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 Barbiturates should not therefore be stopped abruptly, but should be withdrawn by gradual reduction of the dose over a period of days or weeks.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 React 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 euphoriant 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 notes[1] 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′-hydroxyamylobarbital and up to about 30% as *N*-hydroxyamylobarbital, 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.

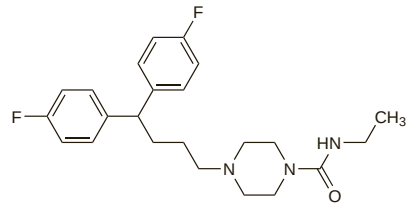
Multi-ingredient: ***Arg.:*** Cuait N; ***Hung.:*** Tardyl†; ***S.Afr.:*** Repasma; ***Thai.:*** Ama; ***UK:*** Tuinal; ***USA:*** Tuinal.

Amperozide *(BAN, rINN)*

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

Аперозид

$C_{23}H_{29}F_2N_3O$ = 401.5.
CAS — 75558-90-6 (amperozide); 75529-73-6 (amperozide hydrochloride).
ATC Vet — QN05AX90.



Profile

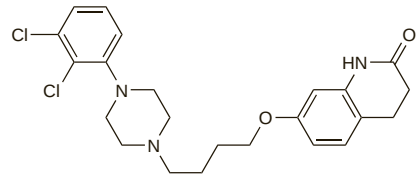
Amperozide is an antipsychotic that has been used in veterinary medicine.

Aripiprazole *(BAN, USAN, rINN)*

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

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.

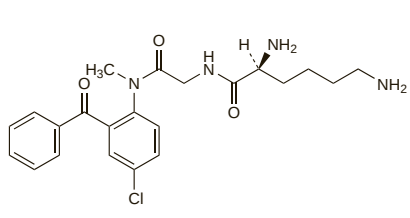
Avizafone *(BAN, rINN)*

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.