Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diamox SR 250mg Modified Release Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Acetazolamide 250 mg
Excipient(s) with known effect: Contains FD + C yellow no. 6 (E110)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule.

Hard shell capsule with clear body and orange cap, containing orange spherical pellets.
Capsules are printed GS 250 in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

It is indicated in the treatment of glaucoma.

4.2 Posology and method of administration

Posology

Adults:
One or two 250mg capsules a day.

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

Older people:
Diamox SR should be used with particular caution in older people 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 be reduced by half or the dosage interval should be increased to every 12 hours.

Method of administration

For oral use only.
Capsules should be swallowed whole. Do not chew or crush.

4.3 Contraindications

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

Diamox SR therapy is contra-indicated in cases of marked kidney disease or dysfunction suprarenal gland failure, and hyperchloraemic 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 contraindicated in patients with hypokalaemia 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 intraocular pressure.

Diamox SR should not be used in patients hypersensitive to sulphonamide or other sulphonamide derivatives.

4.4 Special warnings and precautions for use

Risk of suicide
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.

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

Long term therapy
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 Stevens-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
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.

Electrolyte disorder
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 predispose to, electrolyte and acid/bases imbalances, such as patients with impaired renal function (including elderly patients), pulmonary obstruction, emphysema, patients with diabetes mellitus and patients with impaired alveolar ventilation.

Glycaemic disorders
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.

Kidney stones
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.

4.5 Interaction with other medicinal products and other forms of interactions

Diamox SR 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. Adjustments of dose may be required when Diamox SR is given with cardiac glycosides or hypertensive agents. When given concomitantly Dimaox 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 formulation 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: Sulphonamides may give false negative or decreased values for urinary phenolsulphonphthalein 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.

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding:
Diamox SR has been detected in low levels in the milk of lactating women who have taken Diamox SR. 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

Diamox has major 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.

4.8 Undesirable effects

The following undesirable effects have been reported in treatment with acetazolamide.
Undesirable effects are listed by MedDRA System Organ Classes.
Adverse reactions are ranked by frequency of occurrence, 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 available information).*

System organ Class

Blood and lymphatic system disorders
Endocrine disorders
Metabolism and nutrition disorders
Psychiatric disorders
Nervous system disorders
Eye disorders
Ear and labyrinth disorders
Gastrointestinal disorders
Hepatobiliary disorders
Skin and subcutaneous tissue disorders
Musculoskeletal and connective tissue disorders
Renal and urinary disorders
General disorders and administration site conditions
Investigations

Frequency	**Adverse effects**
Not known	- agranulocytosis, - thrombocytopenia, - thrombocytopenic purpura, - leukopenia, - aplastic anaemia, - bone marrow depression, - pancytopenia
Not Known	- hyperglycaemia* - hypoglycaemia*
Not Known	- metabolic acidosis* - electrolyte imbalance* - hypokalaemia*, ** - hyponatraemia* - decreased appetite
Not known	- depression - loss of libido
Not Known	- paraesthesia - peripheral coldness - headache - dizziness - agitation - ataxia - somnolence - confusional state - paralysis flaccid - convulsion
Not known	- myopia***
Not known	- hearing impaired - tinnitus
Not known	- dysgeusia - nausea - vomiting - diarrhoea - melaena - hematochezia
Rare	- hepatitis - jaundice cholestatic - hepatic necrosis****
Rare *Not known*	- photosensitivity reaction - urticaria, - rash, - erythema multiforme,

	- Stevens-Johnson Syndrome - toxic epidermal necrolysis) -acute generalised exanthematous pustulosis (AGEP)
Not known	- arthralgia
Not known	- polyuria - haematuria - glycosuria - crystalluria - calculus formation - renal colic - renal injury - renal failure - nephrolithiasis*****
Not known	- anaphylactic reaction - pyrexia - flushing - fatigue - thirst - irritability
Not known	- liver function test abnormal

* May occasionally occur during long term therapy.
** Generally transient and rarely clinically significant.
***Transient myopia. This condition invariably subsides upon diminution or withdrawal of the medication.
**** Fulminant.
*****Long - term therapy with acetazolamide increases the risk of nephrolithiasis.

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
Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie

4.9 Overdose

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

Management
No specific antidote.
Treatment should be symptomatic and supportive.
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.

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.
The onset, peak and duration of action are 2h, 3-6h and 18-24h respectively.

Distribution:
In humans, 90-95% of acetazolamide in the blood binds 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.

Biotransformation:
Is not metabolised.

Excretion:
Acetazolamide follows a two-compartment pharmacokinetic model. The first phase has an alpha half life of 16h and a 10-12h elimination half-life.
Renal clearance of unbound acetazolamide correlates well with creatinine clearance.
Is excreted by tubular secretion. 47% of the dose is excreted within 24 hours.

5.3 Preclinical safety data

Nothing of note to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film coated pellets:
Microcrystalline cellulose
Sodium laurilsulfate
Ethyl cellulose
Hydroxypropylmethyl cellulose
Paraffin, light liquid
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)].

Capsule shells:
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Erythrosine (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package. Keep the blisters in the outer carton.

6.5 Nature and contents of container

Blister Packs: 28 or 30 capsules/pack.

Opaque UPVC/PVDC blister pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No Special requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 March 1992
Date of last renewal: 20 March 2007

10 DATE OF REVISION OF THE TEXT

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