2. Greenhill LL, *et al.* Prolactin, growth hormone and growth responses in boys with attention deficit disorder and hyperactivity treated with methylphenidate. *J Am Acad Child Psychiatry* 1984; **23:** 58–67.
3. Klein RG, Mannuzza S. Hyperactive boys almost grown up III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 1988; **45:** 1131–4.

Effects on the liver. Hepatotoxicity with raised liver enzyme values in a 67-year-old woman was associated with the use of methylphenidate hydrochloride 30 mg daily by mouth.[1] Methylphenidate-induced hepatocellular injury was reported in a 19-year-old woman who developed jaundice, fever, and malaise after intravenous abuse of methylphenidate hydrochloride tablets.[2]

1. Goodman CR. Hepatotoxicity due to methylphenidate hydrochloride. *N Y State J Med* 1972; **72:** 2339–40.
2. Mehta H, *et al.* Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. *J Clin Gastroenterol* 1984; **6:** 149–51.

Effects on the skin. A fixed drug eruption of the scrotum has been reported in 2 children treated with methylphenidate for attention deficit disorder.[1]

1. Cohen HA, *et al.* Fixed drug eruption of the scrotum due to methylphenidate. *Ann Pharmacother* 1992; **26:** 1378–9.

Tourette's syndrome. For a discussion on whether central stimulants provoke Tourette's syndrome, see Dexamfetamine Sulfate, p.2153.

Interactions

As for Dexamfetamine Sulfate, p.2153.

Anticoagulants. For the effect of methylphenidate on *ethyl biscoumacetate*, see Central Stimulants under the Interactions of Warfarin, p.1430.

Antidepressants. For the effect of methylphenidate on *tricyclic antidepressants*, see under Amitriptyline, p.379.

Antiepileptics. Methylphenidate blood concentrations decreased, and symptoms of attention deficit hyperactivity disorder worsened, in a 13-year-old girl after starting therapy with *carbamazepine*.[1]

For the effect of methylphenidate on antiepileptics, see under Phenytoin, p.500.

1. Schaller JL, *et al.* Carbamazepine and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 112–13.

Pharmacokinetics

Methylphenidate is readily absorbed from the gastrointestinal tract. The presence of food in the stomach accelerates the rate of absorption but not the total amount absorbed. Peak plasma concentrations are reached about 2 hours after oral doses; methylphenidate undergoes extensive first-pass metabolism. Protein binding is low. It is excreted as metabolites mainly in the urine with small amounts appearing in the faeces; less than 1% appears in the urine as unchanged methylphenidate. The major metabolite is ritalinic acid (2-phenyl-2-piperidyl acetic acid). The plasma elimination half-life is about 2 hours. Methylphenidate is distributed into breast milk.

◊ References.

1. Aoyama T, *et al.* Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44;** 79–84.
2. Aoyama T, *et al.* Pharmacokinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia. *Clin Pharmacol Ther* 1994; **55:** 270–6.
3. Shader RI, *et al.* Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999; **39:** 775–785.
4. Kimko HC, *et al.* Pharmacokinetics and clinical effectiveness of methylphenidate. *Clin Pharmacokinet* 1999; **37:** 457–70.
5. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *J Clin Pharmacol* 2000; **40:** 379–88.
6. Teo SK, *et al.* A single-dose, two-way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects. *J Clin Pharmacol* 2004; **44:** 173–8.
7. Quinn D, *et al.* Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007; **47:** 760–6.

Uses and Administration

Methylphenidate hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p.2154). It is used in the treatment of narcolepsy (p.2148) and as an adjunct to psychological, educational, and social measures in the treatment of hyperactivity disorders in children.

In the treatment of **narcolepsy** the usual oral dose is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In **hyperactivity disorders** in children aged 6 years and over, the usual initial dose is 5 mg once or twice daily by mouth, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses. Methylphenidate may be given before breakfast and lunch. A later dose may be considered if the effect wears off in the evening causing rebound hyperactivity.

Methylphenidate hydrochloride is also available as modified-release preparations for the treatment of hyperactivity disorders. Some modified-release preparations also contain immediate-release methylphenidate within the formulation. Doses of modified-release preparations may vary according to the brand chosen. Recommended doses for one brand of modified-release tablets (*Concerta*: *Janssen-Cilag, UK*; *McNeil, USA*) are as follows:

- children and adolescents aged 6 to 17 years and not currently taking conventional methylphenidate should be started on 18 mg once daily in the morning
- the dose may then be increased at weekly intervals to a maximum of 54 mg once daily; the USA permits a maximum of 72 mg once daily in those aged 13 to 17 years
- the dose in patients already taking conventional methylphenidate should be based on their current dose although the initial dose should not exceed 54 mg once daily

Transdermal patches delivering amounts of methylphenidate ranging from 1.1 to 3.3 mg/hour are available for once-daily application in the treatment of hyperactivity disorders in children aged 6 to 12 years. Patients should be started on the lowest strength patch regardless of any previous methylphenidate use; thereafter, doses should be individually titrated for each patient according to response and increased at weekly intervals if necessary to a maximum of 3.3 mg/hour (at week 4). Patches should be applied to the hip area 2 hours before an effect is needed and removed after a maximum of 9 hours later.

Methylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond, to assess the patient's condition. Treatment is not usually continued beyond puberty, however, in some patients drug therapy may be required into adulthood. In such cases doses are similar to those used in the treatment of narcolepsy.

A single isomer form of methylphenidate, dexmethylphenidate (p.2154) is also used for hyperactivity disorders.

◊ References.

1. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc* 2000; **75:** 711–21.

Depression. Stimulants are no longer recommended as sole treatment for depression (p.373), although they have been tried in augmenting the effect of standard antidepressants such as the SSRIs[1] in patients with refractory depressive disorders.

1. Stoll AL, *et al.* Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 1996; **57:** 72–6.

Disturbed behaviour. Disturbed behaviour can have a number of causes and is usually treated with an antipsychotic or benzodiazepine (see p.954). A review[1] of the published clinical trials between 1966 and June 2004 found that although methylphenidate was likely to improve memory, attention, concentration, and mental processing in patients with traumatic brain injury, its effect on behaviour remains to be determined; the most commonly used dosage was 300 micrograms/kg twice daily.

1. Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann Pharmacother* 2005; **39:** 1309–13.

Hyperactivity. Methylphenidate is one of the main drugs used in hyperactivity, including attention deficit hyperactivity disorder (ADHD) (p.2148).

Small studies have indicated that different aspects of attention deficit disorders in children might respond to different doses of methylphenidate.[1-4] In addition to the morning and noon doses commonly used in hyperactivity disorders, studies[5,6] have shown improved clinical outcome with little adverse effect on sleep patterns if a third late afternoon dose is given.

Modified-release preparations with a slow onset of action have been developed to overcome the short duration of action of methylphenidate although they may be less effective than immediate-release preparations. A study,[7] using a regimen to simulate the prolonged steady plasma concentration profile obtained with the slow-onset, modified-release preparations, has suggested that unlike twice-daily treatment acute tolerance might develop with the use of modified-release preparations. However, a newer modified-release preparation has been reported to be as effective as an immediate-release preparation in short-term studies.[8,9] Transdermal patches containing methylphenidate released over 9 hours are available in the USA.[10]

UK guidelines for the use of methylphenidate in children and adolescents with ADHD are available.[11]

1. Sprague RL, Sleator EK. Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science* 1977; **198:** 1274–6.
2. Tannock R, *et al.* Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. *Pediatrics* 1989; **84:** 648–57.
3. Sebrechts MM, *et al.* Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. *Pediatrics* 1986; **77:** 222–8.
4. Barkley RA, *et al.* Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991; **87:** 519–31.
5. Kent JD, *et al.* Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorders. *Pediatrics* 1995; **96:** 320–5.
6. Stein MA, *et al.* Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 1996; **98:** 748–56.
7. Swanson J, *et al.* Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999; **66:** 295–305.
8. Pelham WE, *et al.* Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Abstract: *Pediatrics* 2001; **107:** 1417. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/6/e105 (accessed 15/04/04)
9. Wolraich ML, *et al.* Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001; **108:** 883–92.
10. Anderson VR, Scott LJ. Methylphenidate transdermal system: in attention-deficit hyperactivity disorder in children. *Drugs* 2006; **66:** 1117–26.
11. NICE. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: review of Technology Appraisal 13 (Technology Appraisal 98, issued March 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA098guidance.pdf (accessed 11/08/08)

Preparations

USP 31: Methylphenidate Hydrochloride Extended-release Tablets; Methylphenidate Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Concerta; Methylin; Ritalina; Rubifen; ***Austral.:*** Attenta; Concerta; Lorentin†; Ritalin; ***Austria:*** Concerta; Ritalin; ***Belg.:*** Concerta; Rilatine; ***Braz.:*** Concerta; Ritalina; ***Canad.:*** Concerta; Riphenidate†; Ritalin; ***Chile:*** Aradix; Concerta; Elem†; Nebapul; Ritalin; Ritrocel; ***Cz.:*** Ritalin; ***Denm.:*** Equasym; Motiron; Ritalin; ***Fin.:*** Concerta; ***Fr.:*** Concerta; Ritaline; ***Ger.:*** Concerta; Equasym; Medikinet; Ritalin; ***Gr.:*** Concerta; Ritaline; ***Hong Kong:*** Concerta; Ritalin; ***Hung.:*** Ritalin; ***Indon.:*** Concerta; Ritalin; ***Irl.:*** Concerta; Equasym; Ritalin; ***Israel:*** Concerta; Metadate; Ritalin; ***Malaysia:*** Concerta; Ritalin; Rubifen; ***Mex.:*** Concerta; Ritalin; Tradea; ***Neth.:*** Concerta; Equasym; Ritalin; Rubifen†; Tifinidat; ***Norw.:*** Concerta; Equasym; Ritalin; ***NZ:*** Concerta; Ritalin; Rubifen; ***Philipp.:*** Concerta; ***Pol.:*** Concerta; ***Port.:*** Concerta; Ritalina; Rubifen; ***S.Afr.:*** Adaphen; Concerta; Ritalin; Ritaphen†; ***Singapore:*** Concerta; Ritalin; Rubifen; ***Spain:*** Concerta; Rubifen; ***Swed.:*** Concerta; Ritalin; ***Switz.:*** Concerta; Ritaline; ***Thai.:*** Concerta; Rubifen†; ***Turk.:*** Concerta; Ritalin; ***UK:*** Concerta; Equasym; Medikinet; Ritalin; Tranquilyn†; ***USA:*** Concerta; Daytrana; Metadate; Methylin; Ritalin; ***Venez.:*** Concerta; Ritalin.

Modafinil *(BAN, USAN, rINN)* ⊗

CEP-1538; CRL-40476; Modafinilo; Modafinilum. 2-[(Diphenylmethyl)sulfinyl]acetamide.

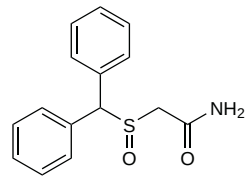
Модафинил

$C_{15}H_{15}NO_2S$ = 273.4.

CAS — 68693-11-8.

ATC — N06BA07.

ATC Vet — QN06BA07.



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

Ph. Eur. 6.2 (Modafinil). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble or practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in alcohol.

USP 31 (Modafinil). A white, odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

The most commonly reported adverse effect of modafinil, affecting about 21% of patients, is headache, which is usually mild or moderate, dose-dependent, and disappears within a few days. Other adverse effects may be a result of CNS stimulation and effects such as nervousness, insomnia, agitation, confusion, personality disorder, tremor, and anxiety have been noted. There may also be gastrointestinal disturbances, including nausea and abdominal pain, dry mouth, diarrhoea, dyspepsia, and constipation, dizziness, and anorexia. Cardiovascular effects such as hypertension, palpitations, and tachycardia have been reported.

Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis, have been reported (see also Effects on the Skin, below). Benign pruritic rashes have also occurred and since it is not possible to predict which skin rashes will become serious, modafinil should be stopped at the first sign of rash unless it is clearly not drug-related. Other hypersensitivity reactions such as angioedema have also been reported rarely.

Psychiatric symptoms including psychosis, depression, hallucinations, suicidal ideation, and mania have been reported. Abnormal liver function tests including dose-related increases in alkaline phosphatase, and dyskinesia have been observed.

Modafinil is contra-indicated in patients with uncontrolled, moderate to severe hypertension or cardiac arrhythmias. It is not recommended in patients with a history of left ventricular hypertrophy or ischaemic ECG changes, chest pain, or other signs of mitral valve prolapse. Modafinil should be given with caution to those with a history of psychosis, depression, or mania.

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.

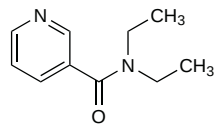
Proprietary Preparations (details are given in Part 3)
Arg.: Forcilin; Vigicer; ***Austral.:*** Modavigil; ***Austria:*** Modasomil; ***Belg.:*** Provigil; ***Canad.:*** Alertec; ***Chile:*** Mentix; Naxelan; Resotyl; ***Cz.:*** Vigil; ***Denm.:*** Modiodal; ***Fr.:*** Modiodal; ***Ger.:*** Vigil; ***Gr.:*** 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.

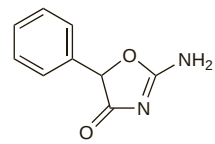
Multi-ingredient: ***Fr.:*** Coramine Glucose; ***Ger.:*** Zellaforte N Plus†; ***Pol.:*** Cardiamid-Coffein; Glucardiamid; ***Switz.:*** Gly-Coramin.

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.