SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diamox SR 250mg Prolonged-release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg acetazolamide

Excipient(s) with known effect

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule

Orange spherical pellets contained in a size ‘1’ capsule with clear body and opaque orange cap. ‘GS 250’ is printed on the orange cap in black text

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glaucoma

4.2 Posology and method of administration

Posology
Adults:
One or two 250mg capsules a day.

Elderly
Acetazolamide 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.

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.

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

There is no relevant use of Acetazolamide in the paediatric population.

Method of administration

Oral use.

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

4.3 Contraindications

Hypersensitivity to active substance or to any of the excipients listed in section 6.1

Acetazolamide should not be used in patients hypersensitive to sulphonamides or other sulphonamide derivatives.

Acetazolamide 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. Acetazolamide 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. Acetazolamide is contra-indicated in patients with hypokalemia and hyponatraemia.

Long-term administration of Acetazolamide 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.

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 acetazolamide 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 acetazolamide 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.

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 section 4.8). In case of AGEP diagnosis, acetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

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.

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.

This medicine contains the ingredient sunset yellow FCF (E110) which may cause allergic reactions.

Information on Sodium Content:

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicaments and other forms of interaction

Acetazolamide 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 acetazolamide is given with cardiac glycosides or hypertensive agents.

When given concomitantly acetazolamide 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 administrating 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 Fertility, pregnancy and lactation

Pregnancy
Acetazolamide should not be used in pregnancy, especially during the first trimester. (See section 5.3)

Breast-feeding
Acetazolamide has been detected in low levels in the milk of lactating women who have taken acetazolamide. Although it is unlikely that this will lead to any harmful effects in the infant, extreme caution should be exercised when acetazolamide is administered to lactating women.

Fertility
No Data available. See section 5.3 Pre-clinical Safety Data.

4.7 Effects on ability to drive and use machines

Acetazolamide has minor or moderate influence on the 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.

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4.8 Undesirable effects

Adverse reactions during short-term therapy are usually non-serious.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: Very common: (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known: cannot be estimated from the available data.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia, Leukopenia, Aplastic anaemia, Bone marrow depression, Pancytopenia

	Not Known	Agranulocytosis
Metabolism and nutrition disorders	Common	Acidosis. The acidosis can usually be corrected by the administration of bicarbonate.
	Uncommon	Hypokalaemia, Metabolic acidosis
	Rare	Appetite disorders, Hyponatraemia, Hyperglycaemia and hypoglycaemia may occasionally occur during long term therapy.
	Very rare	Electrolyte imbalance
	Not known	Thirst
Psychiatric disorders	Uncommon	Depression
	Rare	Confusion
	Very Rare	Irritability, reduced libido
Nervous system disorders	Very common	Paraesthesia, Tingling of extremity
	Uncommon	Dizziness
	Very rare	Headache, Ataxia, Convulsions, Flaccid paralysis, Sensory disturbances
	Not known	Excitement, Occasional instances of drowsiness
Eye disorders	Not known	Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuation of the medication. Choroidal effusion, choroidal detachment
Ear and labyrinth disorders	Uncommon	Impaired hearing and tinnitus
Respiratory, thoracic and mediastinal disorders	Not known	Non-cardiogenic pulmonary oedema
Gastrointestinal disorders	Uncommon	Melaena, Nausea, Vomiting
	Rare	Diarrhoea
	Not known	Taste disturbance
Hepatobiliary disorders	Rare	Fulminant hepatic necrosis, Hepatitis or cholestatic jaundice
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, Rash (including Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
	Rare	Photosensitivity
	Very rare	Thrombocytic purpura
	Not known	acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Uncommon	Osteomalacia with long-term phenytoin therapy
Renal and urinary disorders	Very common	Nephrolithiasis
	Common	Haematuria

	Uncommon	Crystalluria, Renal and ureteral colic, Renal lesions, Renal failure, nephrolithiasis, Calculus formation, Haematuria
	Very rare	Renal tubular necrosis
	Not known	Polyuria, Ureteral pain, Glycosuria
General disorders and administration site conditions	Very rare	Flushing, Fever, Fatigue, Anaphylaxis
Investigations	Uncommon	Abnormal liver function
Injury, poisoning and procedural complications	Not known	Renal injury

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Electrolyte imbalance, development of an acidotic state and central nervous effect might be expected to occur.

Management
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 overdosage when complicated by the presence of renal failure.

No specific antidote.

Treatment should be symptomatic and supportive.

No case of overdose has been reported

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Carbonic anhydrase inhibitors

ATC Code: S01EC01

Mechanism of action

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

Absorption

DIAMOX SR is a sustained release formulation designed to obtain a smooth and continuous clinical response. 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.

Distribution

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.

Elimination

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

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

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. (See section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film coated Pellets:
Microcrystalline Cellulose, sodium Lauryl sulphate, purified water, ethylcellulose, Hydroxypropylmethyl cellulose (E464), mineral oil light and Pigment Blend PB-

230005 Orange [hydroxyl propyl cellulose, titanium dioxide and FD&C Yellow #6/Sunset yellow FCF aluminium lake (15 – 18% grade), Talc and FD&C Yellow #6/Sunset yellow FCF aluminium lake (38 – 42% grade)].

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

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

Blister packs: 36 months
Polypropylene bottles: 24 months

6.4 Special Precautions for Storage

Store below 30 °C

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medical product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd.,

Dashwood House,

69 Old Broad Street,
London, EC2M 1QS,
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

21/10/2024