.

4.4 Special warnings and precautions for use

Pharmacokinetic studies in four volunteers showed that the plasma protein binding and renal clearance of acetazolamide were significantly reduced during chronic salicylate dosing. Salicylate appears to competitively inhibit plasma protein binding of acetazolamide and simultaneously to inhibit acetazolamide renal secretion that may produce serious metabolic acidosis.

When acetazolamide and phenytoin are given together, accelerated development of osteomalacia has been reported. The concurrent use of these two agents should be avoided or else monitoring to detect osteomalacia should be instituted.

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.

Nervous

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation and behaviour emerge.

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, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, haemolytic anaemia, leucopenia, pancytopenia, agranulocytosis, aplastic anaemia and other blood dyscrasias, anaphylaxis, renal and ureteral colic and renal lesions.

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

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

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see Undesirable Effects). In case of AGEP diagnosis, acetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

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.

Choroidal effusion/detachment

Cases of choroidal effusion/detachment have been reported after the use of acetazolamide. Symptoms include acute onset of decreased visual acuity or ocular pain and can occur within hours after initiation of acetazolamide treatment. If choroidal effusion/detachment is suspected, acetazolamide should be discontinued as rapidly as possible.

Non-cardiogenic pulmonary oedema

Severe cases of non-cardiogenic pulmonary oedema have been reported after taking acetazolamide, also after a single dose (see Section 4.8). Non-cardiogenic pulmonary oedema typically developed within minutes to hours after acetazolamide intake. Symptoms included dyspnoea, hypoxia, and

respiratory insufficiency. If non-cardiogenic pulmonary oedema is suspected, acetazolamide should be withdrawn, and supportive treatment should be given. Acetazolamide should not be administered to patients who previously experienced non-cardiogenic pulmonary oedema following acetazolamide intake.

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, patients with diabetes mellitus, and patients with impaired alveolar ventilation), (such as patients with pulmonary obstruction or emphysema). DIAMOX tablets may aggravate acidosis and should be used with caution.

Use in Renal Impairment

In patients with moderate to severe renal impairment, the dose should be reduced by half or the dosage interval should be increased to every 12 hours. In patients with past history of renal calculi, benefit should be balanced against the risks of precipitating further calculi.

Use in Paediatrics

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 DOSAGE & ADMINISTRATION)

Use in the Elderly

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

Patient Monitoring

Monitoring serum electrolyte levels (particularly potassium) and blood pH levels should be considered if overdose with acetazolamide is suspected. In the case of overdosage when complicated by the presence of renal failure, dialysis may be beneficial since acetazolamide is dialyzable.

Interference with Laboratory Tests

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein 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 Interaction with other medicines and other forms of interaction

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.

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

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. There have been isolated reports of increased carbamazepine serum levels with concurrent administration of acetazolamide.

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. 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 WARNINGS).

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

Pregnancy Category B3.

Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) and embryotoxic in mice, rats, hamsters and rabbits, at oral or parenteral doses in excess of ten times those recommended in human beings. 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 during 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 Undesirable effects

Adverse reactions during short-term therapy are minimal. Those effects that have been noted include:

Body as a whole

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

Digestive

Gastrointestinal reactions such as abnormal liver function including cholestatic jaundice, gastrointestinal disturbances such as nausea, vomiting and diarrhoea.

Haematological/ lymphatic

Blood dyscrasias such as aplastic anaemia, agranulocytosis, leukopenia, thrombocytopenia, thrombocytopenic purpura, bone marrow depression and pancytopenia.

Metabolic/Nutritional

Metabolic acidosis and electrolyte imbalance, including hypokalaemia, hyponatraemia, osteomalacia with long-term therapy, taste alteration and hyper/hypoglycaemia. During long-term therapy, metabolic acidosis and hypokalaemia may occur. This can usually be corrected by the administration of bicarbonate and/or potassium.

Nervous

Drowsiness, paraesthesia, particularly a tingling feeling in the extremities and face, depression, excitement, ataxia, confusion, convulsions, dizziness, and irritability.

Respiratory, thoracic and mediastinal disorders

Non-cardiogenic pulmonary oedema

Skin

Allergic skin reactions including urticaria, photosensitivity, Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Thrombocytic purpura and acute generalised exanthematous pustulosis (AGEP).

Special senses

Hearing disturbances and tinnitus have been reported. Transient myopia is rare and invariably subsides upon diminution or discontinuation of the medication. Choroidal effusion, choroidal detachment.

Urogenital

Crystalluria, increased risk of nephrolithiasis with long-term therapy, haematuria, Renal and ureteral coli, renal lesions, calculus formation, abnormal liver function including fulminant hepatic necrosis, hepatitis or cholestatic jaundice, glycosuria, renal failure.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DIAMOX is a 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 oedema).

DIAMOX is not a mercurial diuretic. Rather it 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 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 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.

5.2 Pharmacokinetic properties

No data available.

5.3 Preclinical safety data

No data available.

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

Not applicable.

6.3 Shelf life

24 months. Store below 30°C.

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

DIAMOX is available in bottles (HDPE material) containing 100 tablets.

6.6 Special precautions for disposal <and other handling>

Not applicable.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Arrotex Pharmaceuticals (NZ) Limited:
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9 DATE OF FIRST APPROVAL

15 February 2010

10 DATE OF REVISION OF THE TEXT

21 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Update to precaution section: addition choroidal effusion/detachment, non-cardiogenic pulmonary oedema, and update to nervous system.
4.8	Update to adverse event section: addition of choroidal effusion/detachment, non-cardiogenic pulmonary oedema.