have occasionally been given. Initial doses for elderly and debilitated patients should not exceed 3 mg daily in divided doses.

◊ References.

1. Kaplan SA, *et al.* Biopharmaceutical and clinical pharmacokinetic profile of bromazepam. *J Pharmacokinet Biopharm* 1976; **4:** 1–16.
2. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
3. Erb T, *et al.* Preoperative anxiolysis with minimal sedation in elderly patients: bromazepam or clorazepate-dipotassium? *Acta Anaesthesiol Scand* 1998; **42:** 97–101.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Angular†; Atemperator; Benedorm; Bromatanil; Butecam; Creosedin; Equisedin; Estomina; Fabozepam; Finaten; Gasmol; Lexotanil; Moliva l†; Neurozepam; Nulastres; Octanyl; Sedatus†; Sipcar; Tritopan; ***Austral.:*** Lexotan; ***Austria:*** Lexotanil; ***Belg.:*** Bromatop; Bromidem; Docbromaze; Kelalexan; Lexotan; ***Braz.:*** Bromazepan†; Bromoxon; Brozepax†; Deptran†; Lexotan; Lezepan; Nervium; Neurilan; Novazepam†; Relaxil; Somalium; Uni Bromazepax; ***Canad.:*** Lectopam; ***Chile:*** Lexotanil; Totasedan; ***Cz.:*** Lexaurin; ***Denm.:*** Bromam; Lexotan; ***Fr.:*** Anxyrex†; Lexomil; Quietiline; ***Ger.:*** BromaLich†; Bromaz†; Bromazanil; Bromazep; durazanil; Gityl; Lexostad; Lexotanil; neo OPT; Normoc; ***Gr.:*** Anconevron†; Evagelin; Lexotanil; Libronil-R; Notorium; Pascalium; ***Hong Kong:*** Akamon; Lexilium; Lexotan; ***Indon.:*** Lexotan; ***Irl.:*** Lexotan; ***Israel:*** Lenitin; ***Ital.:*** Brixopan; Compendium; Lexotan; ***Malaysia:*** Akamon; Lexotan; ***Mex.:*** Bropamil†; Lexotan; Otedram; ***Neth.:*** Lexotanil; ***Philipp.:*** Lexotan; ***Pol.:*** Lexotan; Sedam; ***Port.:*** Bromalex; Lexotan; Ultramidol; ***S.Afr.:*** Brazepam; Bromaze; Lexotan; ***Singapore:*** Lexotan; ***Spain:*** Lexatin; ***Switz.:*** Lexotanil; ***Thai.:*** Lexotan; ***Venez.:*** Lexotanil; Nervan.

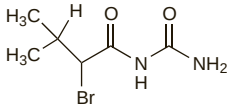
Multi-ingredient: ***Arg.:*** Biorgan B; Colixane B; Debridat B; Eudon; Eumotil-T; Faradil Novo; Fenatrop-A; Miopropan-T; Somasedan; Vegestabil Digest; Veralipral T; ***Braz.:*** Bromopirin; Sulpan; ***Ital.:*** Lexil.

Bromisoval *(rINN)*

Bromisovaali; Bromisovalerylurea; Bromisovalum; Bromsoval; Bromvalerylurea; Bromvaletone; Bromylum. *N*-(2-Bromo-3-methylbutyryl)urea.

Бромизовал

$C_6H_{11}BrN_2O_2$ = 223.1.
CAS — 496-67-3.
ATC — N05CM03.
ATC Vet — QN05CM03.



Pharmacopoeias. In *Jpn.*

Profile

Bromisoval has actions and uses similar to those of carbromal (p.967) but the use of bromides is generally deprecated.

Preparations

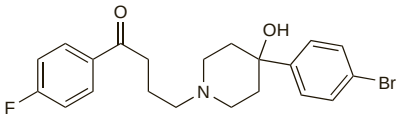
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Pol.:*** Milocardin.

Bromperidol *(BAN, USAN, rINN)*

Bromiperidoli; Brómperidol; Brompéridol; Bromperidoli; Bromperidolis; Bromperidolum; R-11333. 4-[4-(*p*-Bromophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

Бромперидол

$C_{21}H_{23}BrFNO_2$ = 420.3.
CAS — 10457-90-6.
ATC — N05AD06.
ATC Vet — QN05AD06.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Bromperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

Bromperidol Decanoate *(BANM, USAN, rINNM)*

Brompéridol, décanoate de; Bromperidoldekanoat; Brómperidol-dekanoát; Bromperidol-dekanoát; Bromperidoli decanoas; Bromperidolidekanoaatti; Bromperidolio dekanoatas; Decanoato de bromperidol; R-46541.

Бромперидола Деканоат

$C_{31}H_{41}BrFNO_3$ = 574.6.
CAS — 75067-66-2.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Bromperidol Decanoate). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane. It melts at about 60°. Store at a temperature below 25°. Protect from light.

Profile

Bromperidol is a butyrophenone with general properties similar to those of haloperidol (p.1000). It is given in the treatment of schizophrenia (p.955) and other psychoses. Some bromperidol preparations are prepared with the aid of lactic acid and may be stated to contain bromperidol lactate. However, doses are expressed in terms of the equivalent amount of bromperidol. A usual oral dose is 1 to 15 mg daily, although up to 50 mg daily has been given. Elderly patients may require reduced doses of bromperidol. Bromperidol has also been given by intramuscular or intravenous injection.

The long-acting decanoate ester may be used for patients requiring long-term therapy with bromperidol. Doses are expressed in terms of the base; bromperidol decanoate 68.4 mg is equivalent to about 50 mg of bromperidol. Doses equivalent to up to 300 mg of bromperidol every 4 weeks have been given by deep intramuscular injection.

◊ References.

1. Benfield P, *et al.* Bromperidol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in psychoses. *Drugs* 1988; **35:** 670–84.

Schizophrenia. A systematic review[1] suggested that depot bromperidol had some benefits in schizophrenia but was less effective than depot haloperidol or fluphenazine.

1. Wong D, *et al.* Depot bromperidol decanoate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Preparations

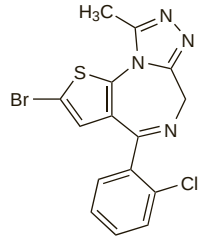
Proprietary Preparations (details are given in Part 3)
Arg.: Bromodol; Erodium; ***Belg.:*** Impromen; ***Ger.:*** Impromen; Tesoprel; ***Ital.:*** Impromen; ***Neth.:*** Impromen; ***Port.:*** Impromen†; ***Thai.:*** Brofed; Impromen†.

Brotizolam *(BAN, USAN, rINN)*

Brotitsolaami; Brotizolamum; Brotyzolam; We-941; We-941-BS. 2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine.

Бротизолам

$C_{15}H_{10}BrClN_4S$ = 393.7.
CAS — 57801-81-7.
ATC — N05CD09.
ATC Vet — QN05CD09.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Brotizolam). A white or yellowish powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble or slightly soluble in methyl alcohol.

Profile

Brotizolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.986). It is given for the short-term (up to 2 weeks) management of insomnia (p.957) in usual oral doses of 250 micrograms at night. The suggested dose for elderly and debilitated patients is 125 micrograms.

Abuse. Reference to abuse of brotizolam in Germany and Hong Kong.[1]

1. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995.

Pharmacokinetics. References.

1. Bechtel WD. Pharmacokinetics and metabolism of brotizolam in humans. *Br J Clin Pharmacol* 1983; **16:** 279S–283S.
2. Jochemsen R, *et al.* Pharmacokinetics of brotizolam in healthy subjects following intravenous and oral administration. *Br J Clin Pharmacol* 1983; **16:** 285S–290S.
3. Tokairin T, *et al.* Inhibition of the metabolism of brotizolam by erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in brotizolam metabolism. *Br J Clin Pharmacol* 2005; **60:** 172–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Lendorm; ***Belg.:*** Lendormin; ***Chile:*** Dormex; Noctilan; ***Denm.:*** Lendorm†; ***Ger.:*** Lendormin; ***Hung.:*** Lendormin; ***Israel:*** Bondormin; ***Ital.:*** Lendormin; Nimbisan; ***Jpn:*** Lendormin; ***Mex.:*** Lindormin; ***Neth.:*** Lendormin; ***Port.:*** Lendormin; ***S.Afr.:*** Lendormin; ***Spain:*** Sintonal; ***Switz.:*** Lendormine†; ***Venez.:*** Lendormin.

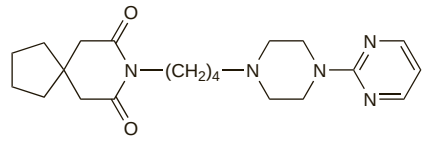
Buspirone Hydrochloride

(BANM, USAN, rINNM)

Buspiron Hidroklorür; Buspirone, chlorhydrate de; Buspironhydrochlorid; Buspironhydroklorid; Buspironi hydrochloridum; Buspironihydrokloridi; Buspironu chlorowodorek; Hidrocloruro de buspirona; MJ-9022-1. 8-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)-butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride.

Буспирона Гидрохлорид

$C_{21}H_{31}N_5O_2$,HCl = 422.0.
CAS — 36505-84-7 (buspirone); 33386-08-2 (buspirone hydrochloride).
ATC — N05BE01.
ATC Vet — QN05BE01.



(buspirone)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Buspirone Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. Protect from light.
USP 31 (Buspirone Hydrochloride). A white crystalline powder. Very soluble in water; sparingly soluble in alcohol and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol; very slightly soluble in ethyl acetate; practically insoluble in hexanes. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Dependence and Adverse Effects

Dizziness, nausea, headache, nervousness, light-headedness, excitement, paraesthesias, sleep disturbances, chest pain, tinnitus, sore throat, and nasal congestion are amongst the most frequent adverse effects reported after the use of buspirone hydrochloride. Other adverse effects have included tachycardia, palpitations, drowsiness, confusion, seizures, dry mouth, fatigue, and sweating. A syndrome of restlessness appearing shortly after the start of treatment has been reported in a small number of patients given buspirone. Buspirone is reported to produce less sedation, and to have a lower potential for dependence, than the benzodiazepines.

Effects on the nervous system. Mild acute hypertension and panic were reported on two occasions after the addition of single 10-mg doses of buspirone to therapy with tricyclic antidepressants in a 40-year-old man with panic disorder. Adrenergic or serotonin dysfunction were postulated as possible mechanisms for the reaction.[1,2] Psychotic reactions associated with buspirone treatment have also been reported in a few patients.[3] There have also been isolated reports of mania,[4] and seizures have been reported, primarily in overdosage.[5]

1. Chignon JM, Lepine JP. Panic and hypertension associated with single dose of buspirone. *Lancet* 1989; **ii:** 46–7.
2. Norman TR, Judd FK. Panic attacks, buspirone, and serotonin function. *Lancet* 1989; **ii:** 615.
3. Friedman R. Possible induction of psychosis by buspirone. *Am J Psychiatry* 1991; **148:** 1606.
4. Price WA, Bielefeld M. Buspirone-induced mania. *J Clin Psychopharmacol* 1989; **9:** 150–1.
5. Catalano G, *et al.* Seizures associated with buspirone overdose: case report and literature review. *Clin Neuropharmacol* 1998; **21:** 347–50.

EXTRAPYRAMIDAL DISORDERS. There have been isolated reports of exacerbation or precipitation of movement disorders[1-4] associated with the use of buspirone. However, buspirone has also been reported to have been of benefit in some patients with tardive dyskinesia (see Extrapyramidal Disorders under Uses and Administration, below).

1. Hammerstad JP, *et al.* Buspirone in Parkinson's disease. *Clin Neuropharmacol* 1986; **9:** 556–60.

2. Ritchie EC, *et al.* Acute generalized myoclonus following buspirone administration. *J Clin Psychiatry* 1988; **49:** 242–3.
3. Strauss A. Oral dyskinesia associated with buspirone use in an elderly woman. *J Clin Psychiatry* 1988; **49:** 322–3.
4. LeWitt PA, *et al.* Persistent movement disorders induced by buspirone. *Mov Disord* 1993; **8:** 331–4.

Precautions

Buspirone hydrochloride should be used with caution in patients with renal or hepatic impairment and is contra-indicated if the impairment is severe. It should not be used in patients with epilepsy or a history of such disorders. It does not exhibit cross-tolerance with benzodiazepines or other common sedatives or hypnotics and will not block symptoms of their withdrawal; they should, therefore, be gradually withdrawn before starting treatment with buspirone. Buspirone may impair the patient's ability to drive or operate machinery.

Diagnosis and testing. Buspirone may interfere with diagnostic assays of urinary catecholamines.[1]

1. Cook FJ, *et al.* Effect of buspirone on urinary catecholamine assays. *N Engl J Med* 1995; **332:** 401.

Hepatic impairment. Caution has been advised when using buspirone in patients with liver disease. The mean peak plasma-buspirone concentration after an oral dose was about 16 times higher in cirrhotic patients than in controls[1] and the elimination half-life was prolonged about twofold. A secondary peak concentration was seen in some subjects, occurring between 4 and 24 hours after a dose in the cirrhotics and after between 2 and 8 hours in controls. Data from a multiple-dose study[2] suggested that there was accumulation of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine in hepatic impairment, but that plasma concentrations appeared to reach steady state after 3 days regardless of the state of liver function. The area under the curve and mean peak concentration for buspirone were both higher in patients with hepatic impairment than in healthy subjects, but there were no significant differences for its metabolites. Specific dosing recommendations could not be made for patients with hepatic impairment because of the high intra- and inter-subject variations in plasma-buspirone concentrations.

1. Dalhoff K, *et al.* Buspirone pharmacokinetics in patients with cirrhosis. *Br J Clin Pharmacol* 1987; **24:** 547–50.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; **46:** 41–7.

Pregnancy and breast feeding. In some *animal* studies, large doses of buspirone during pregnancy had adverse effects on survival and on birth and weanling weight. Recommendations in licensed product information for use during pregnancy or breast feeding vary from avoid, if possible, to contra-indicated.

Renal impairment. Caution has been advised when giving buspirone to patients with renal impairment.[1,2] There is evidence of accumulation of buspirone and its metabolite after repeated doses but plasma concentrations appeared to reach steady state after 3 days regardless of the degree of renal function. At steady state both the area under the curve and maximum concentrations for buspirone and its metabolite were greater in patients with renal failure than in healthy subjects. The metabolite, but not the parent drug, was removed by haemodialysis. Specific dosing recommendations could not be made for patients with renal impairment because of the high intra- and inter-subject variations in buspirone plasma concentrations on repeated dosage.

1. Caccia S, *et al.* Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. *Clin Pharmacokinet* 1988; **14:** 171–7.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; **46:** 41–7.

Interactions

The sedative effects of buspirone may be enhanced if taken with alcohol or other CNS depressants. Because of reports of increased blood pressure in patients receiving buspirone hydrochloride with an MAOI, licensed product information for buspirone recommends that it should not be given with an MAOI.

The metabolism of buspirone is mediated by the cytochrome P450 isoenzyme CYP3A4 and therefore there is the potential for interactions between buspirone and other drugs that inhibit or act as a substrate for this isoenzyme. The dose of buspirone may need to be reduced if given at the same time as potent inhibitors of CYP3A4. Plasma concentrations of buspirone may be reduced by enzyme-inducing drugs such as rifampicin.

Antibacterials. Pretreatment with *erythromycin* in healthy subjects given buspirone resulted in mild to moderate adverse effects associated with increased plasma concentrations of buspirone.[1]

Pretreatment with *rifampicin* greatly reduced plasma concentrations of buspirone in healthy subjects.[2] A reduced anxiolytic effect could be expected if buspirone is used with rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4.

1. Kivistö KT, *et al.* Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; **62:** 348–54.
2. Lamberg TS, *et al.* Concentrations and effects of buspirone are considerably reduced by rifampicin. *Br J Clin Pharmacol* 1998; **45:** 381–5.

Antidepressants. Use of buspirone with *nefazodone* can raise plasma concentrations of buspirone. US licensed product information for nefazodone recommends that the initial dose of buspirone be lowered (e.g. 2.5 mg daily) and subsequent dose adjustments of either drug should be based on clinical assessment. A possible serotonin syndrome (p.416) has been reported[1] in a patient using buspirone with *fluoxetine*.

1. Manos GH. Possible serotonin syndrome associated with buspirone added to fluoxetine. *Ann Pharmacother* 2000; **34:** 871–4.

Antifungals. Pretreatment with *itraconazole* in healthy subjects given buspirone resulted in mild to moderate adverse effects associated with increased plasma concentrations of buspirone.[1]

1. Kivistö KT, *et al.* Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; **62:** 348–54.

Antipsychotics. For the effect of buspirone on serum concentrations of *haloperidol*, see under Chlorpromazine, p.974. For a report of potentially fatal gastrointestinal bleeding and marked hyperglycaemia after use of buspirone with *clozapine*, see under Clozapine, p.984.

Antivirals. Parkinson-like symptoms developed in a 54-year-old man taking a drug regimen that included buspirone, *indinavir*, and *ritonavir*.[1] It was suspected that ritonavir inhibited the metabolism of buspirone, which is mediated by the cytochrome P450 isoenzyme CYP3A4, leading to increased plasma concentrations of the latter. The inhibitory effect of indinavir on CYP3A4 was considered to be less than that of ritonavir. Symptoms resolved after a change in antiviral regimen and reduction in the dose of buspirone.

1. Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. *Ann Pharmacother* 2003; **37:** 202–5.

Calcium-channel blockers. Increases in buspirone plasma concentrations have been seen in healthy subjects pretreated with *diltiazem* or *verapamil*.[1]

1. Lamberg TS, *et al.* Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone. *Clin Pharmacol Ther* 1998; **63:** 640–5.

Grapefruit juice. Grapefruit juice increased the plasma concentrations of buspirone in healthy subjects.[1]

1. Lilja JJ, *et al.* Grapefruit juice substantially increases plasma concentrations of buspirone. *Clin Pharmacol Ther* 1998; **64:** 655–60.

Pharmacokinetics

Buspirone hydrochloride is rapidly absorbed from the gastrointestinal tract reaching peak plasma concentrations within 40 to 90 minutes after an oral dose. Systemic bioavailability is low because of extensive first-pass metabolism, but may be increased if given with food as this delays absorption from the gastrointestinal tract and thereby reduces presystemic clearance. Buspirone is about 95% bound to plasma proteins. Metabolism in the liver is extensive via the cytochrome P450 isoenzyme CYP3A4; hydroxylation yields several inactive metabolites and oxidative dealkylation produces 1-(2-pyrimidinyl)-piperazine, which is reported to be about 25% as potent as the parent drug in one model of anxiolytic activity. The elimination half-life of buspirone is usually about 2 to 4 hours but half-lives of up to 11 hours have been reported. Buspirone is excreted mainly as metabolites in the urine, and also in the faeces.

◊ References.

1. Mahmood I, Sahajwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet* 1999; **36:** 277–87.

Uses and Administration

Buspirone hydrochloride is an azaspirodecanedione (azapirone) anxiolytic. It is reported to be largely lacking in sedative, anticonvulsant, and muscle relaxant actions.

Buspirone hydrochloride is given, in initial oral doses of 5 mg two or three times daily, in the short-term management of anxiety disorders. The dose may be increased in increments of 5 mg at 2- to 3-day intervals if required. The recommended maximum daily dose, to be given in divided doses, is 45 mg in the UK and 60 mg in the USA.

◊ General reviews.

1. Fulton B, Brogden RN. Buspirone: an updated review of its clinical pharmacology and therapeutic applications. *CNS Drugs* 1997; **7:** 68–88.
2. Apter JT, Allen LA. Buspirone: future directions. *J Clin Psychopharmacol* 1999; **19:** 86–93.

Action. Buspirone has dopaminergic, noradrenergic, and serotonin-modulating properties[1] and its anxiolytic effects appear to be related to its action on serotonin (5-hydroxytryptamine, 5-HT) neurotransmission. Buspirone, and the related drugs gepirone (p.999) and ipsapirone (p.1002), are partial agonists at 5-HT_{1A} receptors.[1,2] While such drugs may inhibit serotonin neurotransmission (most likely via 5-HT_{1A} autoreceptor stimulation), they may also have postsynaptic 5-HT_{1A} agonist activity and thus facilitate serotonin neurotransmission.[1] To complicate matters further, 5-HT_{1A} partial agonists have shown both anxiolytic and anxiogenic properties in *animal* models of anxiety. Clinical studies have, however, shown that buspirone is effective in the treatment of generalised anxiety.[1,2]

Clinical studies with buspirone and gepirone suggest that 5-HT_{1A} partial agonists may be useful in the treatment of depression, possibly by downregulation of either 5-HT_{1A} or 5-HT_2 receptors or both.[1] There is some suggestion that buspirone has an anti-aggressive action in humans; it is unclear whether this is mediated via dopaminergic or serotonergic mechanisms.

Buspirone also has characteristics of both a dopamine agonist and antagonist; this may result in stimulation of both growth hormone and prolactin secretion.[3]

1. Glitz DA, Pohl R. 5-HT partial agonists: what is their future? *Drugs* 1991; **41:** 11–18.
2. Marsden CA. The pharmacology of new anxiolytics acting on 5-HT neurones. *Postgrad Med J* 1990; **66** (suppl 2): S2–S6.
3. Meltzer HY, *et al.* The effect of buspirone on prolactin and growth hormone secretion in man. *Arch Gen Psychiatry* 1983; **40:** 1099–1102.

Administration in hepatic or renal impairment. For cautions on the use of buspirone in patients with impaired liver or kidney function see under Precautions, above.

Anxiety disorders. Buspirone has been shown to be as effective as the benzodiazepines in the short-term treatment of generalised anxiety disorder (p.952) and to be less likely to cause sedation or psychomotor and cognitive impairment. It also appears to have a lower propensity for interaction with alcohol and a lower risk of abuse and dependence. However, its usefulness may be limited by a relatively slow response to treatment, which may take up to 2 to 4 weeks to appear. Its efficacy may be reduced in patients who have recently taken benzodiazepines. It appears to be ineffective in panic disorder and convincing evidence of efficacy in other anxiety disorders is lacking.

References.

1. Deakin JFW. A review of clinical efficacy of 5-HT agonists in anxiety and depression. *J Psychopharmacol* 1993; **7:** 283–9.
2. Pecknold JC. A risk-benefit assessment of buspirone in the treatment of anxiety disorders. *Drug Safety* 1997; **16:** 118–32.
3. Fulton B, Brogden RN. Buspirone: an updated review of its clinical pharmacology and therapeutic applications. *CNS Drugs* 1997; **7:** 68–88.
4. Chessick CA, *et al.* Azapirones for generalized anxiety disorder. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/04/08).

Bruxism. SSRI-induced bruxism has been successfully controlled by adjunctive therapy with buspirone.[1,2]

1. Romanelli F, *et al.* Possible paroxetine-induced bruxism. *Ann Pharmacother* 1996; **30:** 1246–7.
2. Bostwick JM, Jaffee MS. Buspirone as an antidote to SSRI-induced bruxism in 4 cases. *J Clin Psychiatry* 1999; **60:** 857–60.

Cerebellar ataxias. In general the management of cerebellar ataxias is mainly supportive; buspirone improved some symptoms of ataxia in a small study of patients with cerebellar cortical activity.[1]

1. Trouillas P, *et al.* Buspirone, a 5-hydroxytryptamine agonist, is active in cerebellar ataxia: results of a double-blind drug placebo study in patients with cerebellar cortical atrophy. *Arch Neurol* 1997; **54:** 749–52.

Depression. Buspirone has been investigated for augmentation of therapy with antidepressants with serotonin reuptake inhibiting activity in patients with refractory depression (p.373), but results have been variable.

References.

1. Fischer P, *et al.* Weak antidepressant response after buspirone augmentation of serotonin reuptake inhibitors in refractory severe depression. *Int Clin Psychopharmacol* 1998; **13:** 83–6.
2. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol* 1998; **18:** 465–9.
3. Landen M, *et al.* A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry* 1998; **59:** 664–8.
4. Appelberg BG, *et al.* Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry* 2001; **62:** 448–52.
5. Önder E, Tural Ü. Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. *J Affect Disord* 2003; **76:** 223–7.

Disturbed behaviour. Buspirone has been tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see Disturbed Behaviour, p.954) but evidence of efficacy is limited. Nonetheless, in the management of dementia, some[1] consider that it might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant or unresponsive to antipsychotics.

1. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)

Extrapyramidal disorders. Although there have been reports[1,2] that buspirone may improve symptoms of drug-induced dyskinesia (p.971), drugs with dopaminergic actions have mostly exacerbated symptoms and there are a few reports of extrapyramidal disorders with buspirone (see under Adverse Effects, above).

1. Moss LE, *et al.* Buspirone in the treatment of tardive dyskinesia. *J Clin Psychopharmacol* 1993; **13:** 204–9.
2. Bonifati V, *et al.* Buspirone in levodopa-induced dyskinesias. *Clin Neuropharmacol* 1994; **17:** 73–82.

Substance dependence. ***ALCOHOL.*** Despite an early study[1] suggesting that buspirone could reduce alcohol craving in alcohol dependent patients, later studies[2-4] have overall failed to confirm that buspirone improves abstinence or reduces alcohol consumption. Although some studies[4,5] have found that buspirone may improve certain psychopathological symptoms in these patients, others[2] have found no such benefit; a meta-analysis[6] of 5 studies favoured the former interpretation.

The management of alcohol withdrawal and abstinence is discussed on p.1626.

1. Bruno F. Buspirone in the treatment of alcoholic patients. *Psychopathology* 1989; **22** (suppl 1): 49–59.
2. Malcolm R, *et al.* A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcohol Clin Exp Res* 1992; **16:** 1007–13.
3. George DT, *et al.* Buspirone does not promote long term abstinence in alcoholics. *Clin Pharmacol Ther* 1995; **57:** 161.
4. Malec E, *et al.* Buspirone in the treatment of alcohol dependence: a placebo-controlled trial. *Alcohol Clin Exp Res* 1996; **20:** 307–12.
5. Kranzler HR, *et al.* Buspirone treatment of anxious alcoholics: a placebo-controlled trial. *Arch Gen Psychiatry* 1994; **51:** 720–31.
6. Malec TS, *et al.* Efficacy of buspirone in alcohol dependence: a review. *Alcohol Clin Exp Res* 1996; **20:** 853–8.

NICOTINE. Buspirone has produced conflicting results[1-5] in the management of smoking cessation (p.2354). Although some studies suggest that in the short-term buspirone can increase the numbers of patients who are able to cease smoking, it does not necessarily decrease withdrawal symptoms.

1. West R, *et al.* Effect of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. *Psychopharmacology (Berl)* 1991; **104:** 91–6.
2. Hilleman DE, *et al.* Effect of buspirone on withdrawal symptoms associated with smoking cessation. *Arch Intern Med* 1992; **152:** 350–2.
3. Hilleman DE, *et al.* Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *J Clin Pharmacol* 1994; **34:** 222–4.
4. Schneider NG, *et al.* Efficacy of buspirone in smoking cessation: a placebo-controlled trial. *Clin Pharmacol Ther* 1996; **60:** 568–75.
5. Farid P, Abate MA. Buspirone use for smoking cessation. *Ann Pharmacother* 1998; **32:** 1362–4.

OPIOIDS. Buspirone has been investigated in the management of opioid withdrawal (p.101) in dependent patients.[1,2]

1. Rose JS, *et al.* Effects of buspirone in withdrawal from opiates. *Am J Addict* 2003; **12:** 253–9.
2. Buydens-Branchey L, *et al.* Efficacy of buspirone in the treatment of opioid withdrawal. *J Clin Psychopharmacol* 2005; **25:** 230–6.

Preparations

USP 31: Buspirone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Ansial†; ***Austral.:*** Buspar; ***Austria:*** Buspar; ***Belg.:*** Buspar; ***Braz.:*** Ansienon†; Ansitec; Buspanil†; Buspar; ***Canad.:*** Buspar; Buspirex†; ***Chile:*** Paxon; ***Cz.:*** Anxiron†; Buspar†; ***Denm.:*** Buspar; Stesiron†; ***Fin.:*** Buspar; Stesiron†; ***Fr.:*** Buspar; ***Ger.:*** Anxut; Bespar; Busp; ***Gr.:*** Anchocalm; Antipsichos; Bergamol; Bespar; Boronex; Epsilat; Hiremon; Hobatstress; Komasin; Lanamont; Lebilon; Ledion; Loxapin; Nadrifor; Nervostal; Nevrorestol; Norbal; Pendium; Stressigal; Svitalark; Tendan†; Tensispes; Trafuril†; Umolit; ***Hong Kong:*** Buspar; Kalmiren; ***Hung.:*** Anxiron; Spitomin; ***India:*** Buscalm; ***Indon.:*** Tran-Q; Xiety; ***Irl.:*** Buspar; ***Israel:*** Buspirol†; Sorbon; ***Ital.:*** Axoren†; Buspar; Buspimen†; ***Mex.:*** Buspar; ***Norw.:*** Buspar; Stesiron†; ***NZ:*** Biron; Buspar; ***Pol.:*** Mabuson; Spamilan; ***Port.:*** Ansiten; Busansil; Buscalma; Buspar; Buspium; Establix†; Itagil; Psibeter; ***S.Afr.:*** Buspar; Pasrin; ***Spain:*** Buspar; Effiplen†; ***Swed.:*** Buspar; ***Switz.:*** Buspar; ***Thai.:*** Anxiolan; ***Turk.:*** Buspon; ***UK:*** Buspar; ***USA:*** Buspar; ***Venez.:*** Dalpas.

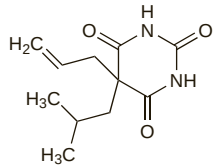
Butalbital *(USAN, rINN)*

Alisobumalum; Allylbarbital; Allylbarbituric Acid; Butalbitaali; Butalbitalum; Itobarbital; Tetrallobarbital. 5-Allyl-5-isobutylbarbituric acid.

Буталбитал

$C_{11}H_{16}N_2O_3$ = 224.3.

CAS — 77-26-9.



NOTE. The name Butalbital has also been applied to talbutal, the *S*-butyl analogue, which was formerly used as a hypnotic and sedative.

Compounded preparations of butalbital may be represented by the following names:

• Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine

Pharmacopoeias. In *US*.

USP 31 (Butalbital). A white odourless crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in alcohol, in chloroform, and in ether; soluble in solutions of fixed alkalis and alkali carbonates. A saturated solution is acid to litmus.

Profile

Butalbital is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used mainly in combination preparations with analgesics in the treatment of occasional tension-type headaches, but other treatments are generally preferred.

Preparations

USP 31: Butalbital and Aspirin Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Fiorinal; Fiorinal C; ratio-Tecnal; ratio-Tecnal C; Trianal; Trianal C; ***Chile:*** Cafergot-PB†; ***Denm.:*** Gynergen Comp; ***Ital.:*** Optalidon; ***S.Afr.:*** Cafergot-PB†; ***Spain:*** Cafergot-PB†; ***Switz.:*** Cafergot-PB; ***USA:*** Amaphen with Codeine; Americet; Anolor; Ascomp with Codeine; Bupap; Butex; Dolgic; Dolgic LQ; Dolgic Plus; Endolor; Esgic; Esgic-Plus; Fioricet; Fioricet with Codeine; Fiorinal; Fiorinal with Codeine; Margesic; Marten-Tab; Medigesic; Pacaps; Phrenilin; Phrenilin w Caffeine and Codeine; Promacet; Prominol; Pyridium Plus; Repan; Repan CF†; Sedapap; Tencet; Tencon; Trellium Plus; Triad.

Butobarbital *(BAN)*

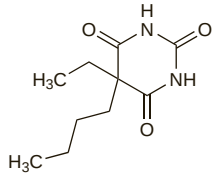
Butethal; Butobarbitaali; Butobarbitalum; Butobarbitone. 5-Butyl-5-ethylbarbituric acid.

$C_{10}H_{16}N_2O_3$ = 212.2.

CAS — 77-28-1.

ATC — N05CA03.

ATC Vet — QN05CA03.



NOTE. Butobarbital should be distinguished from Butabarbital, which is Secbutabarbital (p.1027).

Dependence and Withdrawal

As for Amobarbital, p.962.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p.962.

Interactions

As for Amobarbital, p.962.

Antibacterials. The metabolism of butobarbital may be altered by *metronidazole*.[1]

1. Al Sharifi MA, *et al.* The effect of anti-amoebic drug therapy on the metabolism of butobarbitone. *J Pharm Pharmacol* 1982; **34:** 126–7.

Pharmacokinetics

Butobarbital is metabolised in the liver mainly by hydroxylation; small amounts are excreted in the urine as unchanged drug. It has been reported to have a half-life of about 40 to 55 hours and to be about 26% bound to plasma proteins.

Uses and Administration

Butobarbital is a barbiturate with general properties similar to those of amobarbital (p.962). Its use can no longer be recommended because of the risk of its adverse effects and of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p.957) in patients already taking it. It is given in usual oral doses of 100 to 200 mg at night.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Soneryl.

Multi-ingredient: ***Cz.:*** Dinyl†; ***Fr.:*** Hypnasmine†.

Calcium Bromolactobionate

Bromolactobionato de calcio; Calcium Galactogluconate Bromide. Calcium bromide lactobionate hexahydrate.

$Ca(C_{12}H_{21}O_{12})_2,CaBr_2,6H_2O$ = 1062.6.

CAS — 33659-28-8 (anhydrous calcium bromolactobionate).

Profile

Calcium bromolactobionate has sedative properties and has been given orally in the treatment of insomnia and anxiety disorders. The use of bromides is generally deprecated.

Overdosage. Bromide intoxication has been reported[1] in a patient after overdosage with calcium bromolactobionate tablets.

1. Danel VC, *et al.* Bromide intoxication and pseudohyperchloremia. *Ann Pharmacother* 2001; **35:** 386–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Bromocalcio; Nervolta; Sedofantil; ***Cz.:*** Calabron†; ***Ital.:*** Calcibronat; ***Mex.:*** Calcibronat†; ***Mon.:*** Calcibronat; ***Venez.:*** Sedabron†.

Captodiame Hydrochloride *(BANM, pINNM)*

Captodiame, Chlorhydrate de; Captodiami Hydrochloridum; Captodiamine Hydrochloride; Hidrocloruro de captodiamo. 2-(4-Butylthiobenzhydrylthio)ethyldimethylamine hydrochloride.

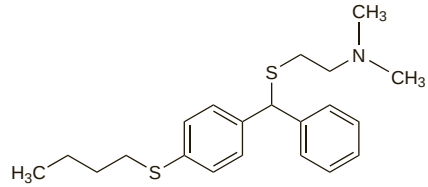
Каптодиама Гидрохлорид

$C_{21}H_{29}NS_2,HCl$ = 396.1.

CAS — 486-17-9 (captodiame); 904-04-1 (captodiame hydrochloride).

ATC — N05BB02.

ATC Vet — QN05BB02.



(captodiame)

Profile

Captodiame hydrochloride has been given in oral doses of 50 mg three times daily for the treatment of anxiety disorders (p.952).

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Covatine.

Carbromal *(BAN, rINN)*

Bromodiethylacetylurea; Carbromalum; Karbromaali; Karbromal. *N*-(2-Bromo-2-ethylbutyryl)urea.

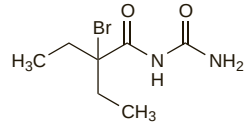
Карбромал

$C_7H_{13}BrN_2O_2$ = 237.1.

CAS — 77-65-6.

ATC — N05CM04.

ATC Vet — QN05CM04.



Profile

Carbromal is a bromureide with general properties similar to those of the barbiturates (see Amobarbital, p.961). It was formerly used for its hypnotic and sedative properties. Chronic use of carbromal could result in bromide accumulation and symptoms resembling bromism (see Bromides, p.2269). The use of bromides is generally deprecated.

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