drugs of this class, including aripiprazole; most of the deaths appeared due to cardiovascular events or infection. See also under Risperidone, p.1024.

The manufacturer subsequently also included a warning in the licensed product information for aripiprazole about evidence of a dose-response relationship between cerebrovascular adverse events and the use of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease.

1. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 24/05/05)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. McQuade RD, *et al.* A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004; **65** (suppl 18): 47–56.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Overdosage. The manufacturer has reported that patients have taken estimated overdoses of up to 1080 mg of aripiprazole with no fatalities. Signs and symptoms have included nausea, vomiting, asthenia, diarrhoea, and somnolence. In one report a 27-year-old woman who ingested 330 mg of aripiprazole with cyclobenzaprine 10 mg and quetiapine 25 mg was found to be drowsy but easily rousable 50 minutes later.[1] Initial treatment consisted of oral activated charcoal; recovery was subsequently uneventful. Serum concentrations of aripiprazole and its main metabolite dehydro-aripiprazole, measured 195 minutes after ingestion, were 596 nanograms/mL and 120 nanograms/mL respectively. In another report[2] a 2½-year-old child vomited and became lethargic within 1 hour of taking 195 mg of aripiprazole (17.1 mg/kg). Activated charcoal was given 3 hours after ingestion but she subsequently became unconscious. However, respiratory support was not required and the child gradually regained consciousness over the next 24 hours. Symptoms of somnolence, ataxia and tremulousness resolved over 7 days. The serum concentration of aripiprazole plus dehydro-aripiprazole was found to be 1873 nanograms/mL 10 hours after ingestion.

1. Carstairs SD, Williams SR. Overdose of aripiprazole, a new type of antipsychotic. *J Emerg Med* 2005; **28:** 311–13.
2. Seifert SA. Aripiprazole (Abilify) overdose in a 2.5 year-old. *J Toxicol Clin Toxicol* 2003; **41:** 647–8.

Pregnancy. For comments on the use of some atypical antipsychotics, including aripiprazole, during pregnancy, see under Precautions of Clozapine, p.983.

Licensed product information states that aripiprazole showed possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Aripiprazole should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

The central effects of other CNS depressants including alcohol may be enhanced by aripiprazole. Aripiprazole may also enhance the effects of antihypertensive drugs. It should be used with caution in patients also receiving drugs that prolong the QT interval or cause electrolyte imbalance.

Aripiprazole is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Ketoconazole, a potent CYP3A4 inhibitor, can increase aripiprazole plasma concentrations by about 60%; licensed product information states that the dose of aripiprazole should be reduced by half when given with ketoconazole. Similarly, the dose of aripiprazole should be halved when given with quinidine, a potent inhibitor of CYP2D6. Conversely, plasma concentrations of aripiprazole may decrease by about 70% when given with carbamazepine, a potent CYP3A4 inducer; the dose of aripiprazole should be doubled if carbamazepine is added to aripiprazole treatment. Similar effects may occur with other potent inhibitors or inducers of these isoenzymes and a reduced or increased dose of aripiprazole, respectively, in such combinations is recommended.

Antiepileptics. For a report of Stevens-Johnson syndrome occurring on use of aripiprazole with *lamotrigine*, see p.486.

Pharmacokinetics

Aripiprazole is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations reached in about 3 to 5 hours. Following intramuscular injection, peak plasma concentrations are reached between 1 to 3 hours. The absolute bioavailability is reported to be 87% with tablet formulations and 100% with the intramuscular injection; it is widely distributed. Aripiprazole is metabolised mainly in the liver and pathways involved include dehydrogenation and hydroxylation, via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and *N*-dealkylation, via CYP3A4. The major metabolite, dehydro-aripiprazole, is also active and represents about 40% of the plasma levels of aripiprazole. The mean elimination half-lives of aripiprazole and dehydro-aripiprazole are about 75 and 95 hours, respectively; in a minority of poor metabolisers the half-life of aripiprazole may be extended to about 146 hours. Protein binding of aripiprazole and its major metabolite is about 99%, mainly to albumin. Elimination is mostly in the faeces (about 55%), with about 25% of a dose appearing in the urine, mainly in the form of metabolites. On the basis of studies in *rats*, it is thought to be distributed into breast milk.

◊ References.

1. Mallikaarjun S, *et al.* Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *J Clin Pharmacol* 2004; **44:** 179–87.

Uses and Administration

Aripiprazole is an atypical antipsychotic that has serotonin 5-HT_{1A}-receptor partial agonist and 5-HT_{2A}-receptor antagonist properties as well as being a partial agonist at dopamine D_2 receptors. It is used in the management of schizophrenia and in acute manic or mixed episodes associated with bipolar disorder. Aripiprazole is also used as an adjunct in the treatment of depression.

For the treatment of **schizophrenia**, aripiprazole is given in an initial oral dose of 10 or 15 mg once daily. The usual maintenance dose is 15 mg once daily although the dose may be adjusted at intervals of not less than 2 weeks up to a maximum of 30 mg daily.

Aripiprazole is also used for the treatment of **mania** associated with bipolar disorder. In the USA, it is given in an initial oral dose of 30 mg once daily, this may subsequently be decreased to 15 mg once daily according to tolerance. Similar doses are licensed in the UK although licensed product information recommends an initial dose of 15 mg once daily.

Aripiprazole may be given by deep intramuscular injection for acute agitation in patients with schizophrenia or bipolar mania. The recommended initial dose is 9.75 mg although some patients may only need 5.25 mg and others up to 15 mg. If necessary, further doses may be given after at least 2 hours, up to a maximum total daily dose of 30 mg. Patients should be switched to oral therapy as soon as possible if ongoing treatment is required.

Aripiprazole is used as adjunctive therapy in **depression**. US licensed product information recommends an initial oral dose of 2 to 5 mg once daily, which may be adjusted in increments of up to 5 mg at intervals of not less than 1 week to a maximum of 15 mg daily. The usual recommended dose is 5 to 10 mg once daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, above for further details.

For details of uses and associated doses in children, see below.

Administration in children. In the USA, aripiprazole may be used for the treatment of schizophrenia in adolescents aged 13 to 17 years and for the treatment of acute manic or mixed episodes associated with bipolar disorder in those aged 10 to 17 years. For both indications, the recommended initial oral dose is 2 mg daily increased to 5 mg daily after 2 days and then to the target dose of 10 mg daily after another 2 days; subsequent dose increases should be made in 5-mg increments up to a total maximum dose of 30 mg daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, above for further details.

Psychiatric disorders. Aripiprazole is used in the management of *schizophrenia* (p.955) and *bipolar disorder* (p.372).[1-9] Although data are scanty, systematic reviews[8,9] have concluded that aripiprazole does not have significant advantages over other atypical and classical antipsychotics in the treatment of schizophrenia. However, it was found to have a lower risk for hyperprolactinaemia and QT interval prolongation compared with other atypical antipsychotics, and a higher risk for insomnia compared with classical antipsychotics. Aripiprazole is also used as an adjunct in the treatment of *depression*.[10,11]

1. McGavin JK, Goa KL. Aripiprazole. *CNS Drugs* 2002; **16:** 779–86.
2. Goodnick PJ, Jerry JM. Aripiprazole: profile on efficacy and safety. *Expert Opin Pharmacother* 2002; **3:** 1773–81.
3. Taylor DM. Aripiprazole: a review of its pharmacology and clinical use. *Int J Clin Pract* 2003; **57:** 49–54.
4. Keck PE, McElroy SL. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. *Expert Opin Invest Drugs* 2003; **12:** 655–62.
5. Bowles TM, Levin GM. Aripiprazole: a new atypical antipsychotic drug. *Ann Pharmacother* 2003; **37:** 687–94.
6. Keck PE, *et al.* A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry* 2003; **160:** 1651–8.
7. Harrison TS, Perry CM. Aripiprazole: a review of its use in schizophrenia and schizoaffective disorder. *Drugs* 2004; **64:** 1715–36.
8. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 15/05/06).
9. Bhattacharjee J, El-Sayeh HGG. Aripiprazole versus typicals for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/04/08).
10. Berman RM, *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007; **68:** 843–53.
11. Marcus RN, *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008; **28:** 156–65.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Arlemide; Groven; Irazem; Siblix; ***Austral.:*** Abilify; ***Belg.:*** Abilify; ***Braz.:*** Abilify; ***Chile:*** Abilify; Azymol; Viza; ***Cz.:*** Abilify; ***Denm.:*** Abilify; ***Fin.:*** Abilify; ***Fr.:*** Abilify; ***Ger.:*** Abilify; ***Gr.:*** Abilify; ***Hong Kong:*** Abilify; ***Hung.:*** Abilify; ***India:*** Real One; ***Indon.:*** Abilify; ***Irl.:*** Abilify; ***Ital.:*** Abilify; ***Malaysia:*** Abilify; ***Mex.:*** Abilify; ***Neth.:*** Abilify; ***Norw.:*** Abilify; ***NZ:*** Abilify; ***Philipp.:*** Abilify; ***Port.:*** Abilify; ***S.Afr.:*** Abilify; ***Singapore:*** Abilify; ***Spain:*** Abilify; ***Swed.:*** Abilify; ***Switz.:*** Abilify; ***Thai.:*** Abilify; ***UK:*** Abilify; ***USA:*** Abilify; ***Venez.:*** Abilify.

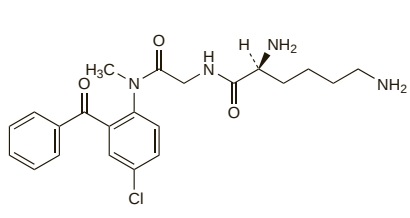
Avizafone *(BAN, rINN)*

Avizafona; Avizafonum; Prodiazepam; Ro-03-7355; Ro-03-7355/000; Ro-03-7355/002 (avizafone hydrochloride). L-Lysyl-(2′-benzoyl-4′-chloro-*N*′-methyl)glycinanilide.

Авизафон

$C_{22}H_{27}ClN_4O_3$ = 430.9.

CAS — 65617-86-9 (avizafone); 60067-16-5 (avizafone hydrochloride).



Profile

Avizafone is rapidly metabolised in the body to diazepam (p.986) and is included as the anticonvulsant component of an intramuscular injection used by military personnel as an antidote to nerve agents. The usual dose of avizafone given in this preparation is 10 mg, repeated every 15 minutes if necessary up to a total dose of 30 mg.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Nerve Agent Antidote L4A1.

Azaperone *(BAN, USAN, rINN)*

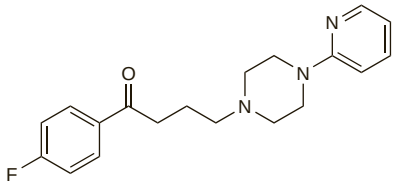
Atsaperoni; Azaperon; Azaperona; Azapérone; Azaperonum; R-1929. 4′-Fluoro-4-[4-(2-pyridyl)piperazin-1-yl]butyrophenone.

Азаперон

$C_{19}H_{22}FN_3O$ = 327.4.

CAS — 1649-18-9.

ATC Vet — QN01AX91; QN05AD90.



Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.

Ph. Eur. 6.2 (Azaperone for Veterinary Use; Azaperone BP(Vet) 2008). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 31 (Azaperone). M.p. 92° to 95°. Protect from light.

Profile

Azaperone is a butyrophenone antipsychotic used as a tranquilliser in veterinary medicine.

Barbital *(BAN, rINN)*

Barbitaali; Barbitál; Barbitalis; Barbitalum; Barbitone; Diemalum; Diethylmalonylurea. 5,5-Diethylbarbituric acid.

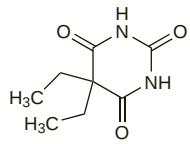
Барбитал

$C_8H_{12}N_2O_3$ = 184.2.

CAS — 57-44-3.

ATC — N05CA04.

ATC Vet — QN05CA04.



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

Ph. Eur. 6.2 (Barbital). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; soluble in boiling water and in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Barbital Sodium *(BANM, rINN)*

Barbital de sodio; Barbital sódico; Barbital sodique; Barbital sodowy; Barbitalum Natricum; Barbitone Sodium; Diemalnatrium; Soluble Barbitone. Sodium 5,5-diethylbarbiturate.

Барбитал Натрий

$C_8H_{11}N_2NaO_3$ = 206.2.

CAS — 144-02-5.

ATC — N05CA04.

ATC Vet — QN05CA04.

Profile

Barbital is a barbiturate with general properties similar to those of amobarbital (p.961). It was formerly used for its hypnotic and sedative properties but barbiturates are no longer considered appropriate for such purposes.

Benperidol *(BAN, USAN, rINN)*

Benpéridol; Benperidoli; Benperidolis; Benperidolum; Benzperidol; CB-8089; McN-JR-4584; R-4584. 1-{1-[3-(4-Fluorobenzoyl)propyl]-4-piperidyl}benzimidazolin-2-one.

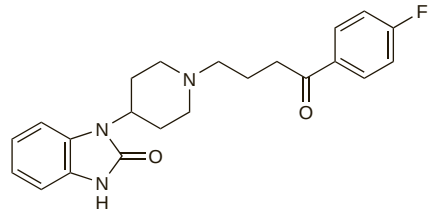
Бенперидол

$C_{22}H_{24}FN_3O_2$ = 381.4.

CAS — 2062-84-2.

ATC — N05AD07.

ATC Vet — QN05AD07.



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

Ph. Eur. 6.2 (Benperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Benperidol is a butyrophenone with general properties similar to those of haloperidol (p.1000). Doses of 0.25 to 1.5 mg daily in divided doses are given orally in the management of deviant sexual behaviour. Elderly or debilitated patients may require reduced doses and half the usual dose may be sufficient.

In some countries benperidol is given by mouth or parenterally for the treatment of psychotic conditions (p.954).

Deviant sexual behaviour. Results of a double-blind placebo-controlled crossover study found no difference between the effect of benperidol 1.25 mg daily, chlorpromazine 125 mg daily, or placebo on sexual drive and arousal in 12 paedophilic sexual offenders, except for a lower frequency of sexual thoughts with benperidol.[1] The effects of benperidol are unlikely to be sufficient to control severe forms of antisocial sexually deviant behaviour. The management of deviant sexual behaviour is discussed under Disturbed Behaviour on p.954.

1. Tennent G, *et al*. The control of deviant sexual behaviour by drugs: a double-blind controlled study of benperidol, chlorpromazine, and placebo. *Arch Sex Behav* 1974; **3:** 261–71.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Frenactil; ***Ger.:*** Glianimon; ***Gr.:*** Glianimon; ***Irl.:*** Anquil†; ***Neth.:*** Frenactil; ***UK:*** Anquil; Benquil†.

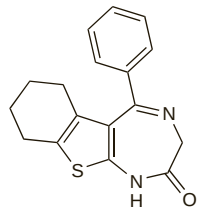
Bentazepam *(USAN, rINN)*

Bentazépam; Bentazepamum; CI-718; QM-6008. 1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-e]-1,4-diazepin-2-one.

Бентазепам

$C_{17}H_{16}N_2OS$ = 296.4.

CAS — 29462-18-8.



Profile

Bentazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given, in usual oral doses of 25 mg every 8 hours, in the short-term treatment of anxiety disorders; it has also been used in insomnia.

Effects on the liver. Severe chronic active hepatitis has been reported in a 65-year-old man who had received long-term treatment with bentazepam.[1]

1. Andrade RJ, *et al*. Bentazepam-associated chronic liver disease. *Lancet* 1994; **343:** 860.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Tiadipona.

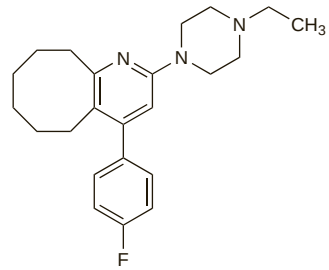
Blonanserin *(rINN)*

AD-5423; Blonanserina; Blonansérine; Blonanserinum. 2-(4-Ethyl-1-piperazinyl)-4-(*p*-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclo-octa[*b*]pyridine.

Блонансерин

$C_{23}H_{30}FN_3$ = 367.5.

CAS — 132810-10-7.



Profile

Blonanserin is an antipsychotic reported to be an antagonist at dopamine D_2 and serotonin ($5\text{-}HT_2$) receptors. It is given orally for the treatment of schizophrenia in an initial dose of 4 mg twice daily, increased gradually according to response thereafter. The usual maintenance dose is 8 to 16 mg daily; the maximum daily dose is 24 mg.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Lonasen.

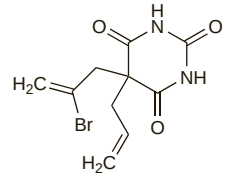
Brallobarbital *(rINN)*

Brallobarbitaali; Brallobarbitalum; Bralobarbital; UCB-5033. 5-Allyl-5-(2-bromoallyl)barbituric acid.

Браллобарбитал

$C_{10}H_{11}BrN_2O_3$ = 287.1.

CAS — 561-86-4.



Profile

Brallobarbital is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used in preparations for the management of insomnia but barbiturates are no longer considered appropriate for such purposes. Brallobarbital calcium has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Port.:*** Vesparax†.

Bromazepam *(BAN, USAN, rINN)*

Bromatsepaami; Brómazepám; Bromazépam; Bromazepamas; Bromazepamum; Ro-5-3350. 7-Bromo-1,3-dihydro-5-(2-pyridyl)-1,4-benzodiazepin-2-one.

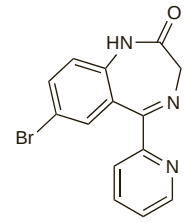
Бромазепам

$C_{14}H_{10}BrN_3O$ = 316.2.

CAS — 1812-30-2.

ATC — N05BA08.

ATC Vet — QN05BA08.



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

Ph. Eur. 6.2 (Bromazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble or sparingly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Bromazepam is a benzodiazepine with general properties similar to those of diazepam (p.992). It has been used in the short-term treatment of anxiety disorders (p.952) occurring alone or associated with insomnia. A usual initial oral dose for anxiety is 6 to 18 mg daily in divided doses. Higher doses up to 60 mg daily