As with other stimulants, there is the possibility of dependence with long-term use. Modafinil has been misused as a so-called 'lifestyle drug' to promote alertness and wakefulness in otherwise healthy subjects.

**Effects on the skin.** The FDA[1] reported that it had received 6 cases of severe cutaneous adverse effects associated with modafinil from its initial marketing in December 1998 to January 2007; of these, 5 required hospitalisation. The cutaneous effects, which included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, were reported in adults and children although use in patients under 16 years of age is unlicensed. The median time to onset was 17.5 days with a range of 5 days to 5 weeks.

1. Modafinil (marketed as Provigil): serious skin reactions. *FDA Drug Safety Newsletter* 2007; **1:** 5–7. Available at: http://www.fda.gov/cder/dsn/2007_fall/2007_fall.pdf (accessed 20/05/08)

### Interactions

Modafinil is partially metabolised by the cytochrome P450 isoenzymes. In addition, it also has enzyme-inducing and -inhibiting activity. Use with other drugs that inhibit, induce, or act as a substrate to these isoenzymes such as oral contraceptives and antiepileptics may result in changes in plasma concentration of modafinil and/or the other drug.

### Pharmacokinetics

Modafinil is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations occurring after 2 to 4 hours. Plasma protein binding is about 60%, mainly to albumin. Modafinil is metabolised in the liver, partially by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5; two major metabolites have been identified: acid modafinil and modafinil sulfone, both of which are inactive. Excretion is mainly through the kidneys with less than 10% of the dose being eliminated unchanged. The elimination half-life after multiple doses is 15 hours.

◊ References.

1. Wong YN, *et al.* A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 1999; **39:** 30–40.
2. Wong YN, *et al.* Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. *J Clin Pharmacol* 1999; **39:** 281–8.

### Uses and Administration

Modafinil is a central stimulant chemically related to adrafinil (p.2149). It is used in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p.2148), obstructive sleep apnoea, and shift-work sleep disorder. In the treatment of the narcoleptic syndrome or obstructive sleep apnoea, modafinil is given orally in a dose of 200 to 400 mg daily, in two divided doses, in the morning and at midday, or as a single dose in the morning. For the treatment of shift-work sleep disorder, the daily dose is 200 mg taken as a single dose 1 hour before starting work. An initial dose of 100 mg daily should be used in the elderly and adjusted as necessary. For doses in hepatic and renal impairment, see below.

Modafinil is usually given as a racemic mixture but preparations containing only the *R*-isomer, armodafinil, are also available, see Armodafinil, p.2150.

Modafinil has also been investigated for the treatment of fatigue associated with multiple sclerosis and for the treatment of hyperactivity disorders.

◊ References.

1. Broughton RJ, *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997; **49:** 444–51.
2. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol* 1998; **43:** 88–97.
3. McClellan KJ, Spencer CM. Modafinil: a review of its pharmacology and clinical efficacy in the management of narcolepsy. *CNS Drugs* 1998; **9:** 311–24.
4. Fry JM. Treatment modalities for narcolepsy. *Neurology* 1998; **50:** S43–S48.
5. Anonymous. Modafinil for narcolepsy. *Med Lett Drugs Ther* 1999; **41:** 30–1.
6. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000; **54:** 1166–75.
7. Kingshott RN, *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2001; **163:** 918–23.
8. Czeisler CA, *et al.* The US Modafinil in Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005; **353:** 476–86. Correction. *ibid.*; 1078.
9. Gill M, *et al.* Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. *Acad Emerg Med* 2006; **13:** 158–65. Correction. *ibid.*; 477.
10. Turner D. A review of the use of modafinil for attention-deficit hyperactivity disorder. *Expert Rev Neurother* 2006; **6:** 455–68.
11. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006; **67:** 554–66.
12. Lindsay SE, *et al.* Use of modafinil for the treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; **40:** 1829–33.

**Administration in hepatic or renal impairment.** The total oral dose of modafinil should be reduced to 100 to 200 mg daily in any patient with severe hepatic or renal impairment.

### Preparations

***USP 31:*** Modafinil Tablets.

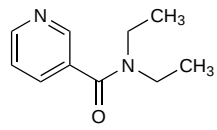
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Forcilin; Vigicer; ***Austral.:*** Modavigil; ***Austria:*** Modasomil; ***Belg.:*** Provigil; ***Canad.:*** Alertec; ***Chile:*** Mentix; Naxelan; Resotyl; ***Cz.:*** Vigil; ***Denm.:*** Modiodal; ***Fr.:*** Modiodal; ***Ger.:*** Vigil; ***Gr.:*** Modiodal; ***Irl.:*** Provigil; ***Israel:*** Provigil; ***Ital.:*** Provigil; ***Mex.:*** Modiodal; ***Neth.:*** Modiodal; ***Norw.:*** Modiodal; ***NZ:*** Modavigil; ***Pol.:*** Vigil; ***Port.:*** Modiodal; ***S.Afr.:*** Provigil; ***Spain:*** Modiodal; ***Swed.:*** Modiodal; ***Switz.:*** Modasomil; ***Turk.:*** Modiodal; ***UK:*** Provigil; ***USA:*** Provigil.

## Nikethamide *(BAN, rINN)* ⊗

Cordiaminum; Nicetamid; Nicéthamide; Nicethamidum; Nicotinic Acid Diethylamide; Nicotinoyldiaethylamidum; Niketamid; Niketamidas; Niketamidi; Nikethamid; Nikethylamide; Niquetamida. *N,N*-Diethylnicotinamide; *N,N*-Diethylpyridine-3-carboxamide.

Никетамид

$C_{10}H_{14}N_2O$ = 178.2.
*CAS — 59-26-7.*
*ATC — R07AB02.*
*ATC Vet — QR07AB02.*



**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), and *Viet.*
**Ph. Eur. 6.2** (Nikethamide). A colourless or slightly yellow oily liquid or crystalline mass. Miscible with water and with alcohol. A 25% solution in water has a pH of 6.0 to 7.8.

### Profile

Nikethamide has actions similar to those of doxapram (p.2155). It was formerly used as a respiratory stimulant but has largely been abandoned because of toxicity. Nikethamide and its calcium thiocyanate salt have also been used in some countries as central stimulants and for hypotensive disorders.

**Porphyria.** Nikethamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

### Preparations

***BP 2008:*** Nikethamide Injection.

**Proprietary Preparations** (details are given in Part 3)
***Pol.:*** Cardiamidum.

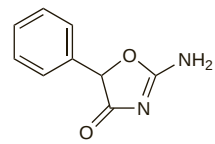
**Multi-ingredient:** ***Fr.:*** Coramine Glucose; ***Ger.:*** Zellaforte N Plus†; ***Pol.:*** Cardiamid-Coffein; Glucardiamid; ***Switz.:*** Gly-Coramin.

## Pemoline *(BAN, USAN, rINN)* ⊗

LA-956; NSC-25159; Pemoliini; Pemolin; Pemolina; Pémoline; Pemolinum; Phenoxazole; Phenylisohydantoin; Phenylpseudohydantoin. 2-Imino-5-phenyl-4-oxazolidinone.

Пемолин

$C_9H_8N_2O_2$ = 176.2.
*CAS — 2152-34-3 (pemoline); 68942-31-4 (pemoline hydrochloride); 18968-99-5 (magnesium pemoline).*
*ATC — N06BA05.*
*ATC Vet — QN06BA05.*



### Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153; however, the effects of over-stimulation and sympathomimetic activity are considered to be less with pemoline.

Reports of liver toxicity in patients taking pemoline (see Effects on the Liver, below) have led to its withdrawal in many countries including the UK and USA. Where available, it is contra-indicated in patients with liver disorders and there are stringent precautions to be observed with its use. Treatment should be initiated only in patients with normal baseline liver function tests and liver function should be monitored every 2 weeks. Pemoline should be stopped if serum alanine aminotransferase is increased to a clinically significant level or there is any increase greater than or equal to twice the upper limit of normal, or if any clinical signs or symptoms suggestive of liver failure develop. Pemoline should also be withdrawn from patients who have failed to show a substantial clinical response within 3 weeks of completing dose titration. There have also been rare or isolated reports of chorea, tics, mania, and neutropenia.

**Abuse.** Paranoid psychosis was observed in a 38-year-old man taking pemoline 75 to 225 mg daily.[1] His compulsive use of the drug, development of tolerance, depressive withdrawal syndrome, and inability to abstain indicated dependence and it was evident that the patient was addicted to pemoline.

Choreoathetosis and rhabdomyolysis developed in a patient following a marked increase in intake of pemoline.[2] Abnormal movements responded to diazepam.

1. Polchert SE, Morse RM. Pemoline abuse. *JAMA* 1985; **254:** 946–7.
2. Briscoe JG, *et al.* Pemoline-induced choreoathetosis and rhabdomyolysis. *Med Toxicol* 1988; **3:** 72–6.

**Effects on growth.** Results of a study in 24 hyperkinetic children suggested that growth suppression was a potential adverse effect of prolonged treatment with clinically effective doses of pemoline and that this effect might be dose-related.[1]

See also under Dexamfetamine Sulfate, p.2153.

1. Dickinson LC, *et al.* Impaired growth in hyperkinetic children receiving pemoline. *J Pediatr* 1979; **94:** 538–41.

**Effects on the liver.** Pemoline has been associated with hepatotoxicity.

Elevated concentrations of serum aspartate aminotransferase and serum alanine aminotransferase have been noted in 2% of children taking pemoline for hyperactivity; the effect was stated to be transient and reversible.[1]

However, more serious reactions have also occurred. Acute hepatitis[2] was associated with pemoline in a 10-year-old boy and the drug was believed to be the cause of fatal fulminant liver failure[3] in a 14-year-old boy and in 2 previously published cases. The UK CSM[4] subsequently became aware of 33 reports of serious hepatic reactions in the USA, including a total of 6 fatalities and the need for liver transplantation in 2 cases; this prompted the withdrawal of pemoline for the treatment of hyperactivity in the UK. Following further reports of liver failure resulting in transplantation or death, the FDA[5] similarly withdrew pemoline in the USA.

1. Anonymous. 'Hyperkinesis' can have many causes, symptoms. *JAMA* 1975; **232:** 1204–16.
2. Patterson JF. Hepatitis associated with pemoline. *South Med J* 1984; **77:** 938.
3. Berkovitch M, *et al.* Pemoline-associated fulminant liver failure: testing the evidence for causation. *Clin Pharmacol Ther* 1995; **57:** 696–8.
4. CSM/MCA. Volital (pemoline) has been withdrawn. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
5. FDA. Alert for healthcare professionals: pemoline tablets and chewable tablets (marketed as Cylert) (issued 24/10/05). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/pemolineHCP.pdf (accessed 24/04/06)

**Effects on the prostate.** Experience in one patient suggested that pemoline might adversely affect the prostate gland or interfere with tests for prostatic acid phosphatase used in the diagnosis of prostatic carcinoma.[1]

1. Lindau W, de Girolami E. Pemoline and the prostate. *Lancet* 1986; **i:** 738.

### Interactions

Hypertensive crisis may possibly occur if pemoline is given with MAOIs. Reduced seizure threshold has been reported in epileptic patients taking pemoline and antiepileptics.

### Pharmacokinetics

Pemoline is readily absorbed from the gastrointestinal tract. About 50% is bound to plasma proteins. It is metabolised in the liver and excreted in the urine as unchanged pemoline and metabolites.

◊ References.

1. Vermeulen NPE, *et al.* Pharmacokinetics of pemoline in plasma, saliva and urine following oral administration. *Br J Clin Pharmacol* 1979; **8:** 459–63.
2. Sallee F, *et al.* Oral pemoline kinetics in hyperactive children. *Clin Pharmacol Ther* 1985; **37:** 606–9.
3. Collier CP, *et al.* Pemoline pharmacokinetics and long term therapy in children with attention deficit disorder and hyperactivity. *Clin Pharmacokinet* 1985; **10:** 269–78.

### Uses and Administration

Pemoline is a central stimulant with actions similar to those of dexamfetamine (p.2154).

It has been used in the management of hyperactivity disorders in children (p.2148). In many countries pemoline was withdrawn from use after reports of serious hepatotoxicity.

Pemoline has been included in preparations also containing yohimbine hydrochloride and methyltestosterone that are claimed to combat failure of sexual desire and functioning in males and females; such preparations are not recommended.

Pemoline has been given with magnesium hydroxide (magnesium pemoline) in an attempt to increase its absorption.