Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diamox Powder for Solution for Injection 500 mg/vial

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Acetazolamide Sodium equivalent to Acetazolamide 500mg.
Excipient(s) with known effect
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
Sterile, white, lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

DIAMOX is an enzyme inhibitor which acts specifically on carbonic anhydrase. It is indicated in the treatment of:

i) **Glaucoma:** DIAMOX is useful in glaucoma (chronic simple (open angle) glaucoma, secondary glaucoma, and perioperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure) because it acts on inflow, decreasing the amount of aqueous secretion.

ii) **Abnormal retention of fluids:** DIAMOX is a diuretic whose effect is due to the effect on the reversible hydration of carbon dioxide and dehydration of carbonic acid reaction in the kidney. The result is renal loss of HCO^{3-} ion which carries out sodium, water and potassium.
DIAMOX can be used in conjunction with other diuretics when effects on several segments of the nephron are desirable in the treatment of fluid retaining states.

iii) **Epilepsy:** In conjunction with other anticonvulsants best results with DIAMOX have been seen in petit mal in children. Good results, however, have been seen in patients, both children and adults, with other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk patterns etc.

4.2 Posology and method of administration

Posology

i. Glaucoma (simple acute congestive and secondary): Adults: 250 -1,000mg per 24 hours, usually in divided doses. **Children:** The usual total daily dose is 125-750mg in divided doses.
ii. **Abnormal retention of fluid:** Congestive heart failure, drug-induced oedema.
Adults: For diuresis, the starting dose is usually 250 -375mg once daily in the morning. 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 a day.
Best results are often obtained on a regime of 250 -375mg daily for two days, rest a day, and repeat, or merely giving the DIAMOX every other day. The use of DIAMOX does not eliminate the need for other therapy, eg. digitalis, bed rest and salt restriction in congestive heart failure and proper supplementation with elements such as potassium in drug-induced oedema.
For cases of fluid retention associated with pre-menstrual tension, a daily dose (single) of 125-375mg is suggested.
iii. **Epilepsy:**
Adults: 250 -1,000mg daily in divided doses. **Children:** 125 -750mg daily in divided doses **Infants:** 125mg daily in divided doses
Use in Patients with Renal Impairment: acetazolamide is contraindicated in patients with a glomerular filtration rate (GFR) of <10 ml/min (see section 4.3). In patients with renal impairment and GFR of >10 ml/min, the dose should be reduced by half or the dosage interval should be increased to every 12 hours.

Method of administration:

Intravenous or intramuscular. Care should be taken with administration of this medicinal product as it has a high alkaline pH (pH 9.2). Extravasation may cause skin necrosis.

4.3 Contraindications

Hypersensitivity to acetazolamide or to any of the excipients listed in section 6.1.
Since acetazolamide is a sulfonamide derivative, cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.
Acetazolamide therapy is contra-indicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of impaired renal function (GFR <10 ml/min), suprarenal gland failure, and hyperchloraemic acidosis.

DIAMOX should not be used in patients with marked liver disease as evidenced by Child-Pugh classification grade B or C.

In addition, acetazolamide should not be used in patients with cirrhosis, or any hepatic dysfunction that may predispose them to hepatic encephalopathy.
Acetazolamide decreases ammonia clearance. DIAMOX is contraindicated in patients with hypokalaemia and hyponatraemia.

Long-term administration of DIAMOX 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.
Acetazolamide should not be used in patients with hyperchloraemic acidosis or in patients with suprarenal gland failure as acetazolamide may worsen associated metabolic abnormalities.

4.4 Special warnings and precautions for use

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.
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.
There have been reports of increased muscular weakness, occasionally severe, in patients with hypokalaemic periodic paralysis who have taken acetazolamide.
When DIAMOX is prescribed for long-term therapy, special precautions are advisable. The patient should be cautioned to report any unusual skin rash. Periodic blood cell counts, and electrolyte levels are recommended. Fatalities have occurred, although rarely, due to severe reactions to sulphonamides including acetazolamide. Severe reactions may include Stevens-Johnson syndrome and toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias and anaphylaxis. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving acetazolamide. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of DIAMOX 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 hypokalaemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Metabolic acidosis, which can be severe, may occur in the elderly with reduced renal function. In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, DIAMOX may aggravate acidosis and should be used with caution.
The preparation should only be used with particular caution in elderly patients, or those with impaired renal function, or with disorders rendering their electrolyte balance precarious or with liver dysfunction. It may cause acidosis in diabetic patients. 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.
The pH of parenteral acetazolamide is approximately 9.2. Care should be taken during intramuscular injection because of alkaline pH and during intravenous administration of alkaline preparations to avoid extravasation and possible development of skin necrosis.
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

This medicine contains less than 1 mmol sodium (23mg) per dose, i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interactions

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 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, e.g. phenytoin. There have been isolated reports of reduced serum concentrations of primidone and its metabolites and increased carbamazepine serum levels withconcurrent 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:
Sulphonamides may give false negative or decreased values for urinary phenolsulphonphthalein and phenol red elimination values for urinary protein, serum non-protein nitrogen 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 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 should not be used in pregnancy, especially during the first trimester.

Breastfeeding

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 is administered to lactating women.

4.7 Effects on ability to drive and use machines

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. Less commonly, fatigue, dizziness and ataxia have been reported. Disorientation has been observed in a few patients with oedema due to hepatic cirrhosis. Such cases should be under close supervision. Transient myopia has been reported. These conditions invariably subside upon diminution or discontinuance of the medication.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention:
Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Not known	Agranulocytosis, thrombocytopenia, thrombocytopenic purpura, leukopenia, aplastic anaemia, bone marrow depression and pancytopenia.
Immune system disorders	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Not known	Hyperglycaemia and hypoglycaemia1 Metabolic acidosis and electrolyte imbalance including hypokalaemia and hyponatraemia2 Decreased appetite and dysgeusia.3
Psychiatric disorders	Not known	Loss of libido, irritability and depression.
Nervous system disorders	Not known	Paraesthesia, particularly a tingling feeling in the extremities, headache, dizziness, agitation, ataxia, somnolence, confusional state, flaccid paralysis and seizures .3
Eye disorders	Not known	Transient myopia4
Ear and labyrinth disorders	Not known	Impaired hearing and tinnitus.
Vascular disorders	Not known	Flushing
Gastrointestinal disorders	Not known	Nausea, vomiting, diarrhoea and melaena.
Hepatobiliary disorders	Not known	Hepatitis, cholestatic jaundice or hepatic necrosis and hepatic function abnormal .
Skin and subcutaneous tissue disorders	Not known	Urticaria, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) and photosensitivity. Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Not known	Osteomalacia and growth retardation in children.
Renal and urinary disorders	Not known	Polyuria, haematuria, glycosuria crystalluria, nephrolithiasis5, renal colic, renal lesions and renal failure.
General disorders and administration site conditions	Not known	Pyrexia, fatigue, thirst and pain at injection site.

[1] May occasionally occur during long term therapy.
[2] These may occur occasionally during long term therapy. Hypokalaemia is generally transient and is rarely clinically significant.
[3] Adverse reactions during short-term therapy are usually non-serious.
[4] This condition invariably subsides upon diminution or withdrawal of the medication.
[5] 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
HPRA Pharmacovigilance,
Earlsfort Terrace,
IRL - Dublin 2;

Tel: +353 1 6764971;
Fax: +353 1 6762517;
Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptom
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 an inhibitor of carbonic anhydrase inhibitors. By inhibiting the reaction catalysed by this enzyme in the renal tubules, acetazolamide increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, and so promotes alkaline diuresis.

Pharmacodynamic effects
Continuous administration of acetazolamide is associated with metabolic acidosis and resultant loss of diuretic activity. Therefore, the effectiveness of Diamox in diuresis diminishes with continuous use.
By inhibiting carbonic anhydrase in the eye, acetazolamide decreases intra-ocular pressure and is therefore useful in the treatment of glaucoma.

5.2 Pharmacokinetic properties

Distribution
It is tightly bound to carbonic anhydrase and accumulates in tissues containing this enzyme, particularly red blood cells and the renal cortex. It is also bound to plasma proteins.

Elimination
Acetazolamide has been estimated to have a plasma half life of about 4 hours. It is excreted unchanged in the urine, renal clearance being enhanced in the alkaline urine.

5.3 Preclinical safety data

Nothing of note for the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medical products.

6.3 Shelf life

Unopened: 5 years.
After opening, use immediately and discard any remaining contents.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

5ml, Type I Ph. Eur., clear, colourless glass vial with a butyl rubber plug and aluminium ring seal.

6.6 Special precautions for disposal and other handling

Reconstitute each vial of DIAMOX Powder for Solution for Injection 500mg/vial with at least 5ml of water for injection prior to use. For single use only. Discard any remaining contents.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/020/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978
Date of last renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT

February 2020