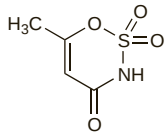
30. Khaw K-T, *et al.* Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. *Lancet* 2001; **357:** 657–63.
31. Ingraham BA, *et al.* Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin* 2008; **24:** 139–49.
32. Bairati I, *et al.* A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. *J Natl Cancer Inst* 2005; **97:** 481–8.
33. Heinonen OP, *et al.* Prostate cancer and supplementation with α-tocopherol and β-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst* 1998; **90:** 440–6.
34. Giovannucci E, *et al.* Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Intern Med* 1998; **129:** 517–24.
35. Willett WC. Diet and cancer: one view at the start of the millennium. *Cancer Epidemiol Biomarkers Prev* 2001; **10:** 3–8.
36. Zhang S, *et al.* A prospective study of folate intake and the risk of breast cancer. *JAMA* 1999; **281:** 1632–7.
37. US Preventive Services Task Force. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Intern Med* 2003; **139:** 51–5.

Acesulfame Potassium *(BANM, rINNM)*

Acesulfam draselná sůl; Acesulfam potasowy; Acesulfame K; Acésulfame potassique; Acesulfamkalium; Acesulfamo kalio druska; Acesulfamo potásico; Acesulfamum kalicum; Aceszulfámkálium; Asesulfaamikalium; E950; H73-3293; H-733293; Hoe-095K; Kalii Acesulfamum. 6-Methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide potassium.

Калия Ацесульфам

$C_4H_4KNO_4S$ = 201.2.
CAS — 55589-62-3.



(acesulfame)

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Acesulfame Potassium). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone.
USNF 26 (Acesulfame Potassium). A white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

Profile

Acesulfame potassium is an intense sweetener about 200 times as sweet as sucrose. It is used in beverages, cosmetics, pharmaceuticals, and foods and does not appear to be affected by cooking.

Preparations

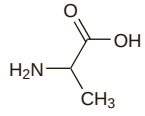
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Equalsweet; Genser Sweet; Rondo Sweet; ***Chile:*** Marco Sweet Light; ***UK:*** Sweet 'n Low; ***Venez.:*** Hermesetas Gold; Sweet 'n' Low†.

Alanine *(USAN, rINN)*

A; Ala; Alaniini; Alanin; Alanina; Alaninas; L-Alanine; Alaninum; NSC-206315. L-2-Aminopropionic acid.

Аланин

$C_3H_7NO_2$ = 89.09.
CAS — 56-41-7.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Alanine). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.
USP 31 (Alanine). White, odourless, crystals or crystalline powder. Freely soluble in water; slightly soluble in 80% alcohol; insoluble in ether. pH of a 5% solution in water is between 5.5 and 7.0. Store in airtight containers.

Profile

Alanine is an aliphatic non-essential amino acid. It is used as a dietary supplement. The dipeptide *N*(2)-L-alanyl-L-glutamine is used similarly.

Hypoglycaemia. References to the investigational use of alanine in the management of insulin-induced hypoglycaemia.[1-4]

1. Wiethop BV, Cryer PE. Glycemic actions of alanine and terbutaline in IDDM. *Diabetes Care* 1993; **16:** 1124–30.
2. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; **16:** 1131–6.
3. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; **20:** 1231–6.
4. Evans ML, *et al.* Alanine infusion during hypoglycaemia partly supports cognitive performance in healthy human subjects. *Diabet Med* 2004; **21:** 440–6.

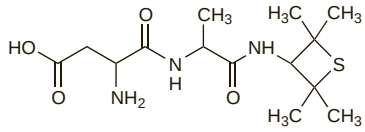
Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Abufene; ***Singapore:*** Abufene.
Multi-ingredient: ***Arg.:*** Normoprost Compuesto; ***Ital.:*** Chetonex; ***Spain:*** Tebetane Compuesto.

Alitame *(USAN)*

CP-54802. (3*S*)-Amino-*N*-{(1*R*)-1-[(2,2,4,4-tetramethyl-3-thietanyl) carbamoyl] ethyl} succinamic acid hydrate.

$C_{14}H_{25}N_3O_4S.2/H_2O$ = 376.5.
CAS — 80863-62-3 (anhydrous alitame); 99016-42-9 (alitame hydrate).



(anhydrous alitame)

Profile

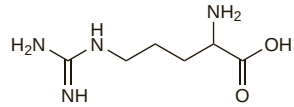
Alitame is an intense sweetener used in foods. It is about 2000 times sweeter than sucrose.

Arginine *(rINN)*

Arg; Arginiini; Arginin; Arginina; Argininas; L-Arginine; Argininum; R. L-2-Amino-5-guanidinovaleric acid.

Аргинин

$C_6H_{14}N_4O_2$ = 174.2.
CAS — 74-79-3.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Arginine). A white or almost white crystalline powder, or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.
USP 31 (Arginine). White, practically odourless crystals. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Arginine Aspartate

Arginiiniaspartaatti; Arginina, aspartato de; Argininaspartat; Arginin-aspartát; Arginine, aspartate d'; Arginini aspartas; Arginino aspartatas; Asparginінum. (2*S*)-2-Amino-5-guanidinopentanoic acid (2*S*)-2-aminobutanedioate.

$C_{10}H_{21}N_5O_6$ = 307.3.
CAS — 7675-83-4.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Arginine Aspartate). White or almost white granules or powder. Very soluble in water, practically insoluble in alcohol and in dichloromethane.

Arginine Glutamate *(BAN, USAN, rINNM)*

Arginine, Glutamate d'; Arginini Glutamas; Glutamato de arginina. L-Arginine L-glutamate.

Аргинина Глутамат

$C_6H_{14}N_4O_2.C_5H_9NO_4$ = 321.3.
CAS — 4320-30-3.
ATC — A05BA01.
ATC Vet — QA05BA01.

Arginine Hydrochloride *(USAN, rINNM)*

Argininihydrokloridi; Arginine, chlorhydrate d'; L-Arginine Monohydrochloride; Arginin-hidroklorid; Arginin-hydrochlorid; Arginhydroklorid; Arginini hydrochloridum; Arginino hidrochloridas; Hidrocloruro de arginina.

Аргинина Гидрохлорид

$C_6H_{14}N_4O_2.HCl$ = 210.7.
CAS — 1119-34-2.
ATC — B05XB01.
ATC Vet — QB05XB01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Arginine Hydrochloride). A white or almost white crystalline powder, or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.
USP 31 (Arginine Hydrochloride). White, practically odourless, crystals or crystalline powder. Freely soluble in water.

Adverse Effects and Precautions

Nausea, vomiting, flushing, headache, numbness, and local venous irritation may occur if arginine solutions are infused too rapidly. Elevated plasma-potassium concentrations have been reported in uraemic patients and arginine should therefore be used with caution in patients with renal disease or anuria. Arginine hydrochloride should be given cautiously to patients with electrolyte disturbances as its high chloride content could lead to the development of hyperchloraemic acidosis.

Extravasation. Full-thickness skin necrosis has been reported[1,2] after extravasation of a 10% solution of arginine hydrochloride. Both osmotic and local hyperkalaemic effects have been proposed as a mechanism for the injury.[1]

1. Bowlby HA, Elanjian SI. Necrosis caused by extravasation of arginine hydrochloride. *Ann Pharmacother* 1992; **26:** 263–4.
2. Salameh Y, Shoufani A. Full-thickness skin necrosis after arginine extravasation—a case report and review of literature. *J Pediatr Surg* 2004; **39:** E9–E11.

Hyperkalaemia. Two alcoholic patients with severe liver disease and moderate renal insufficiency developed severe hyperkalaemia when given arginine hydrochloride and one died.[1] Both patients had received a total of 300 mg of spironolactone some time before arginine hydrochloride, but the contribution of spironolactone to the hyperkalaemia was not known. In a study to investigate the mechanism of metabolic changes due to arginine, plasma-potassium concentrations were found to be significantly higher in diabetic subjects than those for normal subjects, leading the authors to suppose that while arginine-induced hyperkalaemia may be promoted by low insulin blood levels, it could not be attributed to glucagon, pH changes, or aldosterone inhibition.[2]

In another fatal case due to an overdose of arginine,[3] a 21-month-old girl developed an acute metabolic acidosis with transient but severe hyponatraemia, and irreversible brain death; no hyperkalaemia was observed. Unlike the previously reported case, the patient had normal renal function, and the authors supposed the absence of hyperkalaemia to be due to a rapid increase in renal potassium excretion.

1. Bushinsky DA, Gennari FJ. Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 1978; **89:** 632–4.
2. Massara F, *et al.* The risk of pronounced hyperkalaemia after arginine infusion in the diabetic subject. *Diabete Metab* 1981; **7:** 149–53.
3. Gerard JM, Luisiri A. A fatal overdose of arginine hydrochloride. *J Toxicol Clin Toxicol* 1997; **35:** 621–5.

Hypersensitivity. There are 2 reports of anaphylactic reactions shortly after the start of infusions of arginine 5 or 10% given to test growth-hormone output.[1,2] Anaphylaxis to arginine was considered to be a very rare event and only one other apparent allergic reaction had been reported to the manufacturers.

1. Tiwary CM, *et al.* Anaphylactic reaction to arginine infusion. *N Engl J Med* 1973; **288:** 218.
2. Resnick DJ, *et al.* Case report of an anaphylactoid reaction to arginine. *Ann Allergy Asthma Immunol* 2002; **88:** 67–8.

Myocardial infarction. A placebo-controlled trial investigated whether the addition of arginine to standard therapy after myocardial infarction would decrease vascular stiffness and improve left ventricular function. The study was stopped early due to an increased number of deaths in the arginine group. The authors commented that, while the results could be due to chance, nevertheless arginine should not be given to patients after a myocardial infarction.[1]

1. Schulman SP, *et al.* -Arginine therapy in acute myocardial infarction: the Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* 2006; **295:** 58–64.

Uses and Administration

Arginine is a basic amino acid that is essential for infant growth. It is used as a dietary supplement.

Arginine stimulates the release of growth hormone by the pituitary gland and may be used instead of, or in addition to, other tests such as insulin-induced hypoglycaemia, for the evaluation of growth disorders; false-positive and false-negative results are relatively common and evaluation therefore should not be made on the basis of a single arginine test. It is used as a 10% solution of the hydrochloride in usual doses of 30 g by intravenous infusion given over 30 minutes; children should be given 500 mg/kg.