Arginine is used in certain conditions accompanied by hyperammonaemia; for further details see below.

Arginine hydrochloride has also been used as an acidifying agent. In severe metabolic alkalosis intravenous doses have been calculated by the formula:

intravenous dose (in grams) =
desired decrease in plasma-bicarbonate concentration (mEq or mmol/litre)
×
[patient's body-weight (in kg)/9.6]

In forced acid diuresis to hasten drug elimination after overdose a suggested dose has been 10 g intravenously over 30 minutes. However, this has the potential to cause myoglobinuria with acute renal failure, and is rarely used.

Arginine may also be used in the form of the acetylasparaginate, aspartate, citrate, glutamate, oxoglurate, tidiacicate (thiazolidine-2,4-dicarboxylate), and timonacicate (thiazolidine-4-carboxylate). Formulation as an arginine salt is used to improve the solubility of a number of drugs, notably analgesics and antibacterials.

◊ References.

1. Tapiero H, *et al.* Arginine. *Biomed Pharmacother* 2002; **56:** 439–45.
2. Tong BC, Barbul A. Cellular and physiological effects of arginine. *Mini Rev Med Chem* 2004; **4:** 823–32.

Hyperammonaemia. Hyperammonaemia is a characteristic feature of inborn errors of the urea cycle, caused by defects in the enzymes carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (causing hyperargininaemia), or *N*-acetylglutamate synthase (NAGS).[1,2] During the urea cycle, waste ammonia, in the form of the ammonium ion, is normally condensed with bicarbonate and ATP to form carbamoyl phosphate which undergoes several more reactions, including one leading to the synthesis of arginine, and ultimate transformation to urea for excretion. Thus, in defects of this cycle ammonia accumulates and arginine synthesis is deficient.[3] Hyperammonaemia is most severe when the enzyme defect occurs in the early steps of the urea cycle, such as in CPS or OTC deficiency, and is less severe at later stages, as in ASL or arginase deficiency.[2] Hyperammonaemia is often associated with respiratory alkalosis in patients with urea cycle disorders.[3]

The basis of treatment is dietary protein restriction, to decrease the requirement for waste nitrogen synthesis,[4] and the use of drugs to stimulate alternative pathways of waste nitrogen excretion.[5,6] These include arginine, citrulline, sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. In the initial management of severe hyperammonaemia, haemodialysis is preferred over peritoneal dialysis because it is more effective.[3,7]

Arginine supplements are given except in hyperargininaemia.[5,7] Citrulline may be used in some cases instead;[8] it may be useful for CPS and OTC deficiency (in doses of about 170 mg/kg daily or 3.8 g/m^2 daily),[5,6,9] but it is not recommended for patients with ASS or ASL deficiency, as levels of citrulline are already elevated.[5,10] Some recommend citrulline with arginine in acute hyperammonaemia to aid additional removal of nitrogen.[9] For the treatment of acute hyperammonaemia, some recommend a loading dose of arginine 600 mg/kg over 90 minutes pending definitive diagnosis.[3,10] Alternatively, a loading dose of 200 mg/kg or 4 g/m^2 has been advocated for CPS or OTC deficiency,[6,9,10] and 600 mg/kg or 12 g/m^2 for ASS or ASL deficiency.[6,9,10] The same dose as the loading dose is then given over 24 hours, as a constant maintenance infusion,[6,9,10] until conversion to oral medication is made.[10] For long-term management of ASS or ASL deficiency, doses of arginine ranging from 400 to 700 mg/kg daily have been recommended.[5,6,9,10]

Patients also receive treatment with sodium benzoate and sodium phenylacetate[6,10] or sodium phenylbutyrate.[5,6] ASL deficiency can be managed with protein restriction and arginine alone,[6,11] although some still advocate the use of sodium phenylbutyrate.[5,8] When sodium benzoate is conjugated with glycine and excreted as hippuric acid it provides an alternative pathway of nitrogen excretion, while sodium phenylacetate and sodium phenylbutyrate provide a second and even more effective pathway by conjugation with glutamine.[6,7,10] Some consider intravenous sodium benzoate and sodium phenylacetate the treatment of choice in acute hyperammonaemia; sodium phenylbutyrate is recommended for chronic management.[9] In a 25-year, open-label, uncontrolled study, intravenous therapy with sodium phenylacetate and sodium benzoate clearly improved survival in patients with acute hyperammonaemia, with an overall survival rate of 84%; survival was also related to peak plasma ammonium concentration and age. Haemodialysis was also used to control hyperammonaemia, especially in neonates and older patients who were less responsive to intravenous therapy.[12]

It has been suggested that carnitine supplementation (at 100 mg/kg daily[9] either orally or intravenously) should be added to minimise neurological symptoms and toxicity, but its value is uncertain.[4,13] Low carnitine levels have been reported to be uncommon in patients with urea cycle disorders and, in patients treated with sodium benzoate, benzoyl carnitine may form, negating any potential benefit from carnitine supplementation.[8]

Liver transplantation (p.1815) may achieve long-term correction of urea cycle disorders, even in the very young patient, and gene replacement therapy is under investigation.[14]

Hyperammonaemia and hepatic encephalopathy (p.1697) can also arise from other causes[7,13] for which arginine may not be advocated. Carglumic acid (p.2277) is the treatment of choice for patients with hyperammonaemia arising from NAGS deficiency.

1. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S6–S10.
2. Shih VE. Alternative-pathway therapy for hyperammonemia. *N Engl J Med* 2007; **356:** 2321–2.
3. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S1–S5.
4. Leonard JV. The nutritional management of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S40–S45.
5. Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S56–S61.
6. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl): S46–S55.
7. Leonard JV, Morris AAM. Urea cycle disorders. *Semin Neonatol* 2002; **7:** 27–35.
8. Wilcken B. Problems in the management of urea cycle disorders. *Mol Genet Metab* 2004; **81** (suppl): S86–S91.
9. Kleppe S, *et al.* Urea cycle disorders. *Curr Treat Options Neurol* 2003; **5:** 309–19.
10. Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S30–S39.
11. Brusilow SW, *et al.* Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med* 1984; **310:** 1630–4.
12. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356:** 2282–92.
13. Leonard JV, Morris AAM. Inborn errors of metabolism around time of birth. *Lancet* 2000; **356:** 583–7.
14. Lee B, Goss J. Long-term correction of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S62–S71.

Hypotensive action. Arginine is the physiological precursor of nitric oxide and this has been suggested as an explanation for the hypotensive effect that has been reported in healthy subjects[1-3] and hypertensive patients[1,4] given infusions of arginine, although effects unrelated to nitric oxide generation cannot be excluded.[4]

Oral arginine has also been reported to significantly decrease mean systolic blood pressure in hypertensive patients,[5] in patients on haemodialysis, and in renal transplant recipients.[6] In patients with essential hypertension, a single dose of arginine by mouth had no effect on blood pressure, although it did improve endothelium-dependent flow-mediated dilatation of the brachial artery compared with placebo.[7] In patients with pulmonary hypertension, short-term use of arginine has reduced pulmonary arterial pressure.[8-10]

In pregnant women with pre-eclampsia (see Hypertension, p.1171), plasma-arginine concentrations were found to be markedly reduced compared with control subjects.[11] Arginine infusions of 20 g, given to women with mild to moderate gestational hypertension,[12] and 30 g given to pre-eclamptic women,[13] significantly reduced systolic and diastolic blood pressure, with no adverse effect on fetal heart rate in the one study.[12] In a study of pre-eclamptic women given arginine 12 g daily for 2 days by mouth, no significant differences in diastolic blood pressure were seen compared with those receiving placebo.[14] However, in another study of pre-eclamptic women given 3 g arginine daily for 3 weeks, systolic, diastolic and mean arterial pressure were significantly reduced compared with those taking placebo.[15]

Because of apparent improvement in endothelial function with arginine, some interest has surrounded its potential role in other cardiovascular diseases, such as coronary artery disease and heart failure.[16] Decrease in plasma-cholesterol concentrations has also been reported in 2 hypercholesterolaemic patients given arginine infusions.[17] However, long-term supplementation was found not to be helpful (and possibly harmful) in patients with peripheral arterial disease,[18] and arginine therapy has been implicated in increased mortality when given to patients after myocardial infarction (see under Adverse Effects and Precautions, above).

1. Nakaki T, *et al.* L-arginine-induced hypotension. *Lancet* 1990; **336:** 696.
2. Hishikawa K, *et al.* L-arginine-induced hypotension. *Lancet* 1991; **337:** 683–4.
3. Petros AJ, *et al.* L-arginine-induced hypotension. *Lancet* 1991; **337:** 1044–5.
4. Pedrinelli R, *et al.* Pressor, renal and endocrine effects of -arginine in essential hypertensives. *Eur J Clin Pharmacol* 1995; **48:** 195–201.
5. Palloshi A, *et al.* Effect of oral -arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. *Am J Cardiol* 2004; **93:** 933–5.
6. Kelly BS, *et al.* Oral arginine improves blood pressure in renal transplant and hemodialysis patients. *J Parenter Enteral Nutr* 2001; **25:** 194–202.
7. Lekakis JP, *et al.* Oral -arginine improves endothelial dysfunction in patients with essential hypertension. *Int J Cardiol* 2002; **86:** 317–23.
8. Mehta S, *et al.* Short-term pulmonary vasodilation with -arginine in pulmonary hypertension. *Circulation* 1995; **92:** 1539–45.
9. Nagaya N, *et al.* Short-term oral administration of -arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. *Am J Respir Crit Care Med* 2001; **163:** 887–91.
10. Morris CR, *et al.* Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003; **168:** 63–9.
11. D'Aniello G, *et al.* Plasma -arginine is markedly reduced in pregnant women affected by preeclampsia. *J Chromatogr B Biomed Sci Appl* 2001; **753:** 427–31.
12. Neri I, *et al.* Effects of acute L-arginine infusion on non-stress test in hypertensive pregnant women. *J Matern Fetal Neonatal Med* 2004; **16:** 23–6.
13. Facchinetti F, *et al.* -Arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. *J Soc Gynecol Investig* 1999; **6:** 202–7.
14. Staff AC, *et al.* Dietary supplementation with -arginine or placebo in women with pre-eclampsia. *Acta Obstet Gynecol Scand* 2004; **83:** 103–7.
15. Rytlewski K, *et al.* Effects of prolonged oral supplementation with -arginine on blood pressure and nitric oxide synthesis in preeclampsia. *Eur J Clin Invest* 2005; **35:** 32–7.
16. Cheng JWM, Balwin SN. L-arginine in the management of cardiovascular diseases. *Ann Pharmacother* 2001; **35:** 755–64.
17. Korbut R, *et al.* Effect of -arginine on plasminogen-activator inhibitor in hypertensive patients with hypercholesterolemia. *N Engl J Med* 1993; **328:** 287–8.
18. Wilson AM, *et al.* L-arginine supplementation in peripheral arterial disease: no benefit and possible harm. *Circulation* 2007; **116:** 188–95.

Necrotising enterocolitis. A systematic review[1] considered that although there was evidence suggesting that supplementation of the feed of premature neonates with arginine could prevent the development of necrotising enterocolitis (p.173), it was insufficient to recommend the practice without further study.

1. Shah P, Shah V. Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 24/06/08).

Preparations

BP 2008: Arginine Hydrochloride Intravenous Infusion;
USP 31: Arginine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Inteligen†; Laclorene; ***Austria:*** Sangenor; ***Braz.:*** Reforgan; Targifor; ***Fr.:*** Dynamisan; Energitum†; Eucol; Pargine; Sargenor; Tiadilon; ***Ger.:*** Eubiol†; ***Israel:*** Carginine†; ***Ital.:*** Bioarginina; Dynamisan; Sargenor; Sulfile†; ***Malaysia:*** Arginitric; ***Port.:*** Asparten; Bio-Energol Plus; Pan-Astenico R; Sargenor; Sulfile; ***Spain:*** Potenciator; Sargenor; Sargisthene; Sorbenor; ***Switz.:*** Dynamisan; ***USA:*** R-Gene.

Multi-ingredient: ***Arg.:*** Acrea; Holomagnesio Vital; Inteligen Ginseng†; ***Austria:*** Leberinfusion; Rocmaline; ***Braz.:*** Dinavital C; Ornihepat†; Ornitargin; Targifor C; ***Chile:*** Ureadin 30; ***Cz.:*** Citrarginе†; ***Fr.:*** Arginotri-B; Citrarginine†; Epuram†; Fastenyl; Hepagrume; Hepargitol; Rocmaline; Sargenor a la Vitamine C; ***Ger.:*** Glutarsin E†; Polilevo N†; ***Hung.:*** Glutarsin E; Rocmalat†; ***Indon.:*** Sirec; ***Ital.:*** Calciofix; Glutargin†; Ipoazotal Complex; Ipoazotal†; Isoram; Linfoiodine; Polilevo†; Sargenor Plus; Somatron; Tonoplus†; Vitasprint Complex†; ***Spain:*** Dynamogen; Sanieb†; ***Switz.:*** Activital Forte; Arginotri-B; Vitasprint Complex.

Arrowroot

Amylum Marantae; Araruta; Arruruz; Maranta; Pfeilwurzelmehl; Sagú del monte; Yuquilla silvestre.

Profile

Arrowroot consists of the starch granules of the rhizomes of *Maranta arundinacea* (Marantaceae). It has the general properties of starch (p.1968). It has been used as a suspending agent in the preparation of barium meals and has sometimes been used in place of starch in tablet manufacture.

Diarrhoea. In a pilot study in 11 patients with irritable bowel syndrome given 10 mL arrowroot powder three times daily for 1 month, 4 patients reported an improvement in diarrhoea.[1]

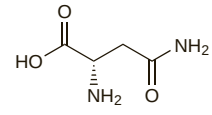
1. Cooke C, *et al.* Arrowroot as a treatment for diarrhoea in irritable bowel syndrome patients: a pilot study. *Arq Gastroenterol* 2000; **37:** 20–4.

Asparagine Monohydrate

L-α-Aminosuccinamic Acid Monohydrate; Asparagiinimonohydraatti; Asparagin monohydrát; Asparagina, monohidrato de; Asparaginas monohidratas; L-Asparagine Monohydrate; Asparagine monohydratée; Asparaginmonohydrat; Asparaginum monohydricum; Asparamide; Aspartamic acid; Aspartic acid beta-amide; N (asparagine); NSC-82391. (2*S*)-2,4-Diamino-4-oxobutanoic acid monohydrate.

$C_4H_8N_2O_3,H_2O$ = 150.1.

CAS — 70-47-3 (anhydrous asparagine); 5794-13-8 (asparagine monohydrate).



(anhydrous asparagine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF*, which specifies the anhydrous form or the monohydrate.

Ph. Eur. 6.2 (Asparagine Monohydrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.0.
USNF 26 (Asparagine). It is anhydrous or contains one molecule of water of hydration. A white, crystalline powder or white crystals. Soluble in water; practically insoluble in alcohol and in ether. Its solutions are acid to litmus. Protect from light.

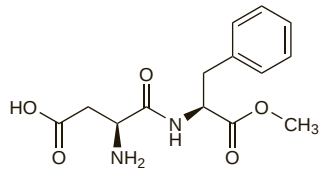
Profile
Asparagine is a non-essential amino acid.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Acutil Fosforo; Neuralfa; Tiofort; ***Spain:*** Agudil.

Aspartame *(BAN, USAN, rINN)*

APM; Aspartaami; Aspartam; Aspartamas; Aspartamo; Aspartamum; Aszpartám; E951; SC-18862. Methyl *N*-L-α-aspartyl-L-phenylalaninate; 3-Amino-*N*-(α-methoxycarbonylphenethyl)succinamic acid; *N*-L-α-aspartyl-L-phenylalanine, 1-methyl ester.

Аспартам
$C_{14}H_{18}N_2O_5$ = 294.3.
CAS — 22839-47-0.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Aspartame). A white or almost white, slightly hygroscopic, crystalline powder. Sparingly or slightly soluble in water and in alcohol; practically insoluble in dichloromethane and in *n*-hexane. Store in airtight containers.
USNF 26 (Aspartame). White, odourless, crystalline powder having a sweet taste. Sparingly soluble in water; slightly soluble in alcohol. pH of a 0.8% solution in water is about 5.

Stability. In the presence of moisture aspartame hydrolyses to form aspartylphenylalanine and a diketopiperazine derivative, with a resulting loss of sweetness.

Adverse Effects and Precautions
Excessive use of aspartame should be avoided by patients with phenylketonuria since one of its metabolic products is phenylalanine. Aspartame's sweetness is lost during prolonged cooking.

Adverse effects. The safety and adverse effects of aspartame as a pharmaceutical excipient have been reviewed.[1,2]

Aspartame is hydrolysed in the gastrointestinal tract to methyl alcohol, aspartic acid, and phenylalanine. However, even with extraordinary consumption, methyl alcohol toxicity stemming from aspartame use is extremely unlikely. Aspartate concentrations in blood do not rise significantly after a very large dose (50 to 100 mg/kg) and therefore toxicity related to aspartate is also not expected to occur. Despite the similarity of aspartate to glutamate, studies in glutamate-sensitive persons have shown that they are not affected by aspartame consumption. Plasma concentrations of phenylalanine are also unlikely to be markedly elevated after modest consumption of aspartame by healthy persons but persons with phenylketonuria should avoid or limit their use of aspartame.

A number of adverse effects have been reported[1,2] after the use of aspartame, either as spontaneously recorded complaints from consumers or as published case reports in the medical literature. Most frequently reported problems have been headache, neuropsychiatric or behavioural symptoms, seizures, gastrointestinal symptoms, and hypersensitivity or dermatological symptoms. Available data do not provide evidence for serious widespread health consequences attendant upon the use of aspartame but it would appear that certain individuals may have an unusual sensitivity to the product. A safety review[3] by the European Commission Scientific Committee on Food (ECSCF) concluded that no causal link could be established between the consumption of aspartame and the occurrence of epilepsy or seizures, or cognition, mood and behaviour; this included individuals considered sensitive to aspartame.

Studies have confirmed aspartame's lack of effect on children's behaviour or cognitive function.[4,5]

An increased incidence of brain cancer was postulated to be related to aspartame use in one report;[6] however, the FDA[7] and the ECSCF[3] maintained that the available evidence did not support an association. Multiple malignancies have been reported[8] in *rats* given doses lower than the current acceptable daily intake of 40 or 50 mg/kg. The European Food Safety Authority assessed this study and concluded,[9] on the basis of all current available evidence, that the increased incidence of cancers in the *rats* was unrelated to aspartame treatment, and that there was no need to further review the safety of aspartame, nor to revise the established acceptable daily intake for aspartame of 40 mg/kg.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). *Med Toxicol* 1988; **3:** 209–40.
2. American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; **99:** 268–78.
3. European Commission Health and Consumer Protection Directorate-General. Opinion of the Scientific Committee on Food: update on the safety of aspartame (expressed on 4 December 2002). Available at: http://europa.eu.int/comm/food/fs/sc/scf/out155_en.pdf (accessed 08/11/05)
4. Shaywitz BA, *et al.* Aspartame, behavior, and cognitive function in children with attention deficit disorder. *Pediatrics* 1994; **93:** 70–5.
5. Wolraich ML, *et al.* Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; **330:** 301–7.
6. Olney JW, *et al.* Increasing brain tumor rates: is there a link to aspartame? *J Neuropathol Exp Neurol* 1996; **55:** 1115–23.
7. Anonymous. Aspartame: no apparent link with brain tumours. *WHO Drug Inf* 1997; **11:** 18–19.
8. Soffritti M, *et al.* First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006; **114:** 379–85.
9. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a new long-term carcinogenicity study on aspartame. *EFSA J* 2006; **356** 1–44. Available at: http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_op_ej356_aspartame_en1,2.pdf (accessed 03/03/08)

Breast feeding. Aspartame 50 mg/kg given orally to healthy women resulted in small but significant increases in breast milk aspartate, phenylalanine, and tyrosine concentrations.[1] However, it was noted that these levels were similar to postprandial milk samples and were unlikely to impact upon total amounts of amino acids ingested by the infant. Furthermore, the dose of aspartame given in the study was considerably higher than the projected intake of about 7.5 to 8.5 mg/kg daily, assuming all sucrose intake were replaced by aspartame, and no aspartame abuse. Nonetheless, the American Academy of Pediatrics[2] considers that caution is required when aspartame is ingested by mothers where either the mother or breast-fed infant has phenylketonuria.

1. Stegink LD, *et al.* Plasma, erythrocyte and human milk levels of free amino acids in lactating women administered aspartame or lactose. *J Nutr* 1979; **109:** 2173–81.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/11/04)

Pharmacokinetics
Aspartame is hydrolysed in the gastrointestinal tract to its 3 primary constituents, methyl alcohol, aspartic acid, and phenylalanine.

Uses
Aspartame is an intense sweetening agent about 180 to 200 times as sweet as sucrose. It is used in foods, beverages, and pharmaceuticals. Each g provides about 17 kJ (4 kcal).

Sickle-cell disease. There is some preliminary evidence that aspartame may have beneficial effects in sickle-cell disease.[1]

1. Manion CV, *et al.* Aspartame effect in sickle cell anemia. *Clin Pharmacol Ther* 2001; **69:** 346–55.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Nutrasweet†; Slap; ***Braz.:*** Dietacil; Dietamina†; Doce Vida†; Finn; ***Canad.:*** Equal; ***Chile:*** Marco Sweett†; Modellsweet†; Naturalist; Originalsweet; Ridersweet†; Valsweet; ***India:*** Lo-Kal†; Low-Cal†; ***Ital.:*** Aspartina; Futura; Suaviter; ***NZ:*** Equal; ***Port.:*** Dolcevita†; ***Rus.:*** Sugarfree (Шугафри); ***Thai.:*** Equal†; Espar; ***Turk.:*** Aspartil; Canderel; Demi Canderel; Diyet Tat; Hermesetas Gold; Nutra-Tat; Sanpa; ***Venez.:*** Dolsiprim†; Dulcolite†; Dulcosil; Edul; Equal†; Hermesetas Gold.

Multi-ingredient: ***Arg.:*** Chuker; Equalsweet; Genser Sweet; Rondo Sweet; Semble; Sucaryl; ***Chile:*** Marco Sweet Light; Nutrasweet†; ***UK:*** Sweet 'n Low; ***Venez.:*** Hermesetas Gold; Sweet 'n' Low†.

Aspartame Acesulfame

L-Phenylalanine, L-α-aspartyl-2-methyl ester, compound with 6-methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide (1:1).
$C_{18}H_{23}O_9N_3S$ = 457.5.
CAS — 106372-55-8.

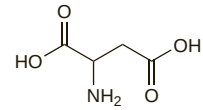
Pharmacopoeias. In *USNF.*
USNF 26 (Aspartame Acesulfame). White, odourless, crystalline powder. Slightly soluble in water and in alcohol. It contains not less than 63.0% and not more than 66.0% of aspartame, calculated on the dried basis, and not less than 34.0% and not more than 37.0% of acesulfame, calculated as the acid form on the dried basis.

Profile
Aspartame acesulfame is a compound of aspartame (see above) and acesulfame (see p.1928), and is used similarly in foods. It is an intense sweetener about 350 times as sweet as sucrose.

Aspartic Acid *(USAN, rINN)*

Acide aspartique; Ácido aspártico; Acidum asparticum; Asp; Asparagiinihappo; Asparaginsyra; L-Aspartic Acid; Asparto rūgštis; Aszparaginsav; D; Kwas asparaginowy; Kyselina asparagová. L-Aminosuccinic acid.

Аспарагиновая Кислота
$C_4H_7NO_4$ = 133.1.
CAS — 56-84-8.



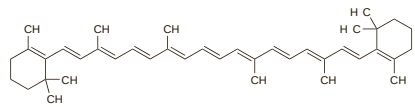
Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.
USP 31 (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in ether; soluble in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile
Aspartic acid is a non-essential amino acid. It is used as a dietary supplement.

Betacarotene *(BAN, rINN)*

all-*trans*-β-Carotene; Beetakaroteeni; Beta Carotene *(USAN)*; Bétacarotène; Betacaroteno; Betacarotenum; Betakaroten; Betakarotenas; Bétakarotin; E160(a); Provitamin A. β,β-Carotene; (*all-E*)-1,1′-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis[2,6,6-trimethylcyclohexene].

Бетакаротен
$C_{40}H_{56}$ = 536.9.
CAS — 7235-40-7.
ATC — A11CA02; D02BB01.
ATC Vet — QA11CA02; QA11HA90; QD02BB01.



Description. Carotene exists in 3 isomeric forms, all of which are converted to some extent into vitamin A in the livers of man and *animals*. Of the 3 isomers of carotene, the *beta* compound is more active than the *alpha-* or *gamma*-isomers. The vitamin A activity of plants is due to the presence of *alpha-*, *beta-*, and *gamma*-carotenes and to kryptoxanthine; that of *animal* tissues is due to both vitamin A and carotene, while fish-liver oils contain vitamin A but no carotene.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Betacarotene). A brown-red or brownish-red crystalline powder. Practically insoluble in water and in dehydrated alcohol; slightly soluble in cyclohexane. It is sensitive to air, heat and light, especially in solution. Store in airtight containers at a temperature not exceeding 25°. Protect from light.
USP 31 (Beta Carotene). Red or reddish-brown to violet-brown crystals or crystalline powder. Insoluble in water, in acids, and in alkalis; practically insoluble in alcohol and in methyl alcohol; soluble in carbon disulfide, in chloroform, and in benzene; sparingly soluble in ether, in petroleum spirit, and in vegetable oils. Store in airtight containers. Protect from light.

Units
Vitamin A activity in foods is expressed in terms of retinol equivalents: 6 micrograms of betacarotene represents 1 retinol equivalent (or 10 of the former International units for provitamin A—see p.1971).

Adverse Effects and Precautions
Loose stools may occasionally occur during treatment with betacarotene and the skin may assume a slightly yellow discoloration. Bruising, dizziness, and arthralgia have been reported rarely.

Excessive intake of betacarotene does not result in hypervitaminosis A (see Pharmacokinetics, below).

Carcinogenicity. For reference to studies finding an increased incidence of lung cancers in individuals given betacarotene sup-