period should be limited to 2 weeks when brotizolam, midazolam, or triazolam are used.[16]

Tolerance to the hypnotic effects of benzodiazepines develops rapidly, with sleep latency and pattern returning to pretreatment levels within a few weeks of starting treatment.

A number of other drugs have been used as alternatives to the benzodiazepines. Zaleplon, zopiclone, and zolpidem act on the same receptors or receptor subtypes as the benzodiazepines although structurally they are unrelated. Their short duration of action makes them more suitable for patients who have trouble falling asleep. The CPMP has recommended that treatment with zolpidem should be limited to a maximum of 4 weeks.[16] It remains to be proven whether these drugs offer any advantages over the benzodiazepines. Indeed, the CSM considers that zopiclone has the same potential for adverse psychiatric reactions, including dependence, as benzodiazepines.[17] NICE[18] in the UK found no compelling evidence of any clinically useful differences between these drugs and the shorter-acting benzodiazepines in terms of effectiveness, adverse effects, or potential for dependence or abuse, and recommends that patients who do not respond to zaleplon, zopiclone, zolpidem, or benzodiazepines should not be switched between these hypnotics; patients may be switched if adverse effects directly related to a specific drug occur.

The use of cloral hydrate and its derivatives as hypnotics is now very limited. They have been used as alternatives to benzodiazepines in the elderly, although there is no convincing evidence of any special value in these patients. They used to be considered useful hypnotics for children but such use is rarely justified.

Clomethiazole has also been used as an alternative to benzodiazepines in the elderly. Nasal and conjunctival irritation may be troublesome, and the danger of overdosage and risk of dependence should be considered.

Some antihistamines have hypnotic properties and a number, including alimemazine, diphenhydramine, doxylamine, and promethazine, are marketed for insomnia. They may cause troublesome antimuscarinic effects and those with longer half-lives may cause hangover effects. Promethazine is also popular for use in children, but such use is not usually justified (see Sudden Infant Death Syndrome under Adverse Effects of Promethazine, p.588, for further details).

Barbiturates are no longer recommended as hypnotics because of their adverse effects. The CSM[19] has advised that barbiturates should only be used for insomnia that is severe and intractable when there are compelling reasons to, and then only in patients already taking barbiturates. It was also advised that attempts should be made to wean patients off barbiturate hypnotics. Similarly, compounds such as ethchlorvynol, glutethimide, and methaqualone are not recommended.

Alcohol is not recommended because it has a short weak hypnotic action, and rebound excitation can result in early morning insomnia. Its diuretic effects can interrupt sleep and chronic use can lead to rapid development of tolerance and addiction.

Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity in the treatment of insomnia. Its efficacy is difficult to substantiate and, since the publication of reports linking tryptophan with the eosinophilic-myalgia syndrome, preparations indicated for insomnia have been withdrawn from the market in many countries.

Melatonin, a hormone believed to be involved in the maintenance of circadian rhythms, may be useful in the treatment of insomnias such as those due to **jet lag**[20] or other disorders (where it might act by resetting the body clock), and in the elderly. However, its benefits have been questioned,[21] and certainly evidence for a direct hypnotic effect is less conclusive; its sleep-inducing properties are usually only seen after very high, supraphysiological concentrations have been attained.[5,6] Ramelteon, a melatonin receptor agonist, is used as a hypnotic in some countries.


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3. NIH Technology Assessment Panel. Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. *JAMA* 1996; **276:** 313–18.
4. Ashton CH. Management of insomnia. *Prescribers' J* 1997; **37:** 1–10.
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14. Summers MO, *et al.* Recent developments in the classification, evaluation, and treatment of insomnia. *Chest* 2006; **130:** 276–86.
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19. CSM/MCA. Barbiturate hypnotics: avoid whenever possible. *Current Problems* 1996; **22:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 30/05/06)
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**Sleep-associated movement disorders.** Parasomnias are motor disorders, with or without autonomic features, that occur during sleep or are exaggerated by sleep. Some of the main parasomnias include nightmares, night terrors, sleepwalking (somnambulism), nocturnal enuresis (p.2180), bruxism (teeth grinding), head banging, and aggression during sleep. Other common movement disorders associated with sleep are restless legs syndrome and periodic limb movements in sleep. Parasomnias are common but rarely require treatment with drugs other than the symptomatic treatment of sleep-related medical problems. The management of some of these conditions is discussed briefly below.

The **restless legs syndrome** is characterised by an unpleasant creeping sensation deep in the legs with an irresistible urge to move them. Symptoms begin during relaxation in the evenings and in bed, and interfere with the ability to fall asleep. The aetiology of this condition is obscure and treatment has been largely empirical.[1-11] Drug treatment may not always be necessary and non-pharmacological methods such as good sleep hygiene should be tried initially.[1,3,7,8,12] There have been reports of efficacy with a wide range of treatments, although few have been well studied. Dopaminergic therapy has emerged as a common first-line treatment, a long-acting agonist, such as cabergoline, pergolide, pramipexole, or ropinirole, being preferred in order to avoid the complications associated with levodopa.[5,6,8-12] Anticonvulsants, such as carbamazepine, clonazepam, and gabapentin may be of use in those intolerant of dopamine agonists or in those who require additional medication.[5,8-11] Other drugs that have been reported to be of benefit include some opioids, clonidine, and the benzodiazepines.[5,7-12] Iron supplementation may be effective if the syndrome is associated with iron deficiency.[2-4,7-12] Many patients with restless legs syndrome exhibit **periodic limb movements in sleep**,[2,3] characterised by repetitive periodic leg and foot jerking during sleep. Treatments tried are similar to those for the restless legs syndrome; clonazepam and levodopa are amongst the drugs shown to be of benefit.

Some **parasomnias** have responded to treatment with benzodiazepines.[13,14] These include bruxism, head banging, aggression during sleep, night terrors, and sleepwalking.


1. Clark MM. Restless legs syndrome *J Am Board Fam Pract* 2001; **14:** 368–74.
2. Odin P, *et al.* Restless legs syndrome. *Eur J Neurol* 2002; **9** (suppl 3): 59–67.
3. Stiasny K, *et al.* Clinical symptomatology and treatment of restless legs syndrome and periodic limb movement disorder. *Sleep Med Rev* 2002; **6:** 253–65.
4. Earley CJ. Restless legs syndrome. *N Engl J Med* 2003; **348:** 2103–9.
5. Schapira AH. Restless legs syndrome: an update on treatment options. *Drugs* 2004; **64:** 149–58.
6. Hening WA, *et al.* American Academy of Sleep Medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 2004; **27:** 560–83. Also available at: http://journalsleep.org/Articles/270329.pdf (accessed 15/08/08)
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8. Thorpy MJ. New paradigms in the treatment of restless legs syndrome. *Neurology* 2005; **64** (suppl 3): S28–S33.
9. Ryan M, Slevin JT. Restless legs syndrome. *Am J Health-Syst Pharm* 2006; **63:** 1599–1612.
10. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest* 2006; **130:** 1596–1604.
11. Hening WA. Current guidelines and standards of practice for restless legs syndrome. *Am J Med* 2007; **120** (suppl 1): S22–S27.
12. Trenkwalder C, *et al.* The restless legs syndrome. *Lancet Neurol* 2005; **4:** 465–75.
13. Stores G. Dramatic parasomnias. *J R Soc Med* 2001; **94:** 173–6.
14. Wills L, Garcia J. Parasomnias: epidemiology and management. *CNS Drugs* 2002; **16:** 803–10.

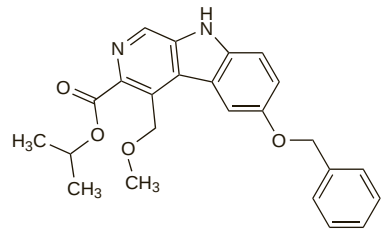

## Abecarnil *(rINN)*

Abécarnil; Abecarnilo; Abecarnilum; ZK-112119. Isopropyl 6-(benzyloxy)-4-(methoxymethyl)-9*H*-pyrido(3,4-*b*)indole-3-carboxylate.

Абекарнил

$C_{24}H_{24}N_2O_4$ = 404.5.

*CAS — 111841-85-1.*



### Profile

Abecarnil is a beta-carboline compound reported to be a partial agonist at benzodiazepine receptors. It has been studied for its anxiolytic and anticonvulsant actions in anxiety disorders and alcohol withdrawal syndrome.

◊ References.


1. Krause W, *et al.* Pharmacokinetics and acute toleration of the β-carboline derivative abecarnil in man. *Arzneimittelforschung* 1990; **40:** 529–32.
2. Karara AH, *et al.* Pharmacokinetics of abecarnil in patients with renal insufficiency. *Clin Pharmacol Ther* 1996; **59:** 520–8.
3. Lydiard RB, *et al.* Abecarnil Work Group. A double-blind evaluation of the safety and efficacy of abecarnil, alprazolam, and placebo in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 1997; **58** (suppl 11): 11–18.
4. Pollack MH, *et al.* Abecarnil for the treatment of generalized anxiety disorder: a placebo-controlled comparison of two dosage ranges of abecarnil and buspirone. *J Clin Psychiatry* 1997; **58** (suppl 11): 19–23.
5. Anton RF, *et al.* A double-blind comparison of abecarnil and diazepam in the treatment of uncomplicated alcohol withdrawal. *Psychopharmacology (Berl)* 1997; **131:** 123–9.
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## Acamprosate Calcium *(BANM, USAN, rINNM)*

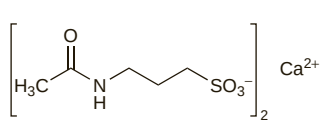
Acamprosate calcique; Acamprosate de Calcium; Acamprosato de calcio; Acamprosatum calcicum; Akamprosaattikalsium; Akamprosát vápenatá sůl; Akamprosatkalcium; Akamprosato kalcio druska; Akamprozát-kalcium; Calcii Acamprosatum; Calcium Acetylhomotaurinate. Calcium 3-acetamido-1-propanesulphate.

Кальций Акампрозат

$C_{10}H_{20}CaN_2O_8S_2$ = 400.5.

*CAS — 77337-76-9 (acamprosate); 77337-73-6 (acamprosate calcium).*

*ATC — N07BB03.*



**Pharmacopoeias.** In *Eur.* (see p.vii).
**Ph. Eur. 6.2** (Acamprosate Calcium). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 5.5 to 7.0.

### Adverse Effects
The main adverse effect of acamprosate is dosage-related diarrhoea; nausea, vomiting, and abdominal pain occur less frequently. Other adverse effects have included pruritus, and occasionally a maculopapular rash; bullous skin reactions have occurred rarely. Depression and fluctuations in libido have also been reported. Hypersensitivity reactions including urticaria, angioedema, and anaphylaxis have been reported very rarely.

**Effects on the skin.** A case of erythema multiforme in a woman with cirrhosis of the liver has been attributed to use of acamprosate[1] although both the diagnosis and any association with acamprosate have been seriously challenged.[2]


1. Fortier-Beaulieu M, *et al.* Possible association of erythema multiforme with acamprosate. *Lancet* 1992; **339:** 991.
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### Precautions
In the UK, acamprosate is contra-indicated in patients with severe hepatic impairment (Child-Pugh Class C). US licensed product information states that acamprosate is not metabolised via the liver and its pharmacokinetics are not altered in those with mild to moderate hepatic impairment (Child-Pugh Classes A and B); no change in dose is required in such patients. (No advice is given regarding use in those with more severe impairment.) For precautions regarding the use of acamprosate in patients with renal impairment, see under Uses and Administration, below.

### Pharmacokinetics
Absorption of acamprosate from the gastrointestinal tract is slow but sustained and is subject to considerable interindividual variation. Steady-state concentrations are achieved after dosage for 7 days. Bioavailability is reduced if given with food. Acamprosate is not protein bound and although it is hydrophilic it is reported to cross the blood-brain barrier. Acamprosate does not appear to be metabolised and is excreted unchanged in the urine. The elimination half-life after oral doses has been reported to be about 33 hours.

◊ References.


1. Saivin S, *et al.* Clinical pharmacokinetics of acamprosate. *Clin Pharmacokinet* 1998; **35:** 331–45.


### Uses and Administration
Acamprosate has a chemical structure similar to that of the endogenous amino acid, homotaurine, which is a structural analogue of gamma-aminobutyric acid (GABA—p.2308) and taurine (p.2395). It is given as the calcium salt to prevent relapse in alcoholics who have been weaned off alcohol. The usual oral dose is 666 mg of acamprosate calcium given three times daily. UK licensed product information also recommends that patients weighing less than 60 kg should be given a dose of 666 mg at breakfast followed by 333 mg at midday and 333 mg at night. For doses in patients with renal impairment, see below. Treatment should be started as soon as possible after alcohol withdrawal and maintained, even if the patient relapses, for the recommended period of 1 year.

**Administration in renal impairment.** It is considered[1] likely that accumulation of acamprosate would occur with prolonged use of therapeutic doses in patients with renal impairment. It has been reported that the mean maximum concentration of acamprosate after a single 666-mg dose was 813 nanograms/mL in 12 patients with moderate or severe renal impairment compared with 198 nanograms/mL in 6 healthy subjects; values for the plasma elimination half-life were 47 and 18 hours, respectively.

Licensed product information in the UK does not recommend the use of acamprosate in patients with renal impairment (serum creatinine greater than 120 micromoles/litre).

In the USA the use of acamprosate is contra-indicated in those with severe renal impairment (creatinine clearance (CC) less than 30 mL/minute). However, in those with moderate impairment (CC 30 to 50 mL/minute), a starting dose of 333 mg three times daily may be given.


1. Wilde MI, Wagstaff AJ. Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 1997; **53:** 1038–53.

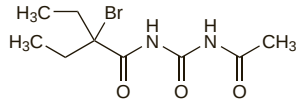

**Alcohol dependence.** Acamprosate is considered to be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p.1626). Reviews[1-4] of placebo-controlled studies conclude that acamprosate helps to prevent relapse and increase the number of drink-free days during a 1-year course of treatment and possibly for up to one year thereafter. Efficacy appears to be dose related but its effects in promoting abstinence may wane during treatment. Use with disulfiram or naltrexone may improve results but a large multicentre study in the USA found that adding acamprosate to naltrexone or behavioural therapy did not produce any additional benefit, and that the drug was ineffective when used alone.[5] Several mechanisms have been proposed to account for acamprosate's action including inhibition of neuronal hyperexcitability by antagonising excitatory amino acids such as glutamate.


1. Wilde MI, Wagstaff AJ. Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 1997; **53:** 1038–53.
2. Anonymous. Acamprosate for alcohol dependence? *Drug Ther Bull* 1997; **35:** 70–2.
3. Mason BJ. Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. *J Clin Psychiatry* 2001; **62** (suppl 20): 42–8.
4. Overman GP, *et al.* Acamprosate for the adjunctive treatment of alcohol dependence. *Ann Pharmacother* 2003; **37:** 1090–9.
5. Anton RF, *et al.* Combined pharmacotherapies and behavioral interventions for alcohol dependence. The COMBINE study: a randomized controlled trial. *JAMA* 2006; **295:** 2003–17.


### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Campral†; ***Austral.:*** Campral; ***Austria:*** Campral; ***Belg.:*** Campral; ***Braz.:*** Campral†; ***Chile:*** Campral; ***Cz.:*** Campral; ***Denm.:*** Campral; ***Fr.:*** Aotal; ***Ger.:*** Campral; ***Hong Kong:*** Campral; ***Hung.:*** Campral; ***Irl.:*** Campral; ***Mex.:*** Campral; ***Neth.:*** Campral; ***Norw.:*** Campral; ***Pol.:*** Campral; ***Port.:*** Campral; ***S.Afr.:*** Besobrial; Sobrial†; ***Singapore:*** Campral†; ***Spain:*** Campral; Zulex; ***Swed.:*** Campral; ***Switz.:*** Campral; ***Turk.:*** Campral; ***UK:*** Campral; ***USA:*** Campral.

## Acecarbromal *(rINN)*
Acécarbromal; Acecarbromalum; Acetcarbromal; Acetylcarbromal. *N*-Acetyl-*N*′-(2-bromo-2-ethylbutyryl)urea.

Ацекарбромал
$C_9H_{15}BrN_2O_3$ = 279.1.
*CAS — 77-66-7.*

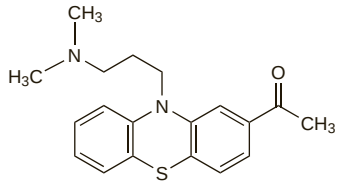


### Profile
Acecarbromal is a bromureide with similar actions to those of carbromal (p.967). It has been used for its sedative properties but the use of bromides is generally deprecated.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
**Multi-ingredient: Cz.:** Afrodor; ***Ger.:*** Afrodor; ***Hung.:*** Afrodor†; ***Rus.:*** Afrodor (Афродор).

## Acepromazine *(BAN, rINN)*
Acepromazin; Acepromazina; Acépromazine; Acepromazinum; Asepromatsiini. 10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

Ацепромазин
$C_{19}H_{22}N_2OS$ = 326.5.
*CAS — 61-00-7.*
*ATC — N05AA04.*
*ATC Vet — QN05AA04.*



## Acepromazine Maleate *(BANM, USAN, rINNM)*
Acépromazine, Maléate d'; Acepromazini Maleas; Acetylpromazine Maleate; Asepromazin Maleat; Maleato de acepromazina. 10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone hydrogen maleate.

Ацепромазина Малеат
$C_{19}H_{22}N_2OS,C_4H_4O_4$ = 442.5.
*CAS — 3598-37-6.*
*ATC — N05AA04.*
*ATC Vet — QN05AA04.*

**Pharmacopoeias.** In *US* for veterinary use only. Also in *BP(Vet)*.
**BP(Vet) 2008** (Acepromazine Maleate). A yellow crystalline powder. Soluble in water and in alcohol; freely soluble in chloroform; slightly soluble in ether. A 1% solution in water has a pH of 4.0 to 4.5.
**USP 31** (Acepromazine Maleate). pH of a 1% solution is between 4.0 and 5.5. Protect from light.

### Profile
Acepromazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has been given orally as the maleate in the treatment of anxiety disorders, hiccups, and nausea and vomiting. Acepromazine, as the base, has also been given in preparations for the management of insomnia.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Denm.:*** Plegicil; ***Turk.:*** Plegicil.
**Multi-ingredient: *Fr.:*** Noctran.

## Acetylcarbromal *(rINN)*
Acétylcarbromal; Acetylcarbromalum; Acetylcarbromal. *N*-Acetyl-*N*′-(2-bromo-2-ethylbutyryl)urea.

Ацетилкарбромал
$C_9H_{15}BrN_2O_3$ = 279.1.
*CAS — 77-66-7.*



### Profile
Acetylcarbromal is a bromureide with similar actions to those of carbromal (p.967). It has been used for its sedative properties but the use of bromides is generally deprecated.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
**Multi-ingredient: Cz.:** Afrodor; ***Ger.:*** Afrodor; ***Hung.:*** Afrodor†; ***Rus.:*** Afrodor (Афродор).

## Acetylpromazine Maleate *(BANM, USAN, rINNM)*
Acépromazine, Maléate d'; Acepromazini Maleas; Acepromazine Maleate; Asepromazin Maleat; Maleato de acepromazina. 10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone hydrogen maleate.

Ацетилпромазина Малеат
$C_{19}H_{22}N_2OS,C_4H_4O_4$ = 442.5.
*CAS — 3598-37-6.*
*ATC — N05AA04.*
*ATC Vet — QN05AA04.*

**Pharmacopoeias.** In *US* for veterinary use only. Also in *BP(Vet)*.
**BP(Vet) 2008** (Acepromazine Maleate). A yellow crystalline powder. Soluble in water and in alcohol; freely soluble in chloroform; slightly soluble in ether. A 1% solution in water has a pH of 4.0 to 4.5.
**USP 31** (Acepromazine Maleate). pH of a 1% solution is between 4.0 and 5.5. Protect from light.

### Profile
Acepromazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has been given orally as the maleate in the treatment of anxiety disorders, hiccups, and nausea and vomiting. Acepromazine, as the base, has also been given in preparations for the management of insomnia.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Denm.:*** Plegicil; ***Turk.:*** Plegicil.
**Multi-ingredient: *Fr.:*** Noctran.

## Acetylpromazine
Acépromazine; Acepromazini Maleas; Acetylpromazine Maleate; Asepromazin Maleat; Maleato de acepromazina. 10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone hydrogen maleate.

Ацетилпромазина Малеат
$C_{19}H_{22}N_2OS,C_4H_4O_4$ = 442.5.
*CAS — 3598-37-6.*
*ATC — N05AA04.*
*ATC Vet — QN05AA04.*

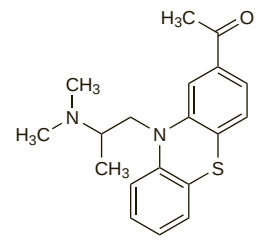
**Pharmacopoeias.** In *US* for veterinary use only. Also in *BP(Vet)*.
**BP(Vet) 2008** (Acepromazine Maleate). A yellow crystalline powder. Soluble in water and in alcohol; freely soluble in chloroform; slightly soluble in ether. A 1% solution in water has a pH of 4.0 to 4.5.
**USP 31** (Acepromazine Maleate). pH of a 1% solution is between 4.0 and 5.5. Protect from light.

### Profile
Acepromazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has been given orally as the maleate in the treatment of anxiety disorders, hiccups, and nausea and vomiting. Acepromazine, as the base, has also been given in preparations for the management of insomnia.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Denm.:*** Plegicil; ***Turk.:*** Plegicil.
**Multi-ingredient: *Fr.:*** Noctran.

## Acepromethazine *(rINN)*
16-64 CB; Acepromethazina; Acéprométazine; Acepromethazinum. 10-(2-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

Ацепрометазин
$C_{19}H_{22}N_2OS$ = 326.5.
*CAS — 13461-01-3.*

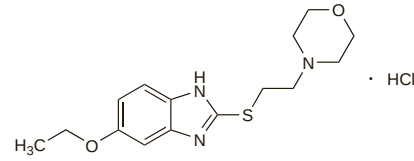


### Profile
Acepromethazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It is available usually as the maleate in preparations for the management of insomnia.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
**Multi-ingredient: *Fr.:*** Mepronizine; Noctran.

## Afobazol
Afobazole; Aphobazole; CM-346; SM-346. 5-Ethoxy-2-{[2-(4-morpholinyl)ethyl]thio}-1*H*-benzimidazole Monohydrochloride.

Афобазол
$C_{15}H_{21}N_3O_2S.HCl$ = 343.9.
*CAS — 173352-39-1.*



NOTE. Afobazol has also been described as the dihydrochloride.

### Profile
Afobazol is a non-benzodiazepine anxiolytic used in the treatment of anxiety disorders. It has been given orally in a usual dose of 10 mg three times daily. A maximum of 60 mg may be given daily.

◊ References.


1. Neznamov GG, *et al.* Aphobazol—new selective anxyolytic drug. *Zh Nevrol Psikhiatr Im S S Korsakova* 2005; **105:** 35–40.


## Allobarbital *(USAN, rINN)*
Allobarbitaali; Allobarbitalum; Allobarbitone; Alobarbital; Diallylbarbitone; Diallylbarbituric Acid; Diallylmalonylurea; Diallymalum; NSC-9324. 5,5-Diallylbarbituric acid.

Аллобарбитал
$C_{10}H_{12}N_2O_3$ = 208.2.
*CAS — 52-43-7.*
*ATC — N05CA21.*
*ATC Vet — QN05CA21.*