

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diamox SR 250mg Capsules
Acetazolamide 250mg Sustained Release Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Acetazolamide 250mg

3 PHARMACEUTICAL FORM

Sustained release capsule with a clear body and orange cap printed “GS 250” in black.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glaucoma

4.2 Posology and method of administration

Capsules should be swallowed whole. Do not chew or crush.

Adults: One or two 250mg capsules a day.

Children: This product is not intended for administration to children.

Use in Elderly Patients: DIAMOX should be used with particular caution in elderly patients or those with potential obstruction in the urinary tract or with disorders rendering their electrolyte balance precarious or with liver dysfunction.

Use in Patients with Renal Impairment: In patients with moderate to severe renal impairment, the dose should not exceed 250mg per day or the dosage interval should be increased to every 12 hours.

4.3 Contra-indications

DIAMOX SR is contra-indicated in situations in which sodium and/or potassium blood levels are depressed, in cases of marked renal impairment and liver disease or dysfunction, suprarenal gland failure, and hyperchloremic acidosis. Diamox should not be used in patients with liver disease or impairment of liver function including cirrhosis as this may increase the risk of hepatic encephalopathy. DIAMOX is contra-indicated in patients with hypokalemia and hyponatraemia.

Long-term administration of DIAMOX SR is contra-indicated 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 intra-ocular pressure.

DIAMOX SR should not be used in patients hypersensitive to sulphonamides or other sulphonamide derivatives including acetazolamide or any excipients in the formulation.

4.4 Special warnings and precautions for use

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

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 for Acetazolamide.

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 or behaviour emerge.

When DIAMOX SR is prescribed for long-term therapy, special precautions are advisable. The patient should be cautioned to report any unusual skin rash. Prior to initiating therapy and at regular intervals during therapy monitoring of blood cell counts and electrolyte levels are recommended. Fatalities have occurred, although rarely, due to severe reactions to sulphonamides including acetazolamide, such as Steven-Johnson syndrome and toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias and anaphylaxis. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of DIAMOX SR therapy.

Hypersensitivity reactions may recur if a sulphonamide or sulphonamide derivative is re-administered, irrespective of the route of administration. If

signs of hypersensitivity reactions or other serious reactions occur, acetazolamide must be discontinued.

Acetazolamide treatment may cause electrolyte imbalances, including hyponatraemia and transient 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 predispose to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients), pulmonary obstruction, emphysema, patients with diabetes mellitus and patients with impaired alveolar ventilation. Severe metabolic acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates.

Both increased 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.

In patients with a past history of renal calculi, benefit should be balanced against the risks of precipitating further calculi.

4.5 Interaction with other medicaments and other forms of interaction

DIAMOX is a sulphonamide derivative. Sulphonamides may potentiate the effects of folic acid antagonists. Possible potentiation of the effects of folic acid antagonists, hypoglycaemics and oral anti-coagulants may occur. Concurrent administration of acetazolamide and acetylsalicylic acid may result in severe toxicity and increase central nervous system toxicity. Severe metabolic acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates. Adjustment of dose may be required when DIAMOX SR is given with cardiac glycosides or hypertensive agents.

When given concomitantly DIAMOX SR modifies the metabolism of phenytoin leading to increased serum levels of phenytoin. Severe osteomalacia has been noted in a few patients taking acetazolamide in combination with other anticonvulsants. There have been isolated reports of reduced primidone and increased carbamazepine serum levels with concurrent administration of acetazolamide.

Concomitant use with other carbonic anhydrase inhibitors is not advisable because of possible additive effects.

Both increases and decreases in blood glucose levels have been described in patients with acetazolamide. This should be taken into consideration in patients treated with anti-diabetic agents.

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

By increasing the pH of urine, acetazolamide may prevent the urinary excretion of methenamine compounds.

Acetazolamide increases lithium excretion due to impaired re-absorption of lithium in the proximal tubule. The effect of lithium carbonate may be decreased.

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

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

Interference with Laboratory and other Diagnostic Tests:

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.

4.6 Pregnancy and Lactation

Use in pregnancy: Acetazolamide has been reported to be teratogenic (defects of the limbs) and embryotoxic in rats, mice, hamsters and rabbits at oral or parenteral doses in excess of ten times those recommended in human beings. Although there is no evidence of these effects in human beings, there are no adequate and well-controlled studies in pregnant women. Therefore, DIAMOX SR 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. Although it is unlikely that this will lead to any harmful effects in the infant, extreme caution should be exercised when DIAMOX SR 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 usually non-serious. Those effects which have been noted include: paraesthesia, particularly a "tingling" feeling in the extremities; some loss of appetite; taste disturbance, polyuria, flushing, thirst, headache, dizziness, fatigue, irritability, excitement, ataxia, depression, reduced libido and occasional instances of drowsiness and confusion. Rarely, photosensitivity has been reported.

During long-term therapy, metabolic acidosis and electrolyte imbalance, including hypokalaemia and hyponatraemia may occasionally occur. Hypokalaemia is generally transient and is rarely clinically significant. Osteomalacia with long-term phenytoin therapy, hyperglycaemia and hypoglycaemia, may occasionally occur during long term therapy. The acidosis can usually be corrected by the administration of bicarbonate.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuation of the medication.

Gastro-intestinal disturbances such as nausea, vomiting and diarrhoea.

DIAMOX is a sulphide derivative and therefore some side-effects similar to those caused by sulphonamides have occasionally been reported. These include fever, agranulocytosis, thrombocytopenia, thrombocytic purpura, leukopenia, and aplastic anaemia, bone marrow depression, pancytopenia, rash (including erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis), anaphylaxis, crystalluria, calculus formation, renal and ureteral colic, and renal lesions. Rarely, fulminant hepatic necrosis has been reported.

Other occasional adverse reactions include: urticaria, melaena, haematuria, glycosuria, impaired hearing and tinnitus, abnormal liver function, renal failure and rarely; hepatitis or cholestatic jaundice, flaccid paralysis, and convulsions.

Long – term therapy with acetazolamide increases the risk of nephrolithiasis.

4.9 Overdose

No specific antidote.

Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state and central nervous effects might be expected to occur. Serum electrolyte levels, (particularly potassium) and blood pH 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 intra-erythrocytic distribution and plasma protein binding properties, acetazolamide is dialyzable. This may be particularly important in the management of acetazolamide overdose when complicated by the presence of renal failure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Acetazolamide is a potent inhibitor of the enzyme 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 the aqueous humor and results in a drop of intraocular pressure and is thus used to treat glaucoma.

5.2 Pharmacokinetic Properties

DIAMOX SR is a sustained release formulation designed to obtain a smooth and continuous clinical response. Acetazolamide is readily absorbed after oral administration and binds tightly to plasma proteins as well as to the enzyme carbonic anhydrase. The drug begins to accumulate in tissues in which this enzyme is present notably red blood cells and the renal cortex. It is also bound to plasma proteins.

Peak plasma levels of the drug are reached 1 - 3 hours after oral administration with whole blood levels reaching peak concentrations approximately one hour later. Plasma levels decay more rapidly than red blood cell or whole blood levels with the elimination frequently being biphasic. The first phase having a half-life in 2 hours and the second phase in 13 hours. This terminal phase half-life corresponds to the leakage from red blood cells.

Acetazolamide is completely cleared by the renal route with the measured unbound renal clearance being some 5 - 6 times greater than creatinine clearance. Overall, clearance is dependent also on plasma protein binding.

5.3 Pre-clinical Safety Data

Nothing of note to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film coated Pellets:

Microcrystalline Cellulose, sodium Lauryl sulphate, purified water, ethylcellulose, Hydroxypropylmethyl cellulose, mineral oil light, methanol, methylene chloride and **opaspray K-1R-2506** orange [hydroxypropyl cellulose, titanium dioxide (E171) and FD & C yellow No 6 (E110)].

Capsules shells:

Gelatine, titanium dioxide (E171), yellow iron oxide (E172) erythrosine (E127).

6.2 Incompatibilities

None

6.3 Shelf-Life

Blister packs: 36 months
Polypropylene bottles: 24 months

6.4 Special Precautions for Storage

Store at controlled room temperature (15°-30°C) in the original pack or in well sealed dispensing containers which prevent access of light and moisture.

6.5 Nature and contents of container

Blister Packs: 28 and **30** Capsules/ Pack

Opaque UPVC/PVDC blister Pack heat sealed with aluminium foil backing in an outer carton

Polypropylene Bottles: 28, 100 & 500 Capsules/ Bottle

Polypropylene bottles with a heat sealed aluminium induction membrane and a white urea screw cap.

6.6 Instruction for Use, Handling and Disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey
CR0 0XT
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 12762/0145

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF
AUTHORISATION**

22 June 2004

10. DATE OF REVISION OF THE TEXT

23/03/2010