SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acetazolamide Tillomed 500 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains acetazolamide 500 mg.

Excipients with known effect:

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

White powder for solution for injection.

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:

i) Glaucoma: Acetazolamide injection 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: Acetazolamide injection 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 a renal loss of HCO3- ion which carries out sodium,
water and potassium.

Acetazolamide injection 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 Acetazolamide injection 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 - 1000mg per 24 hours, usually in divided doses for amounts over 250mg daily.

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 Acetazolamide injection every other day. The use of Acetazolamide injection 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.

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

iii) Epilepsy

Adults: 250 - 1000mg daily in divided doses.

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

The change from other medication to Acetazolamide injection should be gradual.

Elderly: Acetazolamide injection 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.

For reconstitution please refer to section to section 6.6 below.

Method of Administration

Intravenous or intramuscular injection. The direct intravenous route is preferred as intramuscular use is limited by the alkaline pH of the solution.

4.3 Contraindications

Hypersensitivity to acetazolamide or to any of the excipients listed in section 6.1. Acetazolamide injection should not be used in patients hypersensitive to sulphonamides.
Acetazolamide injection 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 injection should not be used in patients with hepatic cirrhosis as this may increase the risk of hepatic encephalopathy.
Long-term administration of Acetazolamide injection 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 lower intraocular 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 injection.

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. When Acetazolamide injection 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, 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 injection therapy.

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 or emphysema patients with diabetes mellitus and patients with impaired alveolar ventilation may be impaired. Severe metabolic

acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates.

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.

In patients with a past history of renal calculi, benefit should be balanced against the risks of precipitating further calculi.

The pH of parenteral acetazolamide is 9.1. Care should be taken during intravenous administration of alkaline preparations to avoid extravasation and possible development of skin necrosis.

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.

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. Concurrent administration of acetazolamide and aspirin may result in severe acidosis and increase central nervous system toxicity. Adjustments of dose may be required when Acetazolamide injection 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 with other carbonic anhydrase inhibitors, concomitant use is not advisable.

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.

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, Acetazolamide injection should not be used in pregnancy, especially during the first trimester.

Breast-feeding
Acetazolamide has been detected in low levels in the milk of lactating women who have taken acetazolamide injection. Although it is unlikely that this will lead to any harmful effects in the infant, extreme caution should be exercised when Acetazolamide injection 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[1]
Immune system disorders	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Not known	Metabolic acidosis and electrolyte imbalance.[2] Decreased appetite, hyponatraemia, hyperglycaemia, hypoglycaemia .
Psychiatric disorders	Not known	Loss of libido, irritability confusional state and depression.[3]
Nervous system disorders	Not known	Paraesthesia, particularly a tingling feeling in the extremities, headache, dizziness, ataxia , somnolence and dysgeusia.[3] Flaccid paralysis and seizures.
Eye disorders	Not known	Transient myopia[4], choroidal effusion, choroidal detachment
Ear and labyrinth disorders	Not known	Impaired hearing and tinnitus
Vascular disorders	Not known	flushing
Respiratory, thoracic and mediastinal disorders	Not known	Non-cardiogenic pulmonary oedema
Gastrointestinal disorders	Not known	Nausea, vomiting, diarrhoea and melaena
Hepatobiliary disorders	Not known	Hepatic necrosis, hepatic function abnormal, and hepatitis or cholestatic jaundice
Skin and subcutaneous tissue disorders	Not known	Urticaria, Rash (including Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis),

		Thrombocytic purpura, Photosensitivity.[3] acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Not known	Haematuria, polyuria, glycosuria crystalluria, nephrolithiasis, renal colic and renal lesions.[1]
General disorders and administration site conditions	Not known	Flushing, fatigue, thirst Pyrexia.[1]

[1] Acetazolamide is a sulphonamide derivative and therefore some side effects similar to those caused by sulphonamides have occasionally been reported.
[2] During long-term therapy, metabolic acidosis and electrolyte imbalance may occasionally occur. This can usually be corrected by the administration of bicarbonate.
[3] Adverse reactions during short-term therapy are usually non-serious.
[4] The condition invariably subsides upon diminution or discontinuation of the medication.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Management

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

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. 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 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

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 to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

None.

6.3. Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C

Use within 12 hours of reconstitution. Contains no preservative. Discard unused portion. Reconstituted solution should be stored in refrigerator at 2°C - 8°C.

6.5 Nature and contents of container

Clear glass vial with dark grey rubber stopper and green colored MT flip-off seal.
Pack size 500mg/vial.

6.6 Special precautions for disposal

Reconstitute each vial of Acetazolamide Injection with at least 5ml of water for injection prior to use. The reconstituted solution is clear and colourless and does not contain an antimicrobial preservative. Any unused solution can be stored in a refrigerator for up to 12 hours but any solution not used within this period must be discarded.

The direct intravenous route of administration is preferred. Intramuscular injection may be employed but is painful due to the alkaline pH of the solution

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 1311/0741

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10/04/2025