SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acetazolamide Tablets 250 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of Acetazolamide.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Acetazolamide Tablets are presented as white flat bevelled edge tablets engraved with R and crescent moon logo on one side and A / 303 either side of a break-line on the other.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acetazolamide Tablets 250 mg are indicated in the treatment of

1. 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. Acetazolamide acts on inflow, decreasing the amount of aqueous secretion.

2. Abnormal retention of fluids

Acetazolamide acts on the reversible hydration of carbon dioxide and hydration of the carbonic acid reaction in the kidney resulting in renal loss of bicarbonate ion which carries out sodium, water and potassium.

It 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.

3. Epilepsy

When used in conjunction with other anticonvulsants best results have been seen in petit mal in children. Good results have been seen in both children and adults with grand mal, mixed seizure patterns and myoclonic jerk patterns.

4.2 Posology and method of administration

Route of administration Oral

Dosage

1. Glaucoma (simple acute congestive and secondary)

Adults: 1-4 tablets, daily, in divided doses for amounts over 250 mg daily.

2. Abnormal retention of fluid: congestive heart failure
drug - induced oedema

Adults: initially 1 - 1½ tablets once daily in the morning

If after an initial response, 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 obtained on a regime of 1 - 1½ tablets daily for two days, rest a day and repeat, or merely on alternate days.

The use of acetazolamide does not eliminate the need for other therapy e.g.. digitalis, bed rest and salt restriction in congestive heart failure and proper supplementation with elements such as potassium in drug-induced oedema.

In cases of fluid retention associated with pre-menstrual tension, a daily dose of 125 - 375mg is suggested.

3. Epilepsy

Adults: 250 - 1000 mg daily in divided doses

Children: 8 - 30 mg / kg body-weight daily in divided doses, and not to exceed 750 mg daily.

The change from other preparations to acetazolamide should be gradual.

Elderly:

Caution should be exercised in using acetazolamide in elderly patients or those with potential obstruction in the urinary tract or with disorders disrupting their electrolyte balance or with liver dysfunction.

4.3 Contraindications

Known hypersensitivity to acetazolamide, sulphonamides or any of the ingredients.

Depressed sodium and/or potassium blood serum levels.

Marked kidney and liver disease or dysfunction.

Suprarenal gland failure, and hyper chloremic acidosis.

Should not be used in patients with hepatic cirrhosis as this may increase the risk of hepatic encephalopathy.

Long term therapy is contraindicated in patients with chronic congestive angle-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

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic 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 acetazolamide dose does not increase the diuresis and it 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.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, cetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

Periodic monitoring of 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 diminution or cessation of acetazolamide therapy.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, acetazolamide which may aggravate acidosis, should be used with caution.

Patients with a past history of renal calculi should be warned that acetazolamide may cause further renal calculi.

4.5 Interaction with other medicinal products and other forms of interaction

When given concurrently, 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.

Concurrent administration with high dose aspirin may potentiate the adverse reactions of acetazolamide. Adjustment of dose may be required when acetazolamide is given with cardiac glycosides or hypertensive agents. It can potentiate the effects of folic acid antagonists, hypoglycaemics and oral anticoagulants.

Ciclosporin; Acetazolamide may elevate ciclosporin levels.

Methanamine: Acetazolamide may prevent the urinary antiseptic effect of methanamine.

Lithium: Acetazolamide increases lithium excretion and the blood lithium levels may be decreased.

Sodium bicarbonate: Acetazolamide and sodium bicarbonate used concurrently increases the risk of renal calculi.

4.6 Pregnancy and lactation

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.

Acetazolamide has been detected in low levels in the milk of lactating women who have taken this drug. 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 necrosis. 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 reported side effects include paraesthesia, particularly a tingling feeling in the extremities, some loss of appetite, altered taste sensation, polyuria, polydipsia, flushing, thirst, headache, dizziness, fatigue, irritability, depression, reduced libido and occasional instances of drowsiness and confusion. Rarely photosensitivity has been reported.

Transient myopia has been reported which invariably subsides upon reduction or withdrawal of the drug.

During long term therapy, metabolic acidosis and electrolyte imbalance may occasionally occur. This can usually be corrected by the administration of bicarbonate.

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

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

Acetazolamide being a sulphonamide derivative may occasionally cause 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 have been reported. Rarely, fulminant hepatic necrosis has been reported.

Other adverse reactions reported occasionally include urticaria, melena, haematuria, glycosuria, impaired hearing and tinnitus, abnormal liver function, renal failure and rarely, hepatitis or cholestatic jaundice, flaccid paralysis and convulsions.

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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There is no specific antidote. Supportive measures with correction of electrolyte and fluid balance are helpful. Symptomatic treatment should be carried out.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Carbonic anhydrase inhibitors, acetazolamide
ATC code: S01E C01

5.1 Pharmacodynamic properties

Acetazolamide is a potent, reversible inhibitor of carbonic anhydrase. The enzyme catalyses the hydration of carbon dioxide and dehydration of carbonic acid.

Action on the kidney: Following the administration of acetazolamide, the urine volume promptly increases. The normally acidic pH becomes alkaline. The urinary concentration of the bicarbonate anion increases and is matched by sodium and substantial amounts of potassium.

The urinary concentration of chloride falls. The increased alkalinity of the urine is necessarily accompanied by a decrease in the excretion of titratable acid and of ammonia.

The above sequence of events may be attributed to the inhibition of H^+ secretion by the renal tubule. This inhibition is indirect in the proximal tubule, is the consequence of inhibition of cytoplasmic carbonic anhydrase, which decreases the availability of protons $Na^+ - H^+$ exchange. In addition, carbonic anhydrase bound to the brush-border membrane is also inhibited. This slows the dehydration of carbonic acid in the lumen and, thereby, the diffusion of CO_2 into the tubular cell. The overall effect is that bicarbonate reabsorption in proximal tubule is reduced by some 80%. More than half of this rejected bicarbonate is reabsorbed in later segments of the nephron by mechanisms that do not involve carbonic anhydrase and that are not yet fully characterised. Acetazolamide also inhibits H^+ secretion by some segments of the distal nephron. These distal mechanisms, which have a lower capacity than do those in the proximal tubule, apparently depend on the cytoplasmic form of carbonic anhydrase but not on the membrane-bound form of the enzyme.

Effect on plasma composition: Acetazolamide increases the urinary excretion of bicarbonate and fixed cation, mostly sodium. As a result, the concentration of bicarbonate in the extracellular fluid decreases and metabolic acidosis results. In metabolic acidosis, the renal response to acetazolamide is greatly reduced; conversely, it is enhanced with metabolic alkalosis. Factors other than the amount of filtered bicarbonate must be determinants of drug action since the extracellular alkalosis of potassium depletion (with presumed intracellular acidosis) decreases the diuretic response.

Acetazolamide produces a marked increase in potassium excretion, attributable to enhanced secretion in the distal nephron. The effects on potassium are most prominent in acute experiments.

Eye: The presence of carbonic anhydrase in a number of intraocular structures, including the ciliary processes, and the high concentration of bicarbonate in the aqueous humour have focussed attention on the role that the enzyme might play in the secretion of aqueous humor. Acetazolamide reduces the rate of aqueous humor formation; intraocular pressure in patients with glaucoma is correspondingly reduced. This action of the drug appears to be independent of systemic acid-base balance.

Central nervous system: An action of acetazolamide on the CNS was first suggested by the frequency of paraesthesias and somnolence as side effects. Subsequently, the drug was found to inhibit epileptic seizures and to decrease the rate of formation of spinal fluid. Metabolic acidosis from ketogenic diets diminishes epileptic seizures, and acetazolamide by virtue of its action on the kidney leads to the production of a systemic acidosis. However, there is undoubtedly a more direct action on CNS function. And increase in local CO2 tension may result from inhibition of the enzyme in the brain, the choroid plexus, or the erythrocytes of the cerebral blood. The exact role of carbonic anhydrase in brain function remains unknown. The concentration of the

enzyme varies from one site to another within the brain. Acetazolamide may reduce the rate of cerebrospinal fluid formation by the choroid plexus, but it may also transiently elevate cerebrospinal fluid pressure as a result of an increase in intracranial blood flow.

5.2 Pharmacokinetic properties

Acetazolamide is readily absorbed from the gastrointestinal tract. Peak concentration in plasma occur within about 2 hours and effective plasma concentration persists for up to 12 hours. It is reported to be extensively bound to plasma proteins. Acetazolamide is tightly bound to plasma proteins. Acetazolamide is tightly bound to carbonic anhydrase and hence, present in greater amounts in those tissues in which the enzyme is present in high concentration, particularly the erythrocytes and the renal cortex. Some carbonic anhydrase inhibitors do not penetrate the erythrocyte. It is not metabolised.

It is excreted by the kidney both by active tubular secretion and passive reabsorption are involved. Excretion is complete within 24 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to that already included in other sections of the SPC.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dicalcium phosphate
Maize starch
Pregelatinised maize starch
Magnesium Stearate
Sodium starch glycolate Type A

6.2 Incompatibilities

None reported.

6.3 Shelf life

Opaque plastic containers: 36 months.
Blister packing: 24 months.

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Store in container provided and protect from heat, light and moisture.

6.5 Nature and contents of container

1. Opaque plastic containers composed of polypropylene tubes and polyethylene tamper evident closures for pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100 and 112.

3. Blister packs of aluminium/opaque PVC, it is subsequently packed in printed boxboard cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112.

6.6 Instructions for use/handling

No special instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER

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RG25 3ED
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8. MARKETING AUTHORISATION NUMBER

PL 20416/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 January 2004

10 DATE OF REVISION OF THE TEXT

03/01/2018