SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Acetazolamide 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg acetazolamide.

Excipient(s) with known effect:
This product contains 56 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, round, NC, tablets, quarter cut on one side and embossed with "AC" on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

- *Glaucoma:* Acetazolamide 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.
- *Abnormal retention of fluids:* Acetazolamide 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. Acetazolamide 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.
- Epilepsy: In conjunction with other anticonvulsants best results with Acetazolamide 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

i) Glaucoma (simple acute congestive and secondary):

Adults: 250 - 1,000 mg (1-4 tablets) per 24 hours, usually in divided doses for amounts over 250 mg daily.

ii) Abnormal retention of fluid: Congestive heart failure, drug-induced oedema.
Adults: For diuresis, the starting dose is usually 250 – 375 mg (1-1$^1/_2$ tablets) 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 – 375 mg (1-1$^1/_2$ tablets) daily for two days, rest a day, and repeat, or merely giving the Acetazolamide every other day. The use of Acetazolamide 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 125-375 mg is suggested.

iii) Epilepsy:
Adults: 250 - 1,000 mg daily in divided doses.
Children: 8-30 mg/kg in daily divided doses and not to exceed 750 mg/day.
The change from other medication to Acetazolamide should be gradual.
Elderly: Acetazolamide should only 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.

4.3. Contraindications

Acetazolamide is contraindicated in situations in which sodium and/or potassium blood levels are depressed, in cases of marked kidney and liver dysfunction, suprarenal gland failure, and hyper-chloremic acidosis. Acetazolamide should not be used in patients with hepatic cirrhosis as this may increase the risk of hepatic encephalopathy.
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 intraocular pressure.
Acetazolamide should not be used in patients hypersensitive to sulphonamides.

4.4. Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis 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 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.
When Acetazolamide 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. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of Acetazolamide therapy.
In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, Acetazolamide may aggravate acidosis and should be used with caution.
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 generalised 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.

Acetazolamide contains lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products 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 aspirin may result in severe acidosis and increase central nervous system toxicity. 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.
Because of possible additive effects, concomitant use with other carbonic anhydrase inhibitors is not advisable.
By increasing the pH of renal tubule urine, acetazolamide reduces the urinary excretion of amphetamine and quinidine and so may enhance the duration of effect of amphetamines and enhance the effect of quinidine.
Ciclosporin: Acetazolamide may elevate ciclosporin levels.
Methenamine: Acetazolamide may prevent the urinary antiseptic effect of methenamine.
Lithium: Acetazolimide increases lithium excretion and the blood lithium levels may be decreased.
Sodium bicarbonate: Acetazolamide and sodium bicarbonate used concurrently increases the risk of renal calculus formation.

4.6. Fertility, pregnancy and lactation

<u>Pregnancy</u>
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, Acetazolamide should not be used in pregnancy, especially during the first trimester.

Lactation
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.

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

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, depression, reduced libido and occasional instances of drowsiness and confusion. Rarely, photosensitivity has been reported.

During long-term therapy, metabolic acidosis and electrolyte imbalance may occasionally occur. This can usually be corrected by the administration of bicarbonate.
Transient myopia has been reported. This condition invariably subsides upon diminution or withdrawal of the medication.

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

Acetazolamide is a sulphonamide 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.

Skin and subcutaneous tissue disorders:
Not known: acute generalised exanthematous pustulosis (AGEP)

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 national reporting system.

4.9. Overdose

No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antiglaucoma preparations and miotics.
ATC code: S01EC01

Acetazolamide is an inhibitor of carbonic anhydrase. 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.
Continuous administration of acetazolamide is associated with metabolic acidosis and resultant loss of diuretic activity. Therefore, the effectiveness of Acetazolamide 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

Acetazolamide is fairly rapidly absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 2 hours after administration by mouth. It has been estimated to have a plasma half-life of about 4 hours. 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. It is excreted unchanged in the urine; renal clearance being enhanced in alkaline urine.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Povidone
Glycerol
Microcrystalline cellulose
Sodium starch glycolate
Lactose monohydrate
Maize starch

Colloidal silicon dioxide
Magnesium stearate
Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 Years.

6.4. Special precautions for storage

Store below 25 ºC. Protect from light and moisture.

6.5. Nature and contents of container

PVC/Aluminium blisters. Pack size of 100 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Strt., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

06390/07568/NMR/2019

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 25 July 2021
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

05/07/2023