upon biliary or pancreatic secretions for absorption from the gastrointestinal tract. They provide 35 kJ (8.3 kcal) per g. They do not provide essential fatty acids.

Medium-chain triglycerides have also been used as bases for pharmaceutical preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Teceeme; ***Austral.:*** Liquigen; MCT Oil; ***Canad.:*** MCT Oil†; ***Fin.:*** Liquigen; MCT Olja; ***Fr.:*** Liquigen; ***Gr.:*** MCT Oil; ***Hung.:*** Structolipid; ***Israel:*** MCT; ***Ital.:*** MCT; Mytic 810; ***Malaysia:*** MCT Oil†; ***NZ:*** Liquigen; MCT Oil; ***Port.:*** MCT Oil; ***Singapore:*** MCT†; ***UK:*** Alembicol D; MCT Oil; ***USA:*** MCT.

Multi-ingredient: ***Arg.:*** Lipofundin MCT/LCT-E; Lipofundin MCT/LCT†; ***Austral.:*** Caprilon; MCT Duocal; ***Austria:*** Lipofundin mit MCT; SMOFlipid; Structolipid; ***Belg.:*** Medialipide†; ***Chile:*** Lipofundin MCT/LCT; Lipovenos MCT/LCT; ***Cz.:*** Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; ***Denm.:*** SMOFlipid; Structolipid; ***Fin.:*** Lipoplus; Nutriflex Lipid; Structolipid; Vasolipid; ***Fr.:*** Liprocil; Medialipide; Structolipide; ***Ger.:*** Gleitgelen; Lipofundin MCT; Lipovenos MCT; Nutriflex Lipid; SMOFlipid; Visine Trockene Augen; ***Gr.:*** Lipofundin MCT/LCT; SMOFlipid; Structolipid; ***Hong Kong:*** Lipofundin MCT/LCT; Nutriflex Lipid; ***Hung.:*** Lipofundin MCT; Lipovenos PLR†; SMOFlipid; ***Indon.:*** Lipofundin MCT/LCT; ***Irl.:*** Caprilon; Liquigen; MCT Duocal†; ***Israel:*** Lipofundin MCT/LCT; ***Ital.:*** Caprilon; Lipofundin MCT; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; Structolipid; ***Mex.:*** Lipofundin MCT/LCT; Lipovenoes MCT†; ***Neth.:*** Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; ***Norw.:*** Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; ***NZ:*** Structolipid; ***Pol.:*** Lipofundin MCT/LCT; SMOFlipid; ***Port.:*** Lipofundina MCT/LCT; Lipoplus; Nutribraun; Structolipid; ***S.Afr.:*** Lipofundin MCT/LCT; ***Singapore:*** Lipofundin MCT/LCT†; ***Spain:*** Lipofundina MCT/LCT; Nutriflex Lipid; Structolipid; ***Swed.:*** Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; ***Switz.:*** Lipofundin MCT/LCT; Nutriflex Lipid; Structolipid; ***Thai.:*** Lipofundin MCT/LCT; Structolipid; ***Turk.:*** Lipofundin MCT/LCT; ***UK:*** Caprilon; Imuderm; Lipidem; Lipofundin MCT/LCT; Liquigen; MCT Duocal; SMOFlipid; Structolipid; ***Venez.:*** Lipofundin MCT/LCT; Propol†.

Molybdenum

Molibdeno; Molybdän; Molybdène.

Mo = 95.96.

Ammonium Molybdate

Amonowy molibdenian; Molibdato de amonio. Hexaammonium molybdate tetrahydrate.

$(NH_4)_6Mo_7O_{24},4H_2O$ = 1236.0.

CAS — 12054-85-2.

Pharmacopoeias. In *US.*

USP 31 (Ammonium Molybdate). Colourless or slightly greenish or yellowish crystals. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Sodium Molybdate

Molibdato de sodio; Molybdenan sodný dihydrát; Natrii molybdas dihydricus; Natrio molibdatas dihidratas; Nátrium-molibdenát-dihidrát; Natriummolybdaattidihydraatti; Natriummolybdatdihydrat; Sodium (molybdate de) dihydraté; Sodu molibdenian.

$Na_2MoO_4,2H_2O$ = 242.0.

Pharmacopoeias. In *Eur.* (see p.vii). *Ger.* also includes a monograph for the anhydrous substance.

Ph. Eur. 6.2 (Sodium Molybdate Dihydrate). A white or almost white powder or colourless crystals. Freely soluble in water.

Adverse Effects

Very high intakes of molybdenum, and associated increases in xanthine oxidase activity, may result in hyperuricaemia, and possibly gout. Molybdenum intoxication may impair the utilisation of copper.

Uses and Administration

Molybdenum is an essential trace element and small amounts, in the form of ammonium molybdate or sodium molybdate, are sometimes added to solutions for total parenteral nutrition. A suggested dose is about 20 to 120 micrograms (0.2 to 1.2 micromoles) elemental molybdenum daily.

Ammonium molybdate is used in veterinary medicine to treat copper poisoning in sheep.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.1925) has been set for molybdenum although a safe intake was believed to be between 50 and 400 micrograms (0.5 and 4 micromoles) daily for adults.[1] In the USA, the recommended dietary allowance is 45 micrograms daily for adults.[2] The tolerable upper intake level is 2 mg daily.[2] WHO make the suggestion that the adult basal requirement for molybdenum could be about 25 micrograms daily,[3] corresponding to approximately 400 nanograms/kg.

Foods contributing to dietary molybdenum include milk, beans, breads, and cereals; however, extreme regional variations occur in molybdenum contents of food crops due to soil differences.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Molybdenum. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996; 144–54.

Preparations

USP 31: Ammonium Molybdate Injection.

Proprietary Preparations (details are given in Part 3)

Fr.: Molybdene Injectable; ***USA:*** Molypen.

Neohesperidin Dihydrochalcone

E959; Neohesperidiinidihydrokalkoni; Neohesperidin DC; Neohesperidin-dihidrochalkonas; Neohesperidin-dihydrochalconum; Neohesperidin-dihydrochalkon; Neohesperidindivätekalkon; Neoheszperidin-dihidro-kalkon; NHDC. 3,5-Dihydroxy-4-[3-(3-hydroxy-4-methoxyphenyl)propionyl]phenyl 2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside.

$C_{28}H_{36}O_{15}$ = 612.6.

CAS — 13241-33-3 (neohesperidin); 20702-77-6 (neohesperidin dihydrochalcone); 18916-17-1 (naringin dihydrochalcone); 65520-51-6 (neoeriocitrin dihydrochalcone).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Neohesperidin-dihydrochalcone). A white or yellowish-white powder. Practically insoluble in water and in dichloromethane; freely soluble in dimethyl sulfoxide; soluble in methyl alcohol. Protect from light.

Profile

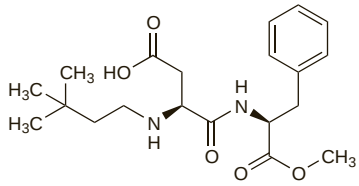
Neohesperidin dihydrochalcone is an intense sweetener derived from naringin, a flavonoid present in citrus peel. It is about 1000 to 1500 times as sweet as sucrose and is used in foods, beverages, and pharmaceuticals. It has a synergistic sweetening effect when used with other sweeteners.

Neotame

Neotamo. *N*-[*N*-(3,3-Dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

$C_{20}H_{30}N_2O_5$ = 378.5.

CAS — 165450-17-9.



Pharmacopoeias. In *USNF.*

USNF 26 (Neotame). Store in a dry place at a temperature not exceeding 40°.

Profile

Neotame is an intense sweetener used in foods and beverages. It has between 7000 and 13 000 times the sweetening power of sucrose and is stable to heat.

◊ References.

1. Anonymous. Neotame—a new artificial sweetener. *Med Lett Drugs Ther* 2002; **44:** 73–4.

Nicotinamide Ascorbate *(rINNM)*

Ascorbato de nicotinamida; Niacinamide Ascorbate; Nicoscorbine; Nicotinamide, Ascorbate de; Nicotinamidi Ascorbas.

Никотинамида Аскорбат

$C_{12}H_{14}N_2O_7$ = 298.2.

CAS — 1987-71-9.

Profile

Nicotinamide ascorbate is a complex of nicotinamide (p.1957) with ascorbic acid (p.1983) that is used in multivitamin preparations. It has also been given with betaine glucuronate and dilolamine glucuronate for liver disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Jetepar; ***Ital.:*** Ietepar†; ***Malaysia:*** Jetepar; ***Philipp.:*** Jetepar; ***Singapore:*** Jetepar.

Nicotinic Acid *(rINN)*

375; Acide nicotinique; Ácido nicotínico; Acidum nicotinicum; Kwas nikotynowy; Kyselina nikotinová; Niacin; Nikotiinihappo; Nikotinik Asit; Nikotino rūgštis; Nikotinsäure; Nikotinsav; Nikotinsyra. Pyridine-3-carboxylic acid.

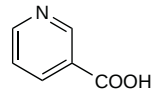
Никотиновая Кислота

$C_6H_5NO_2$ = 123.1.

CAS — 59-67-6.

ATC — C04AC01; C10AD02.

ATC Vet — QC04AC01; QC10AD02.



NOTE. Some published sources use the term niacin as a generic term to include both nicotinic acid and nicotinamide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Nicotinic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water and in boiling alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. Protect from light.

USP 31 (Niacin). White crystals or crystalline powder, odourless or has a slight odour. Soluble 1 in 60 of water; freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; practically insoluble in ether.

Nicotinamide *(rINN)*

Niacinamide; Nicotinamida; Nicotinamidum; Nicotinic Acid Amide; Nicotylamide; Nikotiiniamidi; Nikotinamid; Nikotinamidas; Nikotynamid; Vitamin B_3; Vitamin PP. Pyridine-3-carboxamide.

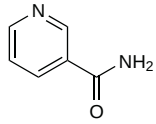
Никотинамид

$C_6H_6N_2O$ = 122.1.

CAS — 98-92-0.

ATC — A11HA01.

ATC Vet — QA11HA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Nicotinamide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 6.0 to 7.5.

USP 31 (Niacinamide). A white crystalline powder, odourless or practically so. Soluble 1 in 1.5 of water, 1 in 10 of boiling water, and 1 in 5.5 of alcohol; soluble in glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects and Treatment

Nicotinic acid has a vasodilator action and when given by mouth or by injection in therapeutic doses it may cause flushing, a sensation of heat, faintness, and a pounding in the head. Flushing may be accompanied by dizziness, tachycardia, palpitations, dyspnoea, sweating, chills, or oedema. These symptoms are transient and various strategies have been proposed to reduce them (see Incidence of Adverse Effects, below). Nicotinamide does not have a vasodilator action.

Other adverse effects that have been reported, especially after high doses of nicotinic acid, include dryness of the skin, pruritus, hyperpigmentation, cramps, diarrhoea, nausea and vomiting, anorexia, activation of peptic ulcer, amblyopia, jaundice and impairment of liver function, decrease in glucose tolerance, hyperglycaemia, and hyperuricaemia. Most of these effects subside on withdrawal of the drug. Hypophosphataemia, a reduction in platelet counts, and prolongation of prothrombin time have also been reported. Insomnia, myalgia, hypotension, and rhinitis may occur rarely.

Topical nicotinamide may cause dryness of the skin and, less frequently, pruritus, erythema, burning sensation, and irritation. Frequency of application should be reduced if these effects occur.

◊ References.

1. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007; **99** (suppl 1): S22–S31.

Incidence of adverse effects. Nicotinic acid produces frequent adverse effects, but they are not usually serious, tend to decrease with time, and some can be minimised by following appropriate instructions for use.[1,2] Dermal and gastrointestinal reactions are most common. Truncal and facial flushing are reported in 90 to 100% of treated patients in large clinical trials; they appear to be prostaglandin-mediated and can be reduced with aspirin 75 mg or 325 mg given shortly before the nicotinic acid, or simply by giving nicotinic acid with food, and by starting therapy with a low dose and gradually increasing this. Flushing may be less common with modified-release formulations.[2]

1. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987; **2:** 10–32.
2. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.

Effects on the eyes. Retrospective survey of hyperlipidaemic patients suggested that dry eyes (sicca syndromes), blurred vision, and swollen eyelids might be associated with nicotinic acid therapy in some patients.[1] The effects appeared to be dose-related and reversible. In 2 patients treatment was stopped because of symptoms suggestive of cystoid macular oedema. Other cases of nicotinic acid maculopathy have been reported.[2,3]

1. Fraunfelder FW, *et al.* Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995; **79:** 54–6.
2. Callanan D, *et al.* Macular edema associated with nicotinic acid (niacin). *JAMA* 1998; **279:** 1702.
3. Spirn MJ, *et al.* Optical coherence tomography findings in nicotinic acid maculopathy. *Am J Ophthalmol* 2003; **135:** 913–14.

Effects on glucose tolerance. Nicotinic acid can reduce glucose tolerance, and this may be problematic in patients with diabetes mellitus,[1,2] although it has been investigated in the prevention of diabetes mellitus (see below).

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.
2. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97:** 313–16.

Effects on the liver. Hepatotoxicity may occur with nicotinic acid.[1-6] Significant elevations of liver enzymes are occasionally seen with nicotinic acid therapy. They are more common in patients given large dosage increases over short periods of time, and in patients treated with modified-release formulations. It has been suggested[7] that since effects on liver function may in some instances lead to hepatic failure and are more common with modified-release dosage forms the use of crystalline immediate-release preparations should be preferred, a view shared by other commentators.[8] However, although studies appear to confirm a more frequent association of hepatotoxicity with modified-release dosage forms[4,9,10] it should be borne in mind that these effects can also occur with the immediate-release preparations, especially at high doses. Some manufacturers of modified-release preparations have stated that cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when patients have substituted modified-release dosage forms for immediate-release crystalline preparations at equivalent doses. There is also a suggestion that not all modified-release preparations are alike in their effects.[11]

1. Henkin Y, *et al.* Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. *JAMA* 1990; **264:** 241–3.
2. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. *JAMA* 1990; **264:** 181.
3. Etchason JA, *et al.* Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 1991; **66:** 23–8.
4. Rader JI, *et al.* Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92:** 77–81.
5. Coppola A, *et al.* Niacin-induced hepatotoxicity: unusual presentations. *South Med J* 1994; **87:** 30–2.
6. Gavilán JC, *et al.* Hepatitis inducida por niacina. *Med Clin (Barc)* 2002; **118:** 558.
7. Palumbo PJ. Rediscovery of crystalline niacin. *Mayo Clin Proc* 1991; **66:** 112–13.
8. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97:** 313–16.
9. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271:** 672–7.
10. Gray DR, *et al.* Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; **121:** 252–8.
11. Lavie CJ, Milani RV. Safety and side-effects of sustained-release niacin. *JAMA* 1994; **272:** 513–14.

Effects on the muscles. Myopathy has been noted with nicotinic acid.[1,2] Rhabdomyolysis has occurred when nicotinic acid was given with lovastatin (see Lipid Regulating Drugs, under Interactions of Simvastatin, p.1393).

1. Litin SC, Anderson CF. Nicotinic-acid associated myopathy: a report of three cases. *Am J Med* 1989; **86:** 481–3.
2. Gharavi AG, *et al.* Niacin-induced myopathy. *Am J Cardiol* 1994; **74:** 841–2.

Hyperuricaemia. Nicotinic acid decreases urinary excretion of uric acid, which may result in elevation of serum uric acid and exacerbation of pre-existing gout.[1]

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.

Precautions

Nicotinic acid should be given cautiously to patients with a history of peptic ulcer disease, and to those with diabetes mellitus, gout, or hepatic impairment. Modified-release preparations should not be substituted for equivalent doses of immediate-release crystalline nicotinic acid preparations, as cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred. Liver function tests and plasma glucose should be frequently monitored.

Interactions

There may be an increased risk of myopathy or rhabdomyolysis when nicotinic acid is used with statins (see Lipid Regulating Drugs, under Interactions of Simvastatin, p.1393). Nicotinic acid may increase the requirements for insulin or oral hypoglycaemics. Aspirin may reduce the clearance of nicotinic acid. *In vitro* studies suggest that colestipol and colestyramine may reduce the availability of nicotinic acid, and some licensed product information recommends an interval of at least 4 to 6 hours between giving nicotinic acid and bile-acid binding resins.

Antiepileptics. For the effect of nicotinamide on *carbamazepine*, see Vitamins, p.475.

Nicotine. A patient started to have flushing and dizziness after her usual doses of nicotinic acid when transdermal nicotine patches were added to her therapy.[1] She had experienced such reactions 3 years previously on starting nicotinic acid therapy, but not since, and it was suggested that on this occasion an interaction might have been responsible.

1. Rockwell KA. Potential interaction between niacin and transdermal nicotine. *Ann Pharmacother* 1993; **27:** 1283–4.

Pharmacokinetics

Nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract after oral doses and widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to *N*-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

◊ References.

1. Pieper JA. Overview of niacin formulations: differences in pharmacokinetics, efficacy, and safety. *Am J Health-Syst Pharm* 2003; **60** (Suppl 2): S9–14.

Human Requirements

The daily human requirement of nicotinic acid, though not definitely known, is probably about 15 to 20 mg. Yeast, meat, fish, potatoes, legumes, and wholemeal cereals are good sources of nicotinic acid and nicotinamide. However they may be present in a bound, unabsorbable form in cereals, especially maize. Nicotinic acid can also be obtained from the conversion of tryptophan in the body, 60 mg of dietary tryptophan being considered equivalent to 1 mg of dietary nicotinic acid, so requirements are influenced by dietary protein intake and if protein intake is adequate there is little need for any preformed vitamin in the diet. There is generally little loss of nicotinic acid from foods during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for nicotinic acid[1] and in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK the reference nutrient intake (RNI) is 6.6 mg niacin equivalent per 1000 kcal daily and the estimated average requirement (EAR) is 5.5 mg niacin equivalent per 1000 kcal daily for adult males and females. One niacin equivalent is equal to 1 mg of dietary nicotinic acid or 60 mg of dietary tryptophan. In the US the RDAs are also expressed in niacin equivalents and are 16 mg daily for adult males and 14 mg daily for adult females; the EAR is 12 mg daily in males and 11 mg daily in females. The tolerable upper intake level for adults is 35 mg daily.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Nicotinic acid and nicotinamide, the form that occurs naturally in the body, are water-soluble vitamin B substances that are converted to nicotinamide adenine dinucleotide (nadide, p.2350) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain.

Nicotinic acid deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a syndrome known as pellagra, characterised by skin lesions, especially on areas exposed to sunlight, with hyperpigmentation and hyperkeratinisation. Other symptoms include diarrhoea, abdominal pain, glossitis, stomatitis, loss of appetite, headache, lethargy, and mental and neurological disturbances. Nicotinic acid deficiency may occur with other vitamin B-complex deficiency states, for example in alcoholism.

Nicotinic acid and nicotinamide are used in the treatment and prevention of **nicotinic acid deficiency**. Nicotinamide is preferred as it does not cause vasodilatation. They are usually given orally, the preferred route, but may also be given by the intramuscular route or by slow intravenous injection. Doses of up to 500 mg daily (of either compound) in divided doses have been recommended.

Nicotinic acid has been used for its **vasodilator** action in the treatment of a variety of disorders; its value is not considered to be established.

In high doses, nicotinic acid has beneficial effects on blood lipid profiles, and has been used, with dietary modification and often with other lipid regulating drugs, in **hyperlipidaemias** (see below). For the immediate-release preparations, up to 600 mg daily in 3 divided oral doses has been given initially, gradually increased over 2 to 4 weeks to doses of up to 6 g daily; adverse effects may be a limiting factor. Alternatively, initial doses of 375 or 500 mg at night have been given as a modified-release preparation and gradually increased according to response to a maintenance dose of 1 to 2 g at bedtime. The daily dose should not be increased by more than 500 mg in any 4-week period. A combination preparation containing nicotinic acid with laropiprant, a prostaglandin D_2 antagonist that inhibits nicotinic acid-induced flushing, may also be used.

Topical nicotinamide is used in the treatment of mild to moderate inflammatory **acne** (see below), typically as a 4% gel applied twice daily.

Nicotinamide has been shown to inhibit the destruction of pancreatic beta cells *in vitro* and is therefore being investigated in the prevention and treatment of type 1 **diabetes mellitus** (see below).

Acne. Topical nicotinamide may be used in the treatment of inflammatory acne (p.1577); nicotinamide 4% was as effective as clindamycin 1% when applied topically twice daily for 8 weeks.[1]

1. Shalita AR, *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34:** 434–7.

Diabetes mellitus. Nicotinic acid can affect glucose tolerance and should be used with care in established diabetes (see Effects on Glucose Tolerance, above). However, the drug has been used successfully in patients with diabetes. Nicotinamide has been reported to induce remission in patients with newly diagnosed type 1 diabetes mellitus (p.431), and may delay the onset of disease.[1,2]

However, a randomised trial found modified-release nicotinamide at 1.2 g/m^2 daily (to a maximum of 3 g daily) to be ineffective in preventing the onset of diabetes mellitus in first-degree relatives of patients with the disease.[3] Nicotinic acid can also raise high-density lipoprotein (HDL)-cholesterol concentrations (see below);[4,5] changes in glucose tolerance were mild enough for the drug to be considered as an alternative to statins and fibrates in diabetic patients.

1. Elliott RB, Chase HP. Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. *Diabetologia* 1991; **34:** 362–5.
2. Pozzilli P, *et al.* Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care* 1996; **19:** 1357–63.
3. European Nicotinamide Diabetes Intervention Trial Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type I diabetes. *Lancet* 2004; **363:** 925–31.
4. Elam MB, *et al.* Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *JAMA* 2000; **284:** 1263–70.
5. Grundy SM, *et al.* Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med* 2002; **162:** 1568–76.

Hyperlipidaemias. The first-line treatment for hyperlipidaemias remains dietary and lifestyle modification; where this fails, drug therapy may be considered (p.1169). Nicotinic acid is reported to have a favourable effect on blood-lipid profiles, raising high-density lipoprotein (HDL)-cholesterol and lowering low-density lipoprotein (LDL)-cholesterol.[1-3] Nicotinic acid is used particularly in familial hypertriglyceridaemia, or in familial combined hyperlipidaemia when both triglyceride and cholesterol concentrations are similarly elevated. Nicotinic acid was less effective than lovastatin at reducing LDL-cholesterol in patients with primary hypercholesterolaemia, but more effective at increasing HDL-cholesterol; lovastatin was better tolerated.[4] A combination of nicotinic acid with lovastatin was found to be comparable to atorvastatin and more effective than simvastatin in reducing LDL-cholesterol, and more effective than either atorvastatin or simvastatin in increasing HDL-cholesterol, in a study of patients with dyslipidaemia.[5] Some have recommended that nicotinic acid be substituted for a statin to lower LDL-cholesterol when patients cannot tolerate a statin.[2] Combination therapy is recommended when the reduction in LDL-cholesterol is insufficient with statin monotherapy,[2,6] or when raising HDL-cholesterol would be beneficial,[7-9] as in patients with type 2 diabetes mellitus, or the metabolic syndrome.[8] The risk of muscle toxicity with this combination is not considered to be significantly different to that with statin monotherapy.[7]

1. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271:** 672–7.
2. McKenney J. Niacin for dyslipidemia: considerations in product selection. *Am J Health-Syst Pharm* 2003; **60:** 995–1005.
3. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. *Drugs* 2005; **65:** 2719–40.
4. Illingworth DR, *et al.* Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. *Arch Intern Med* 1994; **154:** 1586–95.
5. Bays HE, *et al.* Comparison of once-daily, Niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; **91:** 667–72.
6. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003; **78:** 735–42.
7. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med* 2004; **164:** 697–705.
8. Chapman MJ, *et al.* Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; **20:** 1253–68.
9. Yim BT, Chong PH. Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. *Ann Pharmacother* 2003; **37:** 106–15.

Pemphigus. Oral treatment with nicotinamide and a tetracycline[1-6] has controlled lesions in pemphigus and pemphigoid (p.1582), including persistent pemphigoid gestationis,[5] and ocular cicatricial pemphigoid.[6]

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132:** 668–70.
2. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133:** 88–90.
3. Reiche L, *et al.* Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* 1998; **23:** 254–7.
4. Goon ATJ, *et al.* Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. *Singapore Med J* 2000; **41:** 327–30.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13:** 143–6.
6. Dragan L, *et al.* Tetracycline and niacinamide: treatment alternatives in ocular cicatricial pemphigoid. *Cutis* 1999; **63:** 181–3.

Preparations

BP 2008: Nicotinamide Tablets; Nicotinic Acid Tablets; Vitamins B and C Injection;
BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;
USP 31: Niacin Injection; Niacin Tablets; Niacinamide Injection; Niacinamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: NB-3; Niaspan; Nicozinc; ***Austria:*** Direktan; Nicovitol; ***Belg.:*** Ucemine PP; ***Braz.:*** Papuless; ***Canad.:*** Niaspan; ***Chile:*** Cotina; Niacex; Niaspan; Vectidan†; ***Fin.:*** Niaspan; ***Fr.:*** Niaspan; Nicobion; ***Ger.:*** Niaspan; Nicobion; ***Hong Kong:*** Niaspan; ***India:*** Nialip; ***Indon.:*** Niacef; Niaspan; ***Irl.:*** Niaspan; Nicam; ***Mex.:*** Hipocol; Nacro; Pepevit; ***Neth.:*** Niaspan; ***Philipp.:*** Niaspan; ***Port.:*** Niaspan; ***Singapore:*** Niaspan; ***Swed.:*** Niaspan; Nicangin; ***Thai.:*** Nicotabs; ***UK:*** Freederm; Niaspan; Nicam; ***USA:*** Endur-acin; Niaspan; Nicotinex†; Slo-Niacin; ***Venez.:*** Niaspan.

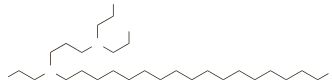
Multi-ingredient: ***Arg.:*** Antikatarata†; Centella Asiatica Compuesta; IP-6; Nicozinc; Parenciasˆ; ***Austral.:*** Bioglan Cirflo†; Chilblain Formula†; Gingo A†; Procholˆ; Silybum Complex†; ***Austria:*** Beneuran Vit B-Komplex†; Diligan; Pertrombon; Spasmocor; ***Belg.:*** Trihistalex; ***Braz.:*** Gaba†; Nicopaverina B6†; Nicopaverina†; ***Canad.:*** PML Crono†; ***Chile:*** Cicapost; Perfungol; Ureadin Forte; Ureadin Rx PS; Ureadin Rx RD; ***Fin.:*** Neurovitan; Vertipam; ***Fr.:*** TTD-B -B ; Vita-Dermacide; ***Ger.:*** Eukalisan N; Hepagrisevit Forte-N†; MerSolˆ; Petehaˆ; Telbibur Nˆ; ***Hung.:*** Paniverin; ***India:*** Diligan; Hepa-Merz; Nutrozyme; Sioneuron; Unienzyme; ***Indon.:*** Biocholes; Cereton; Kitoles; Sotens; ***Irl.:*** Effaclar Al; ***Israel:*** Babyzim; ***Ital.:*** Emazian B12†; Emoantitossina†; Emopon; Epargriseovit; Fisioreve; Folepar B12; Fosforilasi; Neuroftalˆ; Novostatin; Solvobil; Vit-Porphyrinˆ; ***Mon.:*** Monasens; ***Philipp.:*** Jetepar; ***Pol.:*** Dernilan; ***Port.:*** Diligan†; Ureadin Forte; ***Rus.:*** Lidevine (Лидевин); Oftan Catachrom (Офтан Катахром); ***S.Afr.:*** Cosaldonˆ; ***Singapore:*** Erase; ***Spain:*** Depurativo Richelet; Euzymina Lisina I; Euzymina Lisina II; Vitaphakol; ***Swed.:*** Theranylˆ; ***Thai.:*** B-100 Complex; ***Turk.:*** Epargriseovit; ***UK:*** Crampex; Quiet Life; S.P.H.P.; ***USA:*** Advicor; Simcor.

Olaflur *(BAN, USAN, rINN)*

Amine Fluoride 297; GA-297; Olaflurum; SKF-38095. 2,2′-(3-[*N*-(2-Hydroxyethyl)octadecylamino]propylimino)diethanol dihydrofluoride.

Олафлур

$C_{27}H_{60}F_2N_2O_3$ = 498.8.
CAS — 6818-37-7.
ATC — A01AA03.
ATC Vet — QA01AA03.



Profile
Olaflur is used as a source of fluoride (see Sodium Fluoride, p.1962) in the prevention of dental caries. For a report of stomatitis considered to be due to olaflur, see Hypersensitivity, under Sodium Fluoride, p.1963.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Elmexˆ; ***Israel:*** Elmexˆ; ***Pol.:*** Fluormex; ***Port.:*** Elmex.

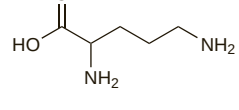
Multi-ingredient: ***Austria:*** Elmex; ***Belg.:*** Elmex; ***Cz.:*** Elmex; ***Fin.:*** Elmex; ***Fr.:*** Elmex Sensitive†; Elmexˆ; Meridolˆ; ***Ger.:*** Elmex; Lawefluor Nˆ; Multifluorid; ***Hung.:*** Elmex; ***Israel:*** Elmex; Meridol; ***Ital.:*** Elmex; ***Neth.:*** Elmex; ***Pol.:*** Fluormex; ***Switz.:*** Elmex; Paro aux fluorures d'amines Gelee.

Ornithine *(rINN)*

α,δ-Diaminovaleric Acid; Orn; L-Ornithine; Ornithinum; Ornitina. L-2,5-Diaminovaleric acid.

Орнитин

$C_5H_{12}N_2O_2$ = 132.2.
CAS — 70-26-8.



Pharmacopoeias. *Ger.* includes Ornithine Aspartate and Ornithine Hydrochloride.

Profile
Ornithine is an aliphatic non-essential amino acid. It is used as a dietary supplement.

The aspartate, hydrochloride, and oxoglurate (ornithine ketoglutarate, see also Parenteral and Enteral Nutrition under Glutamic Acid, p.1947) have been used in various indications including the treatment of hyperammonaemia (p.1929) and hepatic encephalopathy (p.1697).

◊ References.

1. Rapport L, Lockwood B. Ornithine ketoglutarate. *Pharm J* 2001; **266:** 688–90.
2. Coudray-Lucas C, *et al.* Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. *Crit Care Med* 2000; **28:** 1772–6.
3. Kircheis G, *et al.* Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab Brain Dis* 2002; **17:** 453–62.
4. Blonde-Cynober F, *et al.* Use of ornithine alpha-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; **19:** 73–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cere; Hepa; Ornicetil; ***Chile:*** Hepa-Merzˆ; ***Cz.:*** Hepa-Merzˆ; ***Fr.:*** Cetornan; Ornicetil; ***Ger.:*** Hepa-Merz; Hepa-Merz KT; Hepa-Vibolex; ***Hong Kong:*** Hepa-Merz; ***Hung.:*** Hepa-Merz; ***India:*** Hepa-Merz; ***Indon.:*** Hepa-Merz; Hevtin; ***Ital.:*** Ornicetilˆ; Ornil; Ornil KGF; ***Mex.:*** Hepa-Merz; ***Philipp.:*** Hepa-Merz; ***Pol.:*** Hepatil.

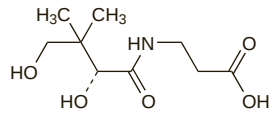
Multi-ingredient: ***Braz.:*** Ornihepatˆ; Ornitargin; ***Fr.:*** Epuramˆ; Ornitaine; ***Ger.:*** Polilevo Nˆ; ***India:*** Biohepˆ; Hepa-Merz; ***Ital.:*** Ipoazotal Complex; Ipoazotalˆ; Polilevoˆ; Somatron; ***Pol.:*** Hepa-Merz.

Pantothenic Acid *(BAN)*

Pantoténico, ácido; Vitamin B_5. (+)-(*R*)-3-(2,4-Dihydroxy-3,3-dimethylbutyramido)propionic acid.

Пантотеновая Кислота; Витамин B5

$C_9H_{17}NO_5$ = 219.2.
CAS — 79-83-4 (D-pantothenic acid); 599-54-2 (DL-pantothenic acid).
ATC — A11HA31; D03AX04.
ATC Vet — QA11HA31; QD03AX04.



(D-pantothenic acid)

Calcium Pantothenate *(BANM, rINN)*

Calcii pantothenas; Calcium, pantothénate de; Dextro Calcium Pantothenate; Kalcio pantotenatas; Kalciumpantotenat; Kalciumpantotenát; Kalsiumpantotenaatti; Pantotenato de calcio; Pantothenan vápenatý; Pantothénate de Calcium; Wapnia pantotenian.

Кальция Пантотенат

$(C_9H_{16}NO_5)_2Ca$ = 476.5.
CAS — 137-08-6 (calcium D-pantothenate); 6381-63-1 (calcium DL-pantothenate);.
ATC — A11HA31; D03AX04.
ATC Vet — QA11HA31; QD03AX04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.* *US* also has a monograph for Racemic Calcium Pantothenate. *Ger.* also includes Sodium Pantothenate.

Ph. Eur. 6.2 (Calcium Pantothenate). A white or almost white, slightly hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution has a pH of 6.8 to 8.0. Store in airtight containers.

USP 31 (Calcium Pantothenate). The calcium salt of the dextrorotatory isomer of pantothenic acid. A white, odourless, slightly hygroscopic powder. Soluble 1 in 3 of water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Store in airtight containers.

USP 31 (Racemic Calcium Pantothenate). A mixture of the calcium salts of the dextrorotatory and laevorotatory isomers of pantothenic acid. The physiological activity of Racemic Calcium Pantothenate is about one-half that of Calcium Pantothenate. A white, slightly hygroscopic powder, having a faint characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Its solutions are neutral or alkaline to litmus. Store in airtight containers.

Adverse Effects
Pantothenic acid is reported to be generally non-toxic.

Eosinophilia. A report of life-threatening eosinophilic pleuropericarditis associated with the use of biotin and pantothenic acid.[1] Symptoms resolved on stopping the vitamins.

1. Debourdeau PM, *et al.* Life-threatening eosinophilic pleuropericardial effusion related to vitamins B and H. *Ann Pharmacother* 2001; **35:** 424–6.

Pharmacokinetics
Pantothenic acid is readily absorbed from the gastrointestinal tract after oral doses. It is widely distributed in the body tissues and appears in breast milk. About 70% of pantothenic acid is excreted unchanged in the urine and about 30% in the faeces.

Human Requirements
Pantothenic acid is widely distributed in foods. Meat, legumes, and whole grain cereals are particularly rich sources; other good sources include eggs, milk, vegetables, and fruits.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) has been set (see p.1925) for pantothenic acid although an intake of 3 to 7 mg daily for adults was believed