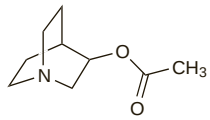
Aceclidine *(USAN, rINN)*

Aceclidina; Acéclidine; Aceclidinum. 1-Azabicyclo[2.2.2]octan-3-ol acetate; 3-Quinuclidinol acetate; 3-Acetoxyquinuclidine.

Ацеклидин

$C_9H_{15}NO_2$ = 169.2.
CAS — 827-61-2.
ATC — S01EB08.
ATC Vet — QS01EB08.



Aceclidine Hydrochloride *(rINNM)*

Acéclidine, Chlorhydrate d'; Aceclidini Hydrochloridum; Hidrocloruro de aceclidina.

Ацеклидина Гидрохлорид

$C_9H_{15}NO_2$,HCl = 205.7.
CAS — 6109-70-2.
ATC — S01EB08.
ATC Vet — QS01EB08.

Profile

Aceclidine hydrochloride is a parasympathomimetic miotic (see Pilocarpine, p.1884) that is a cholinergic agonist. It has been used in eye drops to lower intra-ocular pressure in patients with glaucoma.

Use. Aceclidine has been tried for the management of disturbances of night vision after laser refractive surgery.[1]

1. Randazzo A, *et al*. Pharmacological management of night vision disturbances after refractive surgery: results of a randomized clinical trial. *J Cataract Refract Surg* 2005; **31:** 1764–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Glaucostat†; Glaunorm; ***Ital.:*** Glaunorm; ***Neth.:*** Glaucocare†; ***Port.:*** Glaucostat†.

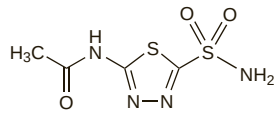
Multi-ingredient: ***Ital.:*** Glautimol.

Acetazolamide *(BAN, rINN)* ⊗

Acetazolam; Acetazolamid; Acetazolamida; Acetazolamidas; Acétazolamide; Acetazolamidum; Asetatsoliamidi; Asetazolamid. 5-Acetamido-1,3,4-thiadiazole-2-sulphonamide; *N*-(5-Sulphamoyl-1,3,4-thiadiazol-2-yl)acetamide.

Ацетазоламид

$C_4H_6N_4O_3S_2$ = 222.2.
CAS — 59-66-5.
ATC — S01EC01.
ATC Vet — QS01EC01.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*
Ph. Eur. 6.2 (Acetazolamide). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.
USP 31 (Acetazolamide). A white to faintly yellowish-white, odourless, crystalline powder. Very slightly soluble in water; sparingly soluble in practically boiling water; slightly soluble in alcohol. Store in airtight containers.

Acetazolamide Sodium *(BANM, rINNM)* ⊗

Acetazolamida sódica; Acétazolamide Sodique; Natrii Acetazolamidum; Sodium Acetazolamide.

Натрий Ацетазоламид

$C_4H_5N_4NaO_3S_2$ = 244.2.
CAS — 1424-27-7.
ATC — S01EC01.
ATC Vet — QS01EC01.

Stability. Solutions of acetazolamide sodium in glucose 5% and sodium chloride 0.9% were stable for 5 days at 25° with a loss of potency of less than 7.2%.[1] At 5° the loss of potency in both solutions was less than 6% after 44 days of storage. Small reductions in pH were recorded, possibly due to the formation of acetic acid during the decomposition of acetazolamide. At –10° the loss in potency after 44 days of storage was less than 3% in both solutions. Results were similar in samples thawed in tap water and in a microwave oven.

An oral suspension of acetazolamide 25 mg/mL prepared from tablets with the aid of sorbitol solution 70% was stable for at least 79 days at 5°, 22°, and 30°. It was recommended that the formulation be maintained at pH 4 to 5 and stored in amber glass bottles.[2]

1. Parasrampuria J, *et al*. Stability of acetazolamide sodium in 5% dextrose or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1987; **44:** 358–60.
2. Alexander KS, *et al.* Stability of acetazolamide in suspension compounded from tablets. *Am J Hosp Pharm* 1991; **48:** 1241–4.

Adverse Effects

Common adverse effects of acetazolamide are malaise, fatigue, depression, excitement, headache, weight loss, and gastrointestinal disturbances. Drowsiness and paraesthesia involving numbness and tingling of the face and extremities are also common with high doses in particular. Diuresis can be troublesome, but generally abates after a few days of continuous therapy. Acidosis may develop during treatment and is generally mild but severe metabolic acidosis has occasionally been reported, especially in elderly or diabetic patients or those with renal impairment. Electrolyte imbalances including hyponatraemia and hypokalaemia may occasionally occur; hypokalaemia is generally transient and rarely clinically significant.

Blood dyscrasias occur rarely and may include aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, and thrombocytopenic purpura. Acetazolamide can give rise to crystalluria, renal calculi, and renal colic; renal lesions, possibly due to a hypersensitivity reaction, have also been reported.

Other adverse reactions include allergic skin reactions, fever, thirst, dizziness, ataxia, irritability, confusion, reduced libido, haematuria, glycosuria, renal failure, abnormal liver function tests, loss of appetite, alterations in taste, transient myopia, and tinnitus and hearing disturbances. Rare reactions include photosensitivity, hepatitis or cholestatic jaundice, flaccid paralysis, and convulsions.

Intramuscular injections are painful owing to the alkalinity of the solution.

Effects on the blood. Severe, often fatal, blood dyscrasias have been reported in patients taking acetazolamide. By 1989, the National Registry of Drug-Induced Ocular Side Effects in the USA[1] had received reports of haematological reactions possibly due to carbonic anhydrase inhibitors in 139 patients, of which 50 cases (36%) were fatal. Most deaths were due to aplastic anaemia. Over half the reactions occurred during the first 6 months of therapy. The value of periodic blood analysis in patients taking carbonic anhydrase inhibitors for prolonged periods has been debated[2-7] but is advised by licensed product information. The US National Registry has recommended[8] that initial and 6-monthly blood analysis should be undertaken.

1. Fraunfelder FT, Bagby GC. Possible hematologic reactions associated with carbonic anhydrase inhibitors. *JAMA* 1989; **261:** 2257.
2. Alm A, *et al.* Monitoring acetazolamide treatment. *Acta Ophthalmol (Copenh)* 1982; **60:** 24–34.
3. Johnson T, Kass MA. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1986; **101:** 128–9.
4. Zimran A, Beutler E. Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts? *Am J Ophthalmol* 1987; **104:** 654–8.
5. Lichter PR. Carbonic anhydrase inhibitors, blood dyscrasias, and standard-of-care. *Ophthalmology* 1988; **95:** 711–12.
6. Mogk LG, Cyrlin MN. Blood dyscrasias and carbonic anhydrase inhibitors. *Ophthalmology* 1988; **95:** 768–71.
7. Miller RD. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 745–6.
8. Fraunfelder FT, *et al*. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 79–81.

Effects on electrolyte balance. Acetazolamide has been reported to cause symptomatic metabolic acidosis in the elderly, in diabetic patients, and in those with renal impairment.[1-6] Raised plasma-acetazolamide concentrations have been reported in elderly patients, probably attributable to reduced renal function, and in 6 of 9 glaucoma patients this was associated with hyperchloraemic metabolic acidosis.[7] A single-dose study[8] in 4 elderly patients found that reduced acetazolamide clearance correlated with renal function. Urea and electrolyte concentrations should be measured before and during treatment with acetazolamide, particularly in the elderly and in other patients, such as diabetics, who may have renal impairment.

1. Maisey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1981; **283:** 1527–8.
2. Goodfield M, *et al.* Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; **284:** 422.
3. Reid W, Harrower ADB. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; **284:** 1114.
4. Heller I, *et al.* Significant metabolic acidosis induced by acetazolamide: not a rare complication. *Arch Intern Med* 1985; **145:** 1815–17.
5. Parker WA, Atkinson B. Acetazolamide therapy and acid-base disturbance. *Can J Hosp Pharm* 1987; **40:** 31–4.
6. Zaidi FH, Kinnear PE. Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes. *Br J Ophthalmol* 2004; **88:** 714–15.
7. Chapron DJ, *et al.* Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.
8. Chapron DJ, *et al.* Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.

Effects on endocrine function. Hirsutism occurred in a 2½-year-old girl after treatment for 16 months with acetazolamide for congenital glaucoma.[1] There was no evidence of virilisation.

1. Weiss IS. Hirsutism after chronic administration of acetazolamide. *Am J Ophthalmol* 1974; **78:** 327–8.

Effects on the kidneys. Large reductions in glomerular filtration rate occurred during treatment with carbonic anhydrase inhibitors in 3 type 1 diabetics with nephropathy and glaucoma.[1] Kidney function improved when the drug was withdrawn.

1. Skøtt P, *et al*. Effect of carbonic anhydrase inhibitors on glomerular filtration rate in diabetic nephropathy. *BMJ* 1987; **294:** 549.

Effects on the liver. For a report of liver damage associated with use of acetazolamide, see Hypersensitivity, below.

Effects on the skin. Rashes, including severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported during acetazolamide therapy; the fact that acetazolamide is a sulfonamide-derivative has been suggested as a cause for these reactions. Photosensitivity has also been noted rarely.

Severe exacerbation of rosacea occurred in a patient taking acetazolamide for glaucoma; the rosacea improved on withdrawal of acetazolamide and relapsed again on its reintroduction.[1]

1. Shah P, *et al.* Severe exacerbation of rosacea by oral acetazolamide. *Br J Dermatol* 1993; **129:** 647–8.

Extravasation. Extravasation was reported in a patient after intravenous acetazolamide and led to severe ulceration requiring surgery to repair the skin defect.[1] It was recommended that 1 to 2 mL of sodium citrate 3.8% should be injected subcutaneously near the site of extravasation in order to neutralise the alkaline effects of the acetazolamide injection.

1. Callear A, Kirkby G. Extravasation of acetazolamide. *Br J Ophthalmol* 1994; **78:** 731.

Hypersensitivity. A 54-year-old man with glaucoma who was treated with acetazolamide 500 mg daily for 26 days developed a generalised erythematous rash and became delirious, dehydrated, markedly jaundiced, with peripheral circulatory failure, and died from cholestatic jaundice with hepatic coma and anuria.[1] Drug-induced hypersensitivity and hepatitis due to acetazolamide was suspected.

Anaphylaxis has also been reported[2] after a single oral dose in a patient who had not previously received acetazolamide. However, the patient was hypersensitive to sulfonamides and the reaction may have been caused by cross-sensitivity.

1. Kristinsson A. Fatal reaction to acetazolamide. *Br J Ophthalmol* 1967; **51:** 348–9.
2. Tzanakis N, *et al.* Anaphylactic shock after a single oral intake of acetazolamide. *Br J Ophthalmol* 1998; **82:** 588.

Precautions

Acetazolamide is contra-indicated in the presence of sodium or potassium depletion, in hyperchloraemic acidosis, in conditions such as Addison's disease and adrenocortical insufficiency, and in marked hepatic or renal impairment. Encephalopathy may be precipitated in patients with hepatic dysfunction. It should not be used in chronic angle-closure glaucoma since it may mask deterioration of the condition. Since acetazolamide is a sulfonamide derivative, it should not be used in patients with a history of sulfonamide hypersensitivity.

Acetazolamide should be given with care to patients likely to develop acidosis or with diabetes mellitus; severe metabolic acidosis may occur in the elderly, and in patients with renal impairment, pulmonary obstruction, or emphysema. Acetazolamide may increase the risk of hyperglycaemia in diabetic patients.

Periodic monitoring of plasma electrolytes and blood count is recommended during long-term therapy and patients should be cautioned to report any unusual skin rashes. Acetazolamide is teratogenic in *animals*.

Some adverse effects such as drowsiness and myopia may affect a patient's ability to perform skilled tasks including driving.

Breast feeding. Acetazolamide has been detected in breast milk.[1] However, there have been no reports of adverse effects in breast-fed infants whose mothers were receiving acetazolamide