

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*. *Jpn* includes Amobarbital Sodium for Injection.

Ph. Eur. 6.2 (Amobarbital Sodium). A white or almost white, hygroscopic, granular powder. Very soluble in carbon dioxide-free water (a small fraction may be insoluble); freely soluble in alcohol. A 10% solution in water has a pH of not more than 11.0. Store in airtight containers.

USP 31 (Amobarbital Sodium). A white, odourless, hygroscopic, friable, granular powder. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. Solutions decompose on standing; decomposition is accelerated by heat. pH of a 10% solution in water is not more than 11.0. Store in airtight containers.

Incompatibility. Amobarbital may be precipitated from preparations containing amobarbital sodium, depending on the concentration and pH. Amobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Dependence and Withdrawal of Barbiturates

The development of dependence is a high risk with amobarbital and other barbiturates and may occur after regular use even in therapeutic doses for short periods. Barbiturates should not therefore be stopped abruptly, but should be withdrawn by gradual reduction of the dose over a period of days or weeks. A long-acting barbiturate such as phenobarbital may be substituted for a short- or intermediate-acting one, followed by gradual reduction of the phenobarbital dose.

Withdrawal symptoms are similar to those of alcohol withdrawal and are characterised after several hours by apprehension and weakness, followed by anxiety, headache, dizziness, irritability, tremors, nausea and vomiting, abdominal cramps, insomnia, distortion in visual perception, muscle twitching, and tachycardia. Orthostatic hypotension and convulsions may develop after a day or two, sometimes leading to status epilepticus. Hallucinations and delirium tremens may develop after several days followed by coma before the symptoms disappear or death occurs.

Adverse Effects

Drowsiness, sedation, and ataxia are the most frequent adverse effects of amobarbital and other barbiturates and are a consequence of dose-related CNS depression. Other adverse effects include respiratory depression, headache, gastrointestinal disturbances, skin reactions, confusion, and memory defects. Paradoxical excitement and irritability may occur, particularly in children, the elderly, and patients in acute pain. Hypersensitivity reactions occur rarely and include skin rashes (erythema multiforme and exfoliative dermatitis, sometimes fatal, have been reported), hepatitis and cholestasis, and photosensitivity. Blood disorders, including megaloblastic anaemia after chronic use of barbiturates, have also occurred occasionally.

Neonatal intoxication, drug dependence, and symptoms resembling vitamin-K deficiency have been reported in infants born to mothers who received barbiturates during pregnancy. Congenital malformations have been reported in children of women who took barbiturates during pregnancy, but the causal role is a matter of some debate.

Nystagmus, miosis, slurred speech, and ataxia may occur with excessive doses of barbiturates. The toxic effects of overdosage result from profound central depression and include coma, respiratory and cardiovascular depression, with hypotension and shock leading to renal failure and death. Hypothermia may occur with subsequent pyrexia on recovery. Erythematous or haemorrhagic blisters reportedly occur in about 6% of patients, but are not characteristic solely of barbiturate poisoning.

Solutions of the sodium salts of barbiturates are extremely alkaline, and necrosis has followed subcutaneous injection. Intravenous injection may be hazardous; hypotension, shock, laryngospasm, and apnoea have occurred particularly after rapid injection. Gangrene has resulted from intra-arterial injection into an extremity.

Overdosage. A detailed review of drug-induced stupor and coma, including that caused by barbiturates.¹

1. Ashton CH, *et al.* Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug Reaction Acute Poisoning Rev* 1989; **8**: 1–59.

Treatment of Adverse Effects

After an overdose of a barbiturate, endotracheal intubation may be necessary if the patient is unconscious. Giving activated charcoal by mouth or nasogastric tube is recommended in patients who have ingested more than 10 mg/kg and present within 1 hour of ingestion; repeat doses may be necessary. Patients should be managed with intensive supportive therapy, with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions, and to the maintenance of the electrolyte balance. Charcoal haemoperfusion can be life-saving in the most severe cases and should be considered if there is no improvement after 24 hours of supportive care. The value of other measures aimed at the active removal of barbiturates is questionable.

Precautions

Amobarbital and other barbiturates are best avoided in elderly and debilitated patients, in young adults, in children, and in those with depression.

Amobarbital is contra-indicated in patients with pulmonary insufficiency, sleep apnoea, pre-existing CNS depression or coma, and severe hepatic impairment, and should be given with caution to those with renal impairment. Barbiturates given to patients in pain may provoke a paradoxical excitatory reaction, unless an analgesic is also given. With continued use, tolerance develops to the sedative or hypnotic effects of the barbiturates to a greater extent than to their lethal effects. Barbiturates may cause drowsiness which may persist the next day; affected patients should not drive or operate machinery.

See Adverse Effects, above, for the hazards of giving barbiturates during pregnancy and Breast Feeding, below, for cautions on their use in nursing mothers.

Dependence readily develops after use of barbiturates with a **withdrawal syndrome** if stopped abruptly (see Dependence and Withdrawal, above).

Barbiturates are abused for their euphoric effects.

Breast feeding. Small amounts of barbiturates are distributed into breast milk, and most authorities, such as the *BNF*, consider that they should not be taken while breast feeding. The American Academy of Pediatrics notes¹ that the long-acting antiepileptic barbiturate, phenobarbital, has been associated with significant effects on some nursing infants, although it suggests that some other barbiturates may be compatible with breast feeding.

1. 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)

Porphyria. Barbiturates including amobarbital have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Interactions

Sedation or respiratory depression may be enhanced by drugs with CNS-depressant properties; in particular alcohol should be avoided. Barbiturates generally induce liver enzymes, and thus increase the rate of metabolism (and decrease the activity) of many other drugs as well as endogenous substances. Continued use may result in induction of their own metabolism. MAOIs may prolong the CNS depressant effects of some barbiturates, probably by inhibition of their metabolism. However, MAOIs, like other antidepressants, also reduce the convulsive threshold and thereby antagonise the anticonvulsant action of barbiturates. For some further interactions involving barbiturates, see under Phenobarbital, p.493.

Pharmacokinetics

Amobarbital is readily absorbed from the gastrointestinal tract. It is about 60% bound to plasma proteins. It has a half-life of about 20 to 25 hours which is considerably extended in neonates. It crosses the placenta and small amounts are distributed into breast milk. Amobarbital is metabolised in the liver; up to about 50% is excreted in the urine as 3'-hydroxyamobarbital and up to about 30% as *N*-hydroxyamobarbital, less than 1% appearing unchanged; up to about 5% is excreted in the faeces.

Uses and Administration

Amobarbital is a barbiturate that has been used as a hypnotic and sedative. Its use can no longer be recommended because of its adverse effects and risk of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p.957) in patients already taking it. The usual oral dose was 100 to 200 mg of the base or 60 to 200 mg of the sodium salt, taken at bedtime. A more rapid onset of effect was obtained with the sodium salt.

Barbiturates with a longer action such as phenobarbital (p.492) are still used in epilepsy and those with a shorter action such as methohexital (p.1788) or thiopental (p.1795) for anaesthesia.

Cerebrovascular disorders. For reference to the use of barbiturate-induced coma in the management of patients with cerebral ischaemia, see p.1796.

Epilepsy. Amobarbital is used for specialised procedures in expert epilepsy centres only. It is given by deep intramuscular or slow intravenous injection as the sodium salt.

Preparations

USP 31: Amobarbital Sodium for Injection; Secobarbital Sodium and Amobarbital Sodium Capsules.

Proprietary Preparations (details are given in Part 3)

Austral: Amytal[†]; Neur-Amyl[†]; **Canad.:** Amytal[†]; **Hung.:** Dorlotyn[†]; **UK:** Amytal; **USA:** Amytal.

Multi-ingredient: **Arg.:** Cuait N; **Hung.:** Tardyl[†]; **S.Afr.:** Repasma; **Thai:** Ama; **UK:** Tuinal; **USA:** Tuinal.

Amperozide (BAN, rINN)

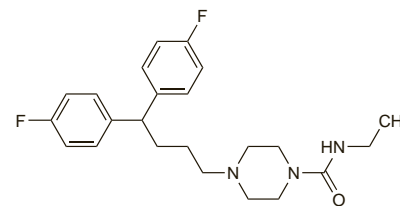
Amperozida; Ampérozide; Amperozidum; FG-5606. 4-[4,4-Bis(4-fluorophenyl)butyl]-N-ethylpiperazine-1-carboxamide.

Амперозид

$C_{23}H_{29}F_2N_3O = 401.5$.

CAS — 75558-90-6 (amperozide); 75529-73-6 (amperozide hydrochloride).

ATC Vet — QN05AX90.



Profile

Amperozide is an antipsychotic that has been used in veterinary medicine.

Aripiprazole (BAN, USAN, rINN)

Aripiprazol; Aripiprazolum; OPC-31; OPC-14597. 7-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one.

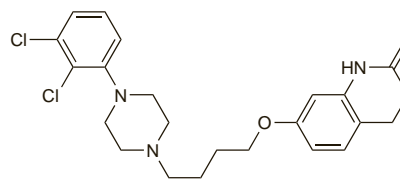
Арипипразол

$C_{23}H_{27}Cl_2N_3O_2 = 448.4$.

CAS — 129722-12-9.

ATC — N05AX12.

ATC Vet — QN05AX12.



Adverse Effects, Treatment, and Precautions

Although aripiprazole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Common adverse effects with aripiprazole include gastrointestinal disorders such as constipation, dyspepsia, nausea, and vomiting, headache, anxiety, insomnia, lightheadedness, and drowsiness. Weight gain has been reported; however, this appears to be slight. The incidence of extrapyramidal effects with aripiprazole is low with akathisia being most commonly reported. Tardive dyskinesia has been reported infrequently and there have been a few cases of neuroleptic malignant syndrome.

Tachycardia and orthostatic hypotension are uncommon with aripiprazole treatment; bradycardia, ventricular arrhythmias, cardiac arrest, and sudden unexplained death have been reported very rarely as have QT prolongation and torsade de pointes. Nonetheless aripiprazole should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension.

Seizures are rare with aripiprazole but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

When aripiprazole is used as an adjunct in depression, patients should be closely monitored during early therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373.

Aripiprazole may affect the performance of skilled tasks including driving.

References

1. Marder SR, *et al.* Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res* 2003; **61**: 123–36.

Dementia. The FDA¹ has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain