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.

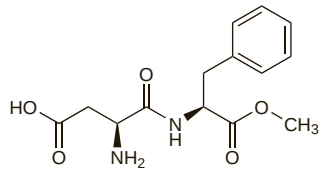
Profile
Asparagine is a non-essential amino acid.

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.

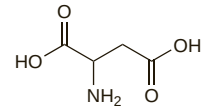
Pharmacopoeias. In *USNF.*
USNF 26 (Aspartame Acesulfame). White, odourless, crystalline powder. Slightly soluble in water and in alcohol. It contains not less than 63.0% and not more than 66.0% of aspartame, calculated on the dried basis, and not less than 34.0% and not more than 37.0% of acesulfame,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



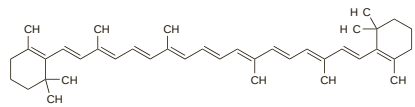
Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids.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