AUSTRALIAN PRODUCT INFORMATION

GLAUMOX™

(ACETAZOLAMIDE) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

acetazolamide sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains acetazolamide sodium, equivalent to 500 mg acetazolamide.

For the full list, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Glaumox is sterile lyophilized powder of acetazolamide sodium in a rubber capped vial. The sterile lyophilised powder is white to faintly yellowish white, crystalline, and odourless. The contents of the vial require reconstitution with water for injections for intravenous administration. The final solution is adjusted to pH 9.6 prior to lyophilisation.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For adjunctive treatment of: oedema due to congestive heart failure; drug-induced oedema; centrencephalic epilepsies (petit mal, unlocalised 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

Preparation and storage of parenteral solution

Each 500 mg vial containing Glaumox sterile acetazolamide sodium should be reconstituted with at least 5 mL of sterile water for injections prior to use. Product is for single use in one patient only. Discard any residue. To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2°- 8°C for not more than 24 hours. Contains no antimicrobial preservative. The direct intravenous route of administration is preferred. Glaumox is intended for short-term usage only when it is not practicable to use acetazolamide in the oral dosage form.

Glaucoma

Glaumox 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 Glaumox 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 Glaumox 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 Glaumox 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. Glaumox 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 Glaumox 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.

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

Warnings

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.

Precautions

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.

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.

Fatalities have occurred, due to severe reactions to sulfonamides and sulfonamide 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, leukopenia, 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 including shock and anaphylaxis 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. To monitor for haematological reactions common to all sulfonamides, it is recommended that a baseline CBC, platelet count and electrolyte levels be obtained on patients prior to initiating Glaumox therapy and at regular intervals during therapy. If significant changes or toxic skin manifestations occur, early discontinuation and institution of appropriate therapy are important. Fatalities have occurred due to severe adverse reactions to sulfonamides.

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.

Other concomitant conditions

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, 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). 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.

Use in hepatic impairment

See Section 4.3 Contraindications.

Use in renal impairment

See Section 4.4 Acid/base and electrolyte balance.

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 dialysable.

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 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.

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

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

Hypoglycaemic 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. 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 acetazolamide 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, Warnings). Concomitant administration with high-dose aspirin may potentiate the adverse reactions of Glaumox.

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 Glaumox and may warrant a reduction in the dose of the anticoagulant. Adjustment of dose may be required when Glaumox is given with cardiac glycosides or antihypertensive agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in 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. Glaumox should not be used in pregnancy, especially during the first trimester.

Australian categorisation definition of Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Use in lactation

Acetazolamide has been detected in low levels in the milk of lactating women who have taken the drug. Therefore, the potential exists for adverse reactions in the infant. Extreme caution should be utilised when Glaumox 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)

Adverse reactions during short-term therapy are minimal.

Effects that have been noted include paraesthesia, particularly a tingling feeling in the extremities and face, some loss of appetite, polyuria, polydipsia, flushing, thirst, headaches, dizziness, fatigue, irritability and occasional instances of drowsiness and confusion.

Rarely, photosensitivity has been reported.

General reactions such as malaise, pain at injection site, fever, growth retardation in children and anaphylactic/ anaphylactoid reactions, including shock and fatalities have been reported.

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

Haematological and lymphatic reactions reported include blood dyscrasias such as aplastic anaemia, agranulocytosis, leukopenia, thrombocytopenia, thrombocytopenic purpura, bone marrow depression and pancytopenia.

Metabolic/nutritional adverse reactions have included metabolic acidosis, electrolyte imbalance, hypokalaemia, hyponatraemia, osteomalacia with long-term therapy, loss of appetite, 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.

Adverse reactions in the nervous system include reports of, drowsiness, paraesthesia, involving numbness and tingling of extremities and face, depression, excitement, ataxia, reduced libido, convulsions, irritability and confusion.

Skin reactions reported with the use of acetazolamide include allergic skin reactions, including urticaria, photosensitivity, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Thrombocytic purpura and acute generalised exanthematous pustulosis (AGEP).

Hearing disturbances, tinnitus and myopia have been reported.

Transient myopia is rare and invariably subsides upon diminution or discontinuation of the medication. Choroidal effusion and choroidal detachment may occur.

Adverse reactions in the urogenital system include crystalluria and increased risk of nephrolithiasis with long-term therapy, renal calculi, renal and ureteral colic, renal lesions, calculus formation, abnormal liver function including fulminant hepatic necrosis, hepatitis or cholestatic jaundice, glycosuria, and renal failure.

Other occasional adverse reactions include urticaria, melaena, haematuria, glycosuria, hepatic insufficiency, flaccid paralysis and convulsions.

Respiratory, thoracic and mediastinal disorders reported include non-cardiogenic pulmonary oedema.

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 is known. Treatment should be symptomatic and supportive, with correction of electrolyte and fluid balance. 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Glaumox (acetazolamide sodium) 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).

Mechanism of action

Acetazolamide 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 desirable in cases of glaucoma. Evidence indicates that Glaumox is useful 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 bicarbonate ions. Alkalinisation of the urine and promotion of diuresis are thus affected.

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

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial contains the excipients hydrochloric acid and sodium hydroxide for pH adjustment.

Contains no antimicrobial preservative.

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 25°C.

Product is for single use in one patient only. Discard any residue. To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2°- 8°C for not more than 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Lyophilised powder is supplied in a clear glass 15 mL single dose vial. Each carton contains 1 single dose vial (AUST R 142075).

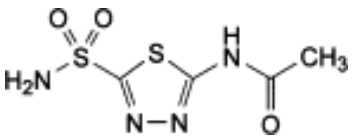
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

The active ingredient of Glaumox is the acetazolamide sodium, or the sodium salt of *N*-(5-sulphamoyl-1,3,4-thiadiazol-2-yl) acetamide. Acetazolamide has a molecular weight of 222.25 ($C_4H_6N_4O_3S_2$).
Acetazolamide sodium is a white or almost white crystalline powder, soluble in water.

Chemical structure



CAS number

The CAS for acetazolamide is 59-66-5.

The CAS for acetazolamide sodium is 1424-27-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Phebra Pty Ltd
17-19 Orion Road
Lane Cove West NSW 2066
Australia
Ph 1800 720 020

New Zealand: AFT Pharmaceuticals Ltd, PO Box 33-203 Takapuna Auckland.

9 DATE OF FIRST APPROVAL

01 Jun 2009

10 DATE OF REVISION

4 April 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Correction of vial size to 15 mL