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 acamprosate1 although both the diagnosis and any association with acamprosate have been seriously challenged.

- 1. Fortier-Beaulieu M, et al. Possible association of erythema multiforme with acamprosate. Lancet 1992; 339: 991.
- Potgieter AS, Opsomer L. Acamprosate as cause of erythema multiforme contested. *Lancet* 1992; 340: 856–7.

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

♦ References.

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 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). Reviews¹⁻⁴ 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.

- 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.
- Anonymous. Acamprosate for alcohol dependence? *Drug Thei Bull* 1997; **35**: 70–2.
- Mason BJ. Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. J Clin Psychiatry 2001; 62 (suppl 20): 42-8.
- 20): 42–8. A Comprosate 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; Fotal; Ger.: Campral; Hong Kong: Campral; Lin: Campral; Morw.: Campral; Norw.: Campral; Pol.: Campral; Norw.: Campral; S.Afr.: Besobrial; Sobrial†; Singapore: Campral†, Spain: Campral; Campral; Singapore: Campral; UK: Campral; UK: Campral; USA: Cam

Acecarbromal (rINN)

Acécarbromal: Acecarbromalum: Acetcarbromal: Acetvlcarbromal. N-Acetyl-N'-(2-bromo-2-ethylbutyryl)urea.

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

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.

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) 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 40 to 45

USP 31 (Acepromazine Maleate), pH of a 1% solution is between 4.0 and 5.5. Protect from light.

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.

Aceprometazine (rINN)

16-64 CB; Aceprometazina; Acéprométazine; Aceprometazinum. 10-(2-Dimethylaminopropyl)phenothiazin-2-yl methyl ke-

Ацепрометазин

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

Aceprometazine 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

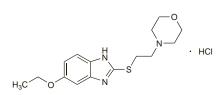
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Fr.: Mepronizine: Noctran.

Afobazol

Afobazole; Aphobazole; CM-346; SM-346. 5-Ethoxy-2-{[2-(4morpholinyl)ethyl]thio}-IH-benzimidazole Monohydrochloride.

 $C_{15}H_{21}N_3O_2S.HCI = 343.9.$ - 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.

H₂C

Allobarbital is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used in combination preparations for the treatment of sleep disorders and pain but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Cz.: Dinyl†; Eunalgit†; **Hung.:** Demalgonil; **Pol.:** Krople Zoladkowe; Pabialgin P; **Turk.:** Spasmo-Panalgine.

Alprazolam (BAN, USAN, rINN)

Alpratsolaami; Alprazolám; Alprazolamas; Alprazolamum; U-31889. 8-Chloro-1-methyl-6-phenyl-4H-1,2,4-triazolo[4,3-a]-[1.4]benzodiazepine.

Алпразолам

 $C_{17}H_{13}CIN_4 = 308.8.$

CAS — 28981-97-7 (alprazolam).

ATC - N05BA12.

ATC Vet - QN05BA12.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of alprazolam:

Benzo; Coffins; Dogbones; Fo' Bars; Fo's; Footballs; Forgetful Pills; Four Bars; French Fries; Gold Bars; Green Bars; Quad bar; School Buses; Sticks; Totem Poles; White Bars; X-Boxes; Xan-Bars; Xannies; Xanny; Zanny; Z-Bars; Zan-Bars; Zannies; Zan-

Pharmacopoeias. In Chin., Eur. (see p.vii), Jpn, and US. Ph. Eur. 6.2 (Alprazolam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Protect from light.

USP 31 (Alprazolam). A white to off-white crystalline powder. Insoluble in water; soluble in alcohol; sparingly soluble in acetone; freely soluble in chloroform; slightly soluble in ethyl acetate.

Dependence and Withdrawal

As for Diazepam, p.987. Dependence may be a particular problem at the high doses used in the treatment of panic attacks.

Adverse Effects and Treatment

As for Diazepam, p.987.

Effects on the liver. A patient receiving phenelzine for depression developed abnormal liver enzyme values on 2 occasions when alprazolam was added to the treatment. 1 It was not possible to say if this was due to alprazolam alone or a synergistic effect with phenelzine.

Roy-Byrne P, et al. Alprazolam-related hepatotoxicity. Lancet 1983; ii: 786–7.

Effects on the skin. There have been some reports of alprazolam-induced photosensitivity. $^{1.2}$

- Kanwar AJ, et al. Photosensitivity due to alprazolam. Dermologica 1990; 181: 75.
- Watanabe Y, et al. Photosensitivity due to alprazolam with positive oral photochallenge test after 17 days administration. J Am Acad Dermatol 1999; 40: 832-3.

Overdosage. A retrospective analysis of 2063 hospital admissions for benzodiazepine overdosage in one region of Australia between January 1987 and October 2002 found that patients who took an overdose of alprazolam were about twice as likely to require admission to intensive care. Flumazenil was required in 14% of the 131 alprazolam overdoses, and ventilation in 16%, which was significantly more than for other benzodiazepines. Given the apparently greater toxicity of alprazolam in overdosage, its increasing prescription to groups at risk of self-poisoning was of concern.

1. Isbister GK, et al. Alprazolam is relatively more toxic than other benzodiazepines in overdose. Br J Clin Pharmacol 2004; 58:

Precautions

As for Diazepam, p.988.

Abuse. High doses of alprazolam taken after maintenance doses of methadone produced a 'high' without pronounced sedation; the drug was also misused by nonopioid-drug abusers. 1 The usual urine toxicology screens for benzodiazepines often give falsenegative results for alprazolam because of the extremely low concentrations of metabolites excreted, making abuse difficult to detect. A subsequent review² considered that the literature did not support the widely held belief that alprazolam had a greater liability for abuse than other benzodiazepines, but the possibility could not be discounted.

- Weddington WW, Carney AC. Alprazolam abuse during methadone maintenance therapy. JAMA 1987; 257: 3363.
- 2. Rush CR, et al. Abuse liability of alprazolam relative to other commonly used benzodiazepines: a review. Neurosci Biobehav Rev 1993; 17: 277-85.

Breast feeding. The American Academy of Pediatrics1 considers that, although the effect of alprazolam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

From a study² of the distribution of alprazolam into breast milk in 8 lactating women it was estimated that the average daily dose of alprazolam ingested by a breast-fed infant would range from 0.3 to 5 micrograms/kg or about 3% of a maternal dose.

- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. Correction. ibid.; 1029. Also available at:
- http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

 2. Oo CY, et al. Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk. Br J Clin Pharmacol 1995; 40: 231-6.

Handling. Care should be taken to prevent inhaling particles of alprazolam and exposing the skin to it.

Hepatic impairment. Alprazolam 1 mg by mouth was absorbed more slowly in 17 patients with alcoholic cirrhosis with no ascites than in 17 healthy subjects. Mean peak alprazolam concentrations were achieved after 3.34 hours in the cirrhosis patients and 1.47 hours in the healthy subjects. Mean elimination half-life for cirrhosis patients was 19.7 hours compared with 11.4 hours for subjects from the healthy group. However, there were no significant differences in the maximum plasma concentrations achieved. The results indicate that alprazolam, in common with other benzodiazepines that undergo oxidative metabolism, would accumulate to a greater extent in patients with alcoholic liver disease than in healthy subjects; the daily dose of alprazolam may need to be reduced by half in this population. See also Administration in Hepatic or Renal Impairment, below.

Juhl RP, et al. Alprazolam pharmacokinetics in alcoholic liver disease. J Clin Pharmacol 1984; 24: 113–19.

Porphyria. Alprazolam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in in-vitro systems.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Alprazolam is well absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being achieved within 1 to 2 hours of a dose. The mean plasma half-life is 11 to 15 hours. Alprazolam is 70 to 80% bound to plasma proteins, mainly albumin. It is metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4. Metabolites include α-hydroxyalprazolam, which is reported to be about half as active as the parent compound, 4-hydroxyalprazolam, and an inactive benzophenone. Plasma concentrations of metabolites are very low. Alprazolam is excreted in urine as unchanged drug and metabolites.

- Greenblatt DJ, Wright CE. Clinical pharmacokinetics of alprazolam: therapeutic implications. Clin Pharmacokinet 1993; 24: 453–71.
- 2. Wright CE, et al. Pharmacokinetics and psychomotor performance of alprazolam: concentration-effect relationship. J Clin Pharmacol 1997: 37: 321-9.
- Kaplan GB, et al. Single-dose pharmacokinetics and pharmaco-dynamics of alprazolam in elderly and young subjects. J Clin Pharmacol 1998; 38: 14–21.
- Park J-Y, et al. Effect of CYP3A5*3 genotype on the pharmacok-inetics and pharmacodynamics of alprazolam in healthy sub-jects. Clin Pharmacol Ther 2006; 79: 590–9.

Uses and Administration

Alprazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term treatment of anxiety disorders in oral doses of 250 to 500 micrograms three times daily, increased where necessary to a total daily dose of 3 or 4 mg. In elderly or debilitated patients, an initial dose of 250 micrograms two or three times daily has been suggested. For doses in patients with hepatic or renal impairment, see below.

Doses of up to 10 mg of alprazolam daily have been used in the treatment of panic attacks. A modifiedrelease preparation of alprazolam is also available for once-daily dosing.

Administration in hepatic or renal impairment. UK licensed product information advises caution when using alprazolam in patients with hepatic or renal impairment; it is contraindicated in those with severe hepatic impairment. In the USA, licensed product information states that patients with advanced liver disease may be given an initial dose of 250 micrograms two or three times daily.

Anxiety disorders. The management of anxiety disorders, including the use of benzodiazepines, is discussed on p.952.

- 1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160:** 191–202.
- 2. Lepola UM, et al. Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. Int Clin Psychopharmacol 1993; 8: 115-18.
- 3. Pollack MH, et al. Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol* 1993; **13:** 257–63.
- Woodman CL, et al. Predictors of response to alprazolam and placebo in patients with panic disorder. J Affect Disord 1994; 30: 5–13.
- Spiegel DA. Efficacy studies of alprazolam in panic disorder. Psychopharmacol Bull 1998; 34: 191–5.

Depression. Although they may be useful for associated anxiety, benzodiazepines are not usually considered appropriate for treatment of depression (p.373); however, some drugs such as alprazolam have been tried for this indication.

Kravitz HM, et al. Alprazolam and depression: a review of risks and benefits. J Clin Psychiatry 1993; 54: (suppl.): 78–84.

Premenstrual syndrome. Alprazolam has been reported ¹⁻³ to have produced a marginal to good response in the premenstrual syndrome (p.2099) but others have not found it to be of benefit,4 and the role of benzodiazepines is limited by their adverse effects. If benzodiazepines are selected it is recommended that in order to reduce the risk of dependence and withdrawal symptoms they should be carefully restricted to the luteal phase in selected patients.5 Withdrawal symptoms may be more severe after shortacting drugs such as alprazolam. Antidepressant drugs such as SSRIs may be preferred.

- 1. Smith S, et al. Treatment of premenstrual syndrome with alpra zolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol* 1987; **70**: 37–43.
- 2. Harrison WM, *et al.* Treatment of premenstrual dysphoria with alprazolam: a controlled study. *Arch Gen Psychiatry* 1990; **47:** 270–5.
- 3. Freeman EW, et al. A double-blind trial of oral progesterone alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995; **274**: 51–7.
- Evans SM, et al. Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. Neuropsychopharmacology 1998; 19: 499–516.
- 5. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. Drug Safety 1994; 10: 160-9.

Tinnitus. Alprazolam has been tried in the management of tinnitus (p.1866).

References.

- Johnson RM, et al. Use of alprazolam for relief of tinnitus: a double-blind study. Arch Otolaryngol Head Neck Surg 1993;
- 2. Huynh L, Fields S. Alprazolam for tinnitus. Ann Pharmacother 1995; 29: 311-12
- 3. Vernon JA, Meikle MB. Masking devices and alprazolam treatment for tinnitus. Otolaryngol Clin North Am 2003; 36: 307-20.

Preparations

USP 31: Alprazolam Oral Suspension; Alprazolam Tablets.

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part 3)

Arg.: Alplax, Alprazol; Amziax, Ansielix, Aplacaina; Bayzolam; Becede; Bestrol; Calmol; Emeral; Isoproxal; Krama; Medronal; Nivelan N; Prenadona; Prinox, Psicosedoi, PTA; Relaxten; Retanţ; Rilow; Tensium; Thiprasolan; Tranquinal; Xanax; Austral.; Alprax Kalma; Xanax, Austral: Alprazatad; Alprazyned; Docalprazo; Topazolam; Xanax; Braz.: Alfron; Altrox; Apraz, Constante; Frontal; Neozolam; Tranquinal; Canad.; Apo-Alpraz; Novo-Alprazo; Nul-Alpraz; Xanax; Chile: Adax; Grifolapram; Prazam; Sanerva; Tricalma; Zotran; Cz.: Frontin; Helex; Neurol; Xanax; Denm.; Alprox, Tafli; Fin.: Alprox, Xanor; Fr.: Xanax; Geriz, Cassadar; Tafli; Xanax; Gr.: Antanax; Saturnil; Xanax; Hong Kong; Alprax; Nalion; Renax; Xanax; Hung.: Frontin; Xanax; India: Alprax; Alprox; Calmax; Gerax; Xanax; Israel: Alpralid; Alprox; Xanagis; Xanax; Israel: Alpralid; Alprox; Xanagis; Xanax; Israel: Alpralid; Alprox; Xanax; Malysia: Alpranax; Apo-Alpraz; Xanax; Mex.: Alzam; Farmapram; Irizz; Neupax; Tafli; Neth.: Xanax; Norw.: Xanor; NZ: Xanax; Polit; Alprax; Nanor; Pol.: Alfobam; Alprazomerck; Alprox; Neurol; Xanax; Zomiren; Port.: Alpronax; Pazolam; Prazam; Unilan; Xanax; Rus.: Alzolam (Avaovan); Helex (Keneck); Neurol (Heypon); Xanax; (Kcauakc)†; S.Afr.: Alzam; Anxirid†; Xaro; Drimpam†; Xanolam†; Xanor; Zopax; Singapore: Apo-Alpraz; Dizolam†; Xanax; Taflax; Alacam; Alnax; Alprax; Anax; Anax; Anpress; Anzion†; Dizolam; Marzolam; Miazolam; Alnax; Alprax; Anax; Anax;