cause the muscarinic symptoms of overdosage may be suppressed leaving only the more serious nicotinic effects (fasciculation and paralysis of voluntary muscle).

Pharmacokinetics
Ambenonium chloride is poorly absorbed from the gastrointestinal tract. It does not appear to be hydrolysed by cholinesterases.

Uses and Administration
Ambenonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632), but of longer duration. Ambenonium chloride is given orally in the treatment of myasthenia gravis (p.629) in usual doses of 5 to 25 mg three or four times daily, adjusted according to response. It may be of value in patients who cannot tolerate neostigmine or pyridostigmine.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Mytelase; ***Fr.:*** Mytelase; ***Gr.:*** Mytelase; ***Hung.:*** Mytelase; ***Pol.:*** Mytelase; ***Swed.:*** Mytelase; ***USA:*** Mytelase.

Amifampridine *(rINN)*

Amifampridina; Amifampridinum; 3,4-Diaminopyridine. Pyridine-3,4-diamine.

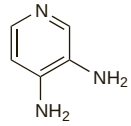
Амифампридин

$C_5H_7N_3$ = 109.1.

CAS — 54-96-6.

ATC — N07XX05.

ATC Vet — QN07XX05.



Profile
Amifampridine has similar actions and uses to fampridine (p.631) but is reported to be more potent in enhancing the release of acetylcholine from nerve terminals. It is used in the Eaton-Lambert myasthenic syndrome (below) and other myasthenic conditions. It has been tried in multiple sclerosis and in botulism. There have been isolated reports of seizures and amifampridine is therefore contra-indicated in patients with epilepsy.

Congenital myasthenia. Congenital or hereditary myasthenia is a heterogeneous group of rare disorders associated with various defects in neuromuscular transmission including presynaptic impairment of acetylcholinesterase release, postsynaptic abnormality of acetylcholine receptors, or a deficiency of acetylcholinesterase.[1] Symptoms may be similar to those of myasthenia gravis (p.629) but there are no immunological abnormalities. Although some forms may respond to anticholinesterases, therapy is usually unsatisfactory. Experience in 16 patients[2] has suggested that amifampridine used alone or with anticholinesterases may be of benefit. Clinical improvement was seen in 5 of 11 patients with congenital myasthenia who were given amifampridine as part of a placebo-controlled study; 3 of the 11 responded to placebo.[3] There have also been reports of benefit from the use of quinidine sulfate in patients with the slow-channel congenital myasthenic syndrome.[4]

1. Engel AG. Congenital myasthenic syndromes. *Neurol Clin North Am* 1994; **12:** 401–37.
2. Palace J, *et al.* 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. *J Neurol Neurosurg Psychiatry* 1991; **54:** 1069–72.
3. Anlar B, *et al.* 3,4-Diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol* 1996; **11:** 458–61.
4. Harper CM, Engel AG. Quinidine sulfate therapy for the slow-channel congenital myasthenic syndrome. *Ann Neurol* 1998; **43:** 480–4.

Eaton-Lambert myasthenic syndrome. Daily doses of up to 100 mg of amifampridine by mouth have been found[1] to be effective in the treatment of both the motor and autonomic deficits of patients with Eaton-Lambert syndrome (p.629). A usual starting dose of 10 mg given three or four times daily increasing if necessary to a maximum of 20 mg given five times daily has been used.[2] However, some workers have recommended limiting the dose to 80 mg daily because of the increased risk of seizures with higher doses.[3] Adverse effects appear to be mainly mild and dose related,[1] although there is a report of cardiac arrest following toxicity.[4] Most patients experience some form of paraesthesia up to 60 minutes after a dose.[1-3] Amifampridine can produce mild excitatory effects and some patients may experience difficulty in sleeping.

1. McEvoy KM, *et al.* 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989; **321:** 1567–71.
2. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; **33:** 205–212.
3. Sanders DB, *et al.* A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000; **54:** 603–7.
4. Boerma CE, *et al.* Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. *J Toxicol Clin Toxicol* 1995; **33:** 249–51.

Multiple sclerosis. Amifampridine has been tried in the management of multiple sclerosis (p.892). In a crossover study[1] involving 36 patients with multiple sclerosis, amifampridine given in a dosage of up to 100 mg daily improved symptoms of leg weakness to a greater extent than placebo but paraesthesia and abdominal pain which occurred in most patients were dose-limiting in some. A systematic review[2] of the use of aminopyridines for symptomatic management of multiple sclerosis was unable to come to any conclusion, and commented on the problem of publication bias in this area.

1. Bever CT, *et al.* Treatment with oral 3,4-diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. *Neurology* 1996; **47:** 1457–62.
2. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).

Distigmine Bromide *(BAN, rINN)*

BC-51; Bispyridostigmine Bromide; Bromuro de distigmina; Distigmiinibromidi; Distigminbromid; Distigmine, Bromure de; Distigmini Bromidum; Hexamarium Bromide. 3,3′-[*N,N*′-Hexamethylenebis(methylcarbamoyloxy)]bis(1-methylpyridinium bromide).

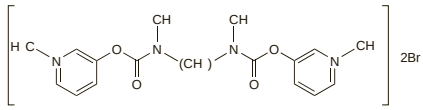
Дистигмина Бромид

$C_{22}H_{32}Br_2N_4O_4$ = 576.3.

CAS — 15876-67-2.

ATC — N07AA03.

ATC Vet — QN07AA03.



Pharmacopoeias. In *Jpn*.

Adverse Effects, Treatment, and Precautions
As for Neostigmine, p.631. The anticholinesterase action of distigmine, and hence its adverse effects, may be prolonged, and if treatment with atropine is required it should be maintained for at least 24 hours. Distigmine may stimulate uterine contractions and UK licensed product information has advised that it should be avoided in pregnancy.

Interactions
As for Neostigmine, p.632.

Pharmacokinetics
Distigmine is poorly absorbed from the gastrointestinal tract.

Uses and Administration
Distigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

Although it is rarely used, distigmine bromide may be given orally with short-acting parasympathomimetics for the treatment of **myasthenia gravis** (p.629); patients being treated with parasympathomimetics tend to prefer pyridostigmine. The initial dose is 5 mg daily before breakfast, increased at intervals of 3 to 4 days if necessary to a maximum of 20 mg daily; children may be given up to 10 mg daily according to age.

Distigmine is one of several drugs that have been used in the prevention and treatment of **postoperative gastrointestinal atony** (see Decreased Gastrointestinal Motility, p.1694). It has also been used in **postoperative urinary retention** (p.2180), although it has been superseded by catheterisation. A dose of 500 micrograms of distigmine bromide was injected intramuscularly about 24 to 72 hours after surgery and repeated at intervals of 1 to 3 days until normal function was restored. Alternatively it has been given orally in a dose of 5 mg daily thirty minutes before breakfast. A similar oral dose, given daily or on alternate days, has been used in the management of **neurogenic bladder**.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Ubretid; ***Cz.:*** Ubretid; ***Fin.:*** Ubretid†; ***Ger.:*** Ubretid; ***Gr.:*** Ubretid; ***Hong Kong:*** Ubretid; ***Hung.:*** Ubretid†; ***Neth.:*** Ubretid; ***Pol.:*** Ubretid; ***Port.:*** Tonus†; ***Rus.:*** Ubretid (Убретид); ***Singapore:*** Ubretid; ***Switz.:*** Ubretid; ***UK:*** Ubretid.

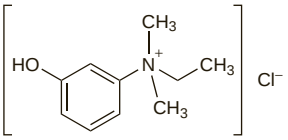
Edrophonium Chloride *(BAN, rINN)*

Cloruro de edrofonio; Edrofonio chloridas; Edrofonium-chlorid; Edrofoniumklorid; Edrofoniumkloridi; Edrofonyum Klorür; Edrophonii chloridum; Édrophonium, chlorure d'. Ethyl(3-hydroxyphenyl)dimethylammonium chloride.

Эдрофония Хлорид

$C_{10}H_{16}ClNO$ = 201.7.

CAS — 312-48-1 (edrophonium); 116-38-1 (edrophonium chloride).



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

Ph. Eur. 6.2 (Edrophonium Chloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Edrophonium Chloride). A white odourless crystalline powder. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; insoluble in chloroform and in ether. A 10% solution in water is practically colourless and the pH is between 4.0 and 5.0.

Adverse Effects, Treatment, and Precautions
As for Neostigmine, p.631.

Interactions
As for Neostigmine, p.632.

Uses and Administration
Edrophonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity. It has actions similar to those of neostigmine (p.632) but its effect on skeletal muscle is claimed to be particularly prominent. It has a rapid onset but short duration of action. In patients with myasthenia gravis, there is immediate subjective improvement and muscle strength increases. This effect usually lasts only for about 5 to 15 minutes, after which time the typical signs and symptoms return; because of its brief action the drug is not suitable for the routine treatment of myasthenia gravis.

Edrophonium chloride is used in **myasthenia gravis** (p.629) both diagnostically and to distinguish between under- or over-treatment with other anticholinesterases.

- The usual *diagnostic procedure* is to inject 2 mg intravenously and, if no adverse reaction occurs within 30 to 45 seconds, to continue with the injection of a further 8 mg. In the UK the recommended total dose for children is 100 micrograms/kg, one-fifth of the dose being given initially, followed 30 seconds later by the remainder if no adverse effects develop; the *BNFC* suggests that this dose may be given to those aged from 1 month to 12 years. In the USA a total dose of 5 mg for children weighing less than 34 kg and 10 mg for heavier children is recommended, with one-fifth of the dose being given initially followed by increments of 1 mg every 30 to 45 seconds; the recommended total dose for infants is 500 micrograms.

  When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection; the usual dose in adults is 10 mg while children below 34 kg in weight may be given 2 mg and heavier children 5 mg; a suggested dose for infants is 0.5 to 1 mg given intramuscularly or subcutaneously. Atropine should always be available when the test is carried out in order to treat any severe muscarinic reactions that may occur.
- To *detect under- or over-treatment*, test doses of 1 to 2 mg of edrophonium chloride are given intravenously to distinguish severe symptoms of myasthenia gravis due to inadequate therapy from the effects of overdosage with anticholinesterase drugs. If treat-