

A. INGREDIENT NAME:

DIAMINOPYRIDINE (3,4)

B. Chemical Name:

3,4-Pyridinediamine

C. Common Name:

3,4-DAP, C₅H₇N₃

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

98+%

E. Information about how the ingredient is supplied:

Pale brown crystalline powder

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

McEvoy, K. M. 4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med*, 1989; 321: 1567-1571.

Russell, J. W. Treatment of stable chronic demyelinating polyneuropathy with 3,4-diaminopyridine. *Mayo Clin Proc*, 1995; 70: 532-539.

Newsom-Davis, J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J*, 1993; 33: 205-212.

McEvoy, K. M. Clinical evaluations in myasthenic syndromes. *N Engl J Med*, 1989; 321: 1567.

1998-3454 B1 - 02 - 21 - BDL08

Bever, C.T., Anderson, P. A., and Leslie, J. 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(6): 1457-1462.

Oh, S. J., Kim, D.S., and Head, T. C. 3,4-diaminopyridine, which is not readily available in the United States, is recommended as the preferred drug for LEMS. *Muscle Nerve*, 1997; 20(9): 1146-1152.

Anlar, B., Varli, K., and Ozdirim, E. 3,4-diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol*, 1996; 11(6): 458-461.

Aisen, M. L., Sevilla, D., and Edelstein, L. A double-blind placebo-controlled study of 3,4-diaminopyridine in amyotrophic lateral sclerosis patients on a rehabilitation unit. *J Neurol Sci*, 1996; 138(1-2): 93-96.

H. Information about dosage forms used:

Orally

I. Information about strength:

10-20mg, three to four daily

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 218-220° with decomposition
Incompatibilities: Strong acid, Strong oxidizing agents

L. Formulations:

M. Miscellaneous Information:

instillation of carbachol eye drops and lasts for 4 to 8 hours; reduction in intra-ocular pressure lasts for 8 hours.

Carbachol is also administered intra-ocularly, 0.4 to 0.5 mL of a 0.01% solution being instilled into the anterior chamber of the eye, to produce miosis in cataract surgery. The maximum degree of miosis is usually obtained within 2 to 5 minutes of intra-ocular instillation and miosis lasts for 24 to 48 hours.

Carbachol has been used as an alternative to catheterisation in the treatment of urinary retention in a dose of 2 mg given three times daily by mouth. For the acute symptoms of postoperative urinary retention doses of 250 µg have been given subcutaneously repeated twice if necessary at 30-minute intervals. Carbachol should not be given by the intravenous or intramuscular routes.

Carbachol does not readily penetrate the cornea and eye drops are usually prepared with a wetting agent to enhance penetration. A lipid-soluble derivative, N-demethylated carbachol has been studied for use in glaucoma.¹

1. Hung PT, et al. Ocular hypotensive effects of N-demethylated carbachol on open angle glaucoma. *Arch Ophthalmol* 1982; 100: 262-4.

Ocular surgery. Some consider carbachol to be the agent of choice for the management of increased intra-ocular pressure after cataract extraction.^{1,2}

1. Ruiz RS, et al. Effects of carbachol and acetylcholine on intraocular pressure after cataract extraction. *Am J Ophthalmol* 1989; 107: 7-10.
2. Hollands RH, et al. Control of intraocular pressure after cataract extraction. *Can J Ophthalmol* 1990; 25: 128-32.

Urinary incontinence. For a discussion on the use of parasympathomimetics in the management of urinary incontinence, see under Uses and Administration of Bethanechol Chloride, p.1113.

Proprietary Names

Carbamann, Doryl, Isopto Karbakolin, Miosial, Spersacarbaychol.

Multi-ingredient preparations. Bestrolina, GT 50, Mios, Risunal A, Risunal B.

Preparation details are given in Part 3.

Choline Alfoscerate (4848-h)

Choline Alfoscerate (rINN).

Choline Glycerophosphate; 1-α-Glycerolphosphorylcholine. Choline hydroxide, (R)-2,3-dihydroxypropyl hydrogen phosphate, inner salt. $C_8H_{20}NO_6P = 257.2$.

CAS — 28319-77-9.

Choline alfoscerate is reported to have cholinergic activity and has been used by intravenous or intramuscular administration in the treatment of Alzheimer's disease and other dementias.

References

1. Trabucchi M, et al. Changes in the interactions between CNS cholinergic and dopaminergic neurons induced by α-glycerolphosphorylcholine, a cholinomimetic drug. *Pharmacol (Sci)* 1986; 41: 323-34.
2. Di Pern R, et al. A multicentre trial to evaluate the efficacy and tolerability of α-glycerolphosphorylcholine versus cytosine diphosphocholine in patients with vascular dementia. *J Int Med Res* 1991; 19: 330-41.

Proprietary Names

Brezal, Delect, Gliatilin.

Preparation details are given in Part 3.

Demecarium Bromide (4512-n)

Demecarium Bromide (BAN, rINN).

BC-48. N,N'-Decamethylenebis(N,N,N-trimethyl-3-methylcarbamoyloxylanilinium) dibromide. $C_{32}H_{52}Br_2N_4O_4 = 716.6$.

CAS — 56-94-0.

Pharmacopoeias. In U.S.

A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and alcohol; soluble in ether; sparingly soluble in acetone. A 1% solution in water has a pH of 5 to 7. Store in airtight containers. Protect from light.

Adverse Effects

As for Neostigmine Methylsulphate, p.1116 and Ecothiopate Iodide, below. The anticholinesterase action of demecarium, and hence its adverse effects, may be prolonged.

As for Ecotioipate Iodide, p.1115.

Praidoxime has been reported to be more active in counteracting the effects of dyflos and ecotioipate than of demecarium.

Uses and Administration

Demecarium is a quaternary ammonium compound which is an inhibitor of cholinesterase with actions similar to those of ecotioipate (see below). Its miotic action begins within about 15 to 60 minutes of its application and may persist for a week or more. It causes a reduction in intra-ocular pressure which is maximal in 24 hours and may persist for 9 days or more.

Demecarium bromide has been used in the treatment of open-angle glaucoma particularly in aphakic patients, and those in whom other agents have proved inadequate. The dosage varies, 1 to 2 drops of a 0.125% or 0.25% solution being instilled from twice weekly to twice daily, preferably at bedtime.

Demecarium bromide has also been used in the diagnosis and management of accommodative convergent strabismus (esotropia).

Proprietary Names

Humorsol, Tosmien.

Preparation details are given in Part 3.

3,4-Diaminopyridine (19064-m)

3,4-Diaminopyridine has similar actions and uses to 4-aminopyridine (see p.1112) but is reported to be more potent in enhancing the release of acetylcholine from nerve terminals.

Administration of 3,4-diaminopyridine by mouth in daily doses of up to 100 mg in a double-blind, placebo-controlled, crossover study was found to be effective in the treatment of both the motor and autonomic deficits of 12 patients with Eaton-Lambert syndrome. One patient receiving 100 mg daily had a single seizure after 10 months of therapy but adverse effects in other patients were minimal and dose-related. In 4 patients addition of pyridostigmine to treatment produced additional benefits. — McEvoy KM, et al. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989; 321: 1567-71.

Distigmine Bromide (4513-h)

Distigmine Bromide (BAN, rINN).

BC-51; Bispyridostigmine Bromide; Hexamarium Bromide. 3,3'-(N,N'-Hexamethylenebis(methylcarbamoyloxy))bis(1-methylpyridinium bromide). $C_{22}H_{32}Br_2N_4O_4 = 576.3$.

CAS — 15876-67-2.

Pharmacopoeias. In Jpn.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.1116. 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.

Absorption and Fate

Distigmine is poorly absorbed from the gastro-intestinal tract.

Uses and Administration

Distigmine is a quaternary ammonium compound which is an inhibitor of cholinesterase activity with actions similar to those of neostigmine (see p.1117) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

It is used in the prevention and treatment of postoperative intestinal atony and urinary retention: 500 µg of distigmine bromide may be injected intramuscularly about 12 hours after surgery and may be repeated every 24 hours until normal function is restored. It may also be given by mouth in a dose of 5 mg daily thirty minutes before breakfast. A similar dose by mouth, given daily or on alternate days, has been employed in the management of neurogenic bladder.

Distigmine bromide in conjunction with short-acting parasympathomimetics has been given for the treatment of myasthenia gravis, but should only be given by mouth. Doses of up to 20 mg daily for adults and up to 10 mg daily for children have been used, adjusted according to individual response.

Proprietary Names

Ubreid.

Preparation details are given in Part 3.

Dyflos (4514-m)

Dyflos (BAN).

DFP; Difluorophosphate; Di-isopropyl Fluorophosphate; Di-isopropyl phosphorodifluoridate.

isopropyl phosphorodifluoridate.

$C_6H_{14}FO_2P = 184.1$.

CAS — 55-91-4.

Pharmacopoeias. In U.S.

A clear, colourless, or faintly yellow liquid. Specific gravity about 1.05. Sparingly soluble in water, alcohol and vegetable oils. It is decomposed by the evolution of hydrogen fluoride. Store 15° in sealed containers.

CAUTION. The vapour of dyflos is very toxic. Contact material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours. Dyflos removed from the skin by washing with soap and water.

Adverse Effects

As for Neostigmine Methylsulphate, p.1116 and p.1117, and p.1118, below.

The anticholinesterase action of dyflos, and hence its adverse effects, may be prolonged. Its vapour is irritating to the eye and mucous membranes.

Systemic toxicity also occurs after inhalation of vapour. Prolonged use of dyflos in the eye may cause a reversible depigmentation of the lid margin in skinned patients.

Treatment of Adverse Effects and Precautions

As for Ecotioipate Iodide, p.1115.

Absorption and Fate

Dyflos is readily absorbed from the gastro-intestinal tract from skin and mucous membranes, and from the eye. Dyflos interacts with cholinesterases producing phosphorylated and phosphorylated derivatives which are then hydrolysed by phosphorotriphosphatases. The products of hydrolysis are excreted mainly in the urine.

Uses and Administration

Dyflos is an irreversible inhibitor of cholinesterase with actions similar to those of ecotioipate (see p.1115). Dyflos has a powerful miotic action which begins within 10 minutes and may persist for up to 4 weeks, with a reduction in intra-ocular pressure which is maximal in 24 hours and may persist for a week.

Dyflos is used mainly in the treatment of glaucoma particularly in aphakic patients, and those in whom other agents have proved inadequate. It is also employed in the diagnosis and management of accommodative convergent strabismus (esotropia).

Dyflos is administered locally usually as a 0.1% ethanolic solution or as a 0.1% ethanolic ointment preferably at night before bedtime.

Proprietary Names

Difluoril, Floropyl.

Preparation details are given in Part 3.

Ecotioipate Iodide (4515-b)

Ecotioipate iodide is an irreversible cholinesterase with a prolonged duration of action. It is used as a miotic in the treatment of glaucoma when other agents have proved inadequate.

Ecotioipate Iodide (BAN, rINN).

Ecotioipate Iodide; Ecotioipate Iodide; (2-Diethoxyphosphorylthioethyl)-trimethylammonium iodide. $C_9H_{21}INO_3PS = 383.2$.

CAS — 6736-03-4 (ecotioipate); 513-10-0 (ecotioipate iodide).

Pharmacopoeias. In Br., Gr., Jpn. and U.S.

A white crystalline hygroscopic powder with a strong odour. Soluble 1 in 1 of water, 1 in 25 of alcohol. Soluble in 3 of methyl alcohol; practically insoluble in other organic solvents. A solution in water has a pH of 7. The B.P. requires storage between 2° and 8°. It requires storage preferably at a temperature below 15°. Store in airtight containers. Protect from light.

Adverse Effects

As for Neostigmine Methylsulphate, p.1116 and p.1117, and p.1118, below. Ecotioipate is an irreversible cholinesterase inhibitor; its action, and hence its adverse effects, may be prolonged.

Plasma and erythrocyte cholinesterases may be inhibited by treatment with eye drops of ecotioipate, or other long-acting anticholinesterase agents; systemic toxicity occurs more frequently with shorter-acting miotics. Acute intussusception, or precipitation of acute glaucoma, may occasionally follow treatment with ecotioipate in iris cysts (especially in children) or lens dislocation may develop following prolonged treatment.

Albion, Switz.: Doryl; Miostat; Spersacarbachol; USA: Miostat.
 Conjugate preparations. Ger.: GT 501; Ital.: Mios; Romania: Risunal A; Risunal B.

Line Alfoscerate (4948-h)

Alfoscerate (INN).
 Glyceronosonate: 1- α -Glycerolphosphorylcholine hydroxide, (R)-2,3-dihydroxypropyl hydrogen phosphate salt.
 NO_xP = 257.2.
 28319-77-9.

Alfoscerate is reported to be a precursor of choline and has been tried by oral, intrave- or intramuscular administration in the treat- ment of Alzheimer's disease and other dementias. As mentioned in the discussion on the treat- ment of dementia (see p.1413) this type of treatment is considered to produce useful improvement.

Uchi M, et al. Changes in the interactions between CNS serergic and dopaminergic neurons induced by L- α -glycerophosphorylcholine, a cholinomimetic drug. *Pharmacol Sci* 1986; 41: 323-34.
 Puri R, et al. A multicentre trial to evaluate the efficacy and safety of α -glycerolphosphorylcholine versus cytosine di- phosphocholine in patients with vascular dementia. *J Int Med* 1991; 19: 330-41.

Names of preparations are listed below; details are given in Part 3.
 Proprietary Preparations
 Austral.: Delect; Glaxo.

Demecarium Bromide (4512-n)

Demecarium Bromide (BAN, INN).
 N,N'-Decamethylenebis(N,N,N-trimethyl-3-methyl-2-benzoyloxycarbonyl) dibromide.
 C₂₂H₃₂N₄O₄ = 716.6.
 56-94-0.
 Pharmacopoeias. In US.

White or slightly yellow, slightly hygroscopic, crystalline solid. Freely soluble in water and in alcohol; soluble in benzene; sparingly soluble in acetone. A 1% solution in water has a pH of 5 to 7. Store in airtight containers. Protect from light.

Adverse Effects

For Neostigmine, p.1422 and Ecothiopate Iodide, p.1420. For adverse effects of miotics, see also Pilocarpine, p.1426.

Treatment of Adverse Effects

For Ecothiopate Iodide, p.1420.
 Atropine has been reported to be more active in counteracting the effects of dyflol and ecothiopate than demecarium.

Precautions

For Neostigmine, p.1423 and Ecothiopate Iodide, p.1420. For precautions of miotics, see also Pilocarpine, p.1426.

Uses and Administration

Demecarium is a quaternary ammonium compound which is a reversible inhibitor of cholinesterase with a long duration of action similar to that of ecothiopate iodide (see p.1420). Its miotic action begins within about 15 to 60 minutes of its application and may persist for a week or more. It causes a reduction in intra-ocular pressure which is maximal in 24 hours and may persist for 9 days or more.

Demecarium bromide has been used in the treatment of open-angle glaucoma particularly in aphakic patients and those in whom other agents have proved inadequate (see p.1414). The dosage varies, 1 to 2 drops of a 0.125% or 0.25% solution being instilled four to six times weekly to twice daily, preferably at bedtime. Demecarium bromide has also been used in the diagnosis and management of accommodative

convergent strabismus (accommodative esotropia) as mentioned in the discussion on the treatment of strabismus on p.1416.

Preparations

Names of preparations are listed below; details are given in Part 3.
 Official Preparations
 USP 23: Demecarium Bromide Ophthalmic Solution.
 Proprietary Preparations
 UK: Tosmilen; USA: Humorsol.

3,4-Diaminopyridine (19064-m)

3,4-Diaminopyridine has similar actions and uses to fampridine (see p.1421) 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 and other myasthenic conditions. It has been tried in multiple sclerosis and in botulism.

No improvement was observed with 3,4-diaminopyridine in a controlled study of patients with chronic demyelinating neuropathy.¹

1. Russell JW, et al. Treatment of stable chronic demyelinating polyneuropathy with 3,4-diaminopyridine. *Mayo Clin Proc* 1995; 70: 532-9.

Eaton-Lambert myasthenic syndrome. Administration of 3,4-diaminopyridine by mouth in daily doses of up to 100 mg has been found to be effective in the treatment of both the motor and autonomic deficits of patients with Eaton-Lambert syndrome.¹ 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 Adverse effects appear to be mainly mild and dose related.¹ Most patients experience some form of paraesthesia up to 60 minutes after administration.^{1,2} 3,4-Diaminopyridine can produce mild excitatory effects and some patients may experience difficulty in sleeping. There have been isolated reports of seizures and 3,4-diaminopyridine is therefore contra-indicated in patients with epilepsy. Other treatments of Eaton-Lambert myasthenic syndrome are discussed on p.1414.

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. Newsome-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers J* 1993; 3: 213-212.

Distigmine Bromide (4513-h)

Distigmine Bromide (BAN, INN).
 BC-51: Bispyridostigmine Bromide; Hexamamium Bromide. 3,3'-(N,N'-Hexamethylenebis(methylcarbamoyloxy))bis(1-methylpyridinium bromide).
 C₂₂H₃₂Br₂N₄O₄ = 576.3.
 CAS — 15876-67-2.
 Pharmacopoeias. In Jpn.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.1422. 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.

Pharmacokinetics

Distigmine is poorly absorbed from the gastro-intestinal tract.

Uses and Administration

Distigmine is a quaternary ammonium compound which is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (see p.1423) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

It is one of several agents that may be used in the prevention and treatment of postoperative intestinal atony (see p.1193). It is also used in urinary retention, although catheterisation is generally preferred (see p.489). A dose of 300 μ g of distigmine bromide may be injected intramuscularly about 12 hours after surgery and may be repeated every 24 hours until

normal function is restored. It may also be given by mouth in a dose of 5 mg daily thirty minutes before breakfast. A similar dose by mouth, given daily or on alternate days, has been employed in the management of neurogenic bladder.

Distigmine bromide in conjunction with short-acting parasympathomimetics is also used for the treatment of myasthenia gravis, but should only be given by mouth. Also, as discussed under the section on the treatment of myasthenia gravis, patients being treated with parasympathomimetics tend to prefer pyridostigmine (see p.1415). Doses of up to 20 mg daily for adults and up to 10 mg daily for children are given, adjusted according to individual response.

Preparations

Names of preparations are listed below; details are given in Part 3.
 Proprietary Preparations
 Aust.: Ubretid; Austral.: Ubretid; Eire: Ubretid; Ger.: Ubretid; Veik.: Ubretid; S.Afr.: Ubretid; Switz.: Ubretid; UK: Ubretid.

Dyflol (4514-m)

Dyflol (BAN).
 DFP: Difluorophosphate; Di-isopropyl Fluorophosphonate; Di-isopropylfluorophosphonate; Fluostigmine; Isoflurophosphate. Di-isopropyl phosphorofluoridate.
 C₆H₁₄FO₂P = 184.1.
 CAS — 55-91-4.
 Pharmacopoeias. In US.

A clear, colourless, or faintly yellow liquid. Specific gravity about 1.05. Sparingly soluble in water; soluble in alcohol and in vegetable oils. It is decomposed by moisture with the evolution of hydrogen fluoride. Store at 8° to 15° in sealed containers.

CAUTION. The vapour of dyflol is very toxic. The eyes, nose, and mouth should be protected when handling dyflol, and contact with the skin should be avoided. Dyflol can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Adverse Effects

As for Neostigmine Methylsulphate, p.1422 and Ecothiopate Iodide, p.1420. For adverse effects of miotics, see also Pilocarpine, p.1426.

The anticholinesterase action of dyflol, and hence its adverse effects, may be prolonged. Its vapour is extremely irritating to the eye and mucous membranes.

Systemic toxicity also occurs after inhalation of the vapour. Prolonged use of dyflol in the eye may cause slowly reversible depigmentation of the lid margins in dark-skinned patients.

Treatment of Adverse Effects

As for Ecothiopate Iodide, p.1420.

Precautions

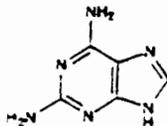
As for Neostigmine, p.1423 and Ecothiopate Iodide, p.1420. For precautions of miotics, see also Pilocarpine, p.1426.

Pharmacokinetics

Dyflol is readily absorbed from the gastro-intestinal tract, from skin and mucous membranes, and from the lungs. Dyflol interacts with cholinesterases producing stable phosphorylated and phosphonylated derivatives which are then hydrolysed by phosphoroliposphatases. These products of hydrolysis are excreted mainly in the urine.

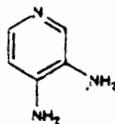
Uses and Administration

Dyflol is an irreversible inhibitor of cholinesterase with actions similar to those of ecothiopate iodide (see p.1420). Dyflol has a powerful miotic action which begins within 5 to 10 minutes and may persist for up to 4 weeks; it causes a reduction in intra-ocular pressure which is maximal in 24 hours and may persist for a week.



Crystals from ethanol - water, mp 302°. uv max (pH 1.9): 241, 282 nm (log ϵ 3.98, 4.00).

3029. 3,4-Diaminopyridine. 3,4-Pyridinediamine. 3,4-DAP. C₅H₆N₂; mol wt 109.13. C 55.03%, H 6.47%, N 38.50%. **Potassium channel blocker; antagonizes non-depolarizing neuromuscular blockade.** Prepn: O. Bremer, *Ann.* 518, 274 (1935); J. W. Clark-Lewis, R. P. Singh, *J. Chem. Soc.* 1962, 2379; J. B. Campbell et al., *J. Heterocycl. Chem.* 23, 669 (1986). HPLC determ in serum: J. Leslie, C. T. Bever, *J. Chromatog.* 496, 214 (1989). Acute toxicity: P. Lechat et al., *Ann. Pharm. Franc.* 26, 345 (1968). Effect on neuromuscular transmission: J. Molgo et al., *Eur. J. Pharmacol.* 61, 25 (1980); R. H. Thomsen, D. F. Wilson, *J. Pharmacol. Exp. Ther.* 227, 260 (1983). **Evaluation in human botulism:** A. P. Bail et al., *Quart. J. Med.* 48, 473 (1979). **Clinical evaluations in myasthenic syndromes:** K. M. McEvoy et al., *N. Engl. J. Med.* 321, 1567 (1989); J. Palace et al., *J. Neurol. Neurosurg. Psychiatr.* 54, 1069 (1991); in multiple sclerosis: C. T. Bever, Jr. et al., *Ann. Neurol.* 27, 421 (1990); *idem. ibid.* 36, 5118 (1994).



Needles from water, mp 220° (Clark-Lewis, Singh); also reported as white to beige crystals from water, mp 218-219° (Campbell). Readily sol in water, alcohol; slightly sol in ether. LD₅₀ i.v. in mice: 13 mg/kg (Lechat).

USE: Intermediate in synthesis of heterocyclic compds.

3030. Diamond. A crystalline form of carbon. Mined as a mineral, principally in South Africa. (Non-commercial) synthesis from other carbon compds (e.g., lignin) by means of elevated temperatures (about 2700°) and pressures (about 800,000 lbs/sq inch): Desch, *Nature* 152, 148 (1943); Neuhäus, *Angew. Chem.* 66, 525 (1954); Hall, *Chem. Eng. News* 33, 718 (1955); Bridgman, *Sci. Amer.* 1955, 46; Hall, *J. Chem. Ed.* 38, 484 (1961); Bundy, *Ann. N.Y. Acad. Sci.* vol. 105, art 17, pp 951-982 (1964). Books: S. Tolansky, *History and Use of Diamond* (London, 1962) 166 pp; R. Berman, *Physical Properties of Diamond* (Oxford, 1965) 442 pp.

Face-centered cubic crystal lattice. Burns when heated with a hot enough flame (over 300°, oxygen torch). d_{25}^{25} 3.513. n_D^{25} 2.4173. Hardness = 10 (Mohs' scale). Sp heat at 100°K: 0.606 cal/g-atom/°K. Entropy at 298.16°K: 0.5684 cal/g-atom/°K. Band gap energy: 6.7 eV. Dielectric constant 5.7. Electron mobility: ~1800 cm²/v-sec. Hole mobility: 1200 cm²/v-sec. Can be pulverized in a steel mortar. Attacked by laboratory-type cleaning soln (potassium dichromate - concd H₂SO₄). In the jewelry trade the unit of weight for diamonds is one carat = 200 mg. *Ref: Wall Street J.* 164, no. 36, p 10 (Aug 19, 1964).

USE: Jewelry. Polishing, grinding, cutting glass, bearings for delicate instruments; manifold dies for tungsten wire and similar hard wires, making styli for recorder heads, long-lasting phonograph needles. In semiconductor research.

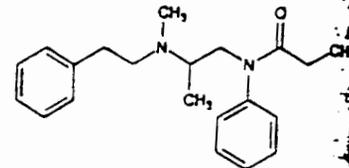
3031. Diamond Ink. Etching ink. A mixture of HF, BaSO₄, and fluorides.

Milky-white liq with a heavy sediment. Shake well before using and warm gently in a lead dish. Keep in plastic, hard-rubber or intern. paraffin-coated bottles.

USE: For etching glass.

3032. Diampromide. N-[2-(Methyl(2-phenylethyl)amino)propyl]-N-phenylpropanamide; N-[2-(methylphenethylamino)propyl]propionanilide. C₂₁H₂₉N₂O; mol wt 324.47. C 77.47%, H 8.70%, N 3.83%. Synthesis: Wright et

al., *J. Am. Chem. Soc.* 81, 1518 (1959); U.S. pat. (1960 to American Cyanamid).

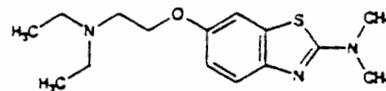


Liquid, bp₇₆₀ 174-178°. n_D^{25} 1.546. Sulfate, C₂₁H₂₉N₂O₂S, crystals from ethanol 110-111°.

Note: This is a controlled substance (opiate) list, U.S. Code of Federal Regulations, Title 21 Part (1995).

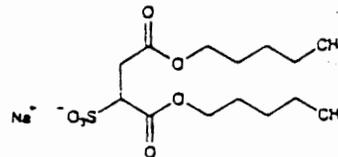
THERAP CAT: Analgesic (narcotic).

3033. Diamthazole Dihydrochloride. 6-[2-(Di-n-oethoxy)-N,N-dimethyl-2-benzothiazolamine dihydrochloride; 6-[2-(diethylamino)ethoxy]-2-dimethylaminocole dihydrochloride; 2-dimethylamino-6-(β-diethyl-ethoxy)benzothiazole dihydrochloride; dimazole dihydrochloride; Ro-2-2453; Asterol Dihydrochloride. Atoms: H₂Cl₂N₂O₂S; mol wt 366.35. C 49.18%, H 6.11, 19.35%, N 11.47%, O 4.37%, S 8.75%. Prepn: Steigler, U.S. pat. 2,578,757 (1951 to Hoffmann-La Roche).



Crystals, dec 269°. mp 240-243°. Freely sol in methanol, ethanol. A 5% aq soln has a pH of ~2. **THERAP CAT:** Antifungal.

3034. Diamyl Sodium Sulfo succinate. Sulfonic acid 1,4-dipentyl ester sodium salt; sulfo succinic pentyl ester sodium salt; Aerosol AY; Alphasol AY. Na₂O₂S; mol wt 360.40. C 46.66%, H 6.99%, Na 31.08%, S 8.90%. The amyl or 1-methylbutyl diester monosodium salt of sulfo succinic acid or a mixture of wetting agent prep'd by the action of the appropriate esters on maleic anhydride followed by addition of sodium sulfite: Jaeger, U.S. pats. 2,028,091 and 2,176,423 (1939 to Am. Cyanamid).



Available as a mixture of white, hard pellets and soly in water at 25° = 392 g/liter; at 70° = 502 g/liter. Maximum concn of electrolyte soln in which 1% of the wetting agent is sol: 3% NaCl; 2-4% NH₄Cl (turbid); (NH₄)₂HPO₄ (turbid); 4% NaNO₃ (slightly turbid); Na₂SO₄ (very slightly turbid). Also sol in pine oil, acetone, hot kerosene, carbon tetrachloride, hot olive oil; insol in liq petrolatum. Surface tension in water: 0.001% = 69.4 dyn/cm; 0.02% = 68.3 dyn/cm; 0.1% = 50.2 dyn/cm; 0.25% = 41.6 dyn/cm; 1% = 28.5 dyn/cm. Interfacial tension 1% in water vs liq petrolatum: 5 seconds = 7.55 dyn/cm; 30 seconds = 7.03 dyn/cm; 15 minutes = 7.03 dyn/cm. Interfacial tension 0.1% in water vs liq petrolatum: 5 seconds = 28.5 dyn/cm; 30 seconds = 28.5 dyn/cm; 15 minutes = 28.5 dyn/cm. Stable in acid and neutral solns, hydrolyzed in alkaline solns.

USE: As emulsifier in emulsion polymerization and as wetting agent.

3035. 1,2-Dianilinoethane. N,N'-Diphenyl-1,2-diamine; N,N'-diphenylethanediamine; N,N'-diphenyl-

National Library of Medicine: IGM Full Record Screen



Order Documents	Other Years	Log off IGM
-----------------	-------------	-------------

Next Record	Details Of Search	Return to Results	Return to Search Screen	Previous Record
-------------	-------------------	-------------------	-------------------------	-----------------



TITLE: Treatment with oral 3,4 diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial.

AUTHOR: Bever CT Jr; Anderson PA; Leslie J; Panitch HS; Dhib-Jalbut S; Khan OA; Milo R; Hebel JR; Conway KL; Katz E; Johnson KP

AUTHOR AFFILIATION: Department of Neurology, School of Medicine, University of Maryland, Baltimore, USA.

SOURCE: Neurology 1996 Dec;47(6):1457-62

NLM CIT. ID: 97120056

ABSTRACT: To examine the efficacy and toxicity of oral 3,4 diaminopyridine (DAP) in dosages up to 100 mg/day, 36 patients with multiple sclerosis (MS) enrolled in a randomized, double-blind, placebo-controlled, crossover trial. The primary outcome measure was improvement of a prospectively defined neurologic deficit, which was leg weakness in 34 patients. Secondary outcome measures included the patient's subjective response, scored manual motor testing (MMT) of leg strength, scored leg strength from videotaped motor testing (VMT), quadriceps and hamstrings strength (QMT) measured by isometric dynamometry, neuropsychological testing (NPT), ambulation index (AI), and Expanded Disability Status Scale (EDSS) score. Paresthesias and abdominal pain were common and were dose limiting in eight patients. Three patients had episodes of confusion, and one patient had a seizure while on DAP. Eight patients withdrew from the study, leaving 28 evaluable patients for the efficacy analysis. The prospectively defined neurologic deficit improved in 24 patients-22 on DAP and 2 on placebo (p = 0.0005). All improvements were in leg weakness. Subjective response and measures of leg strength and function (MMT, VMT, QMT, and AI) improved on DAP compared with placebo. Neither NPT nor EDSS scores improved. DAP treatment can induce improvements in leg strength in MS patients, but toxicity is limiting in many patients.

MAIN MESH SUBJECTS: Leg/*PHYSIOPATHOLOGY
Multiple Sclerosis/*DRUG THERAPY/PHYSIOPATHOLOGY
4-Aminopyridine/*ANALOGS & DERIVATIVES/ADMINISTRATION & DOSAGE

ADDITIONAL MESH SUBJECTS: Administration, Oral
Adult
Aged
Double-Blind Method
Female
Human
Male
Middle Age
Support, Non-U.S. Gov't

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 504-24-5 (4-Aminopyridine)
54-96-6 (3,4-diaminopyridine)

National Library of Medicine: IGM Full Record Screen



Order Documents	Other Years	Log off IGM
Next Record	Details Of Search	Return to Results
	Return to Search Screen	Previous Record



TITLE: Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome.

AUTHOR: Oh SJ; Kim DS; Head TC; Claussen GC

AUTHOR AFFILIATION: Department of Neurology, University of Alabama at Birmingham 35294, USA.

SOURCE: Muscle Nerve 1997 Sep;20(9):1146-52

NLM CIT. ID: 97416721

ABSTRACT: Guanidine hydrochloride is known to be highly effective in the symptomatic treatment of the Lambert-Eaton myasthenic syndrome (LEMS). However, because of its potentially dangerous side reactions of hematologic abnormalities and renal insufficiency, 3,4-diaminopyridine, which is not readily available in the United States, is recommended as the preferred drug for LEMS. We used low-dose guanidine and pyridostigmine combination therapy in 9 patients with LEMS and analyzed its long-term safety and effectiveness. In all patients, a liberal amount of pyridostigmine was used, while daily guanidine dose was kept below 1000 mg a day, and guanidine was given between pyridostigmine dosings. This combination therapy was used for 3-102 months (mean: 34.1 months) and improved clinical status in all patients. Although guanidine had to be discontinued due to severe gastrointestinal symptoms in 3 cases, no serious side reactions such as bone marrow suppressions or signs of renal insufficiency developed in any case. Thus, we conclude that low-dose guanidine therapy is relatively safe and effective for long-term symptomatic treatment of LEMS when it is combined with pyridostigmine.

MAIN MESH SUBJECTS: Cholinesterase Inhibitors/*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS/THERAPEUTIC USE
Guanidines/*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS/THERAPEUTIC USE
Lambert-Eaton Myasthenic Syndrome/COMPLICATIONS/*DRUG THERAPY/ PHYSIOPATHOLOGY
Pyridostigmine Bromide/*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS/ THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS: Adult
Aged
Dose-Response Relationship, Drug
Electrophysiology
Female
Human
Male
Middle Age
Neoplasms/COMPLICATIONS/THERAPY
Time Factors
Treatment Outcome

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Cholinesterase Inhibitors)
0 (Guanidines)
101-26-8 (Pyridostigmine Bromide)
113-00-8 (Guanidine)



TITLE: 3,4-diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial.

AUTHOR: Anlar B; Varli K; Ozdirim E; Ertan M

AUTHOR AFFILIATION: Department of Pediatric Neurology, Hacettepe University, Ankara, Turkey.

SOURCE: J Child Neurol 1996 Nov;11(6):458-61

NLM CIT. ID: 97118599

ABSTRACT: Eleven patients with congenital and five with juvenile myasthenia gravis, aged 5 to 24 years, were given 3,4-diaminopyridine in a double-blind, placebo-controlled, crossover study. Clinical improvement was observed in 5 of 11 congenital myasthenia patients, and placebo effect, in 3 of 11. Juvenile myasthenia patients did not respond. Single-fiber electromyographic studies did not reveal any changes correlating with the clinical status of the patient. This study demonstrates the importance of double-blind and placebo-controlled studies to determine the effect of 3,4-diaminopyridine in congenital myasthenia. This drug may have different effects on various presynaptic and postsynaptic defects of neuromuscular transmission resulting in congenital myasthenia syndromes.

MAIN MESH SUBJECTS: Myasthenia Gravis/CONGENITAL/DIAGNOSIS/*DRUG THERAPY
4-Aminopyridine/*ANALOGS & DERIVATIVES/THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS: Adolescence
Adult
Child
Child, Preschool
Cross-Over Studies
Double-Blind Method
Electromyography/DRUG EFFECTS
Female
Human
Male
Neurologic Examination/DRUG EFFECTS

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 504-24-5 (4-Aminopyridine)
54-96-6 (3,4-diaminopyridine)



Order Documents

92-97 Other Years

Log off IGM

Next Record

Details Of Search

Return to Results

Return to Search Screen

Previous Record

3,4-DIAMINOPYRIDINE

Rodent oral LD50 is in the toxic range of <100 mg/kg. Its toxicity has not been thoroughly investigated.

Can cause eye, skin, and pulmonary irritation. It is contraindicated in patients with epilepsy, has caused paresthesias, abdominal pain, confusion, seizures, and cardiac arrest in one patient with Myasthenia gravis.

It has been used in the treatment of Myasthenia Gravis, Multiple Sclerosis and other nerve-muscle disorders. Doses used are from 10-20 mg p.o., 3 to 4 times daily.

REFERENCES

1. Lahiri DK, Farlow MR, Nurnberger JI Jr, et al. Effects of cholinesterase inhibitors on the secretion of beta-amyloid precursor protein in cell cultures. *Ann N Y Acad Sci* 1997; 826:416-21.
2. Oh SJ, Kim DS, Head TC, et al. Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; 20(9):1146-52.
3. Sadeh M, River Y, Argov Z. Stimulated single-fiber electromyography in Lambert-Eaton myasthenic syndrome before and after 3,4-diaminopyridine. *Muscle Nerve* 1997; 20(6):735-9.
4. Miller A. Current and investigational therapies used to alter the course of disease in multiple sclerosis. *South Med J* 1997; 90(4):367-75.
5. Lin MJ, Lin-Shiau SY. Ruthenium red, a novel enhancer of K⁺ currents at mouse motor nerve terminals. *Neuropharmacology* 1996; 35(5):615-23.
6. Dolezal V, Huang HY, Schobert A, et al. 3,4-Diaminopyridine mask the inhibition of noradrenaline release from chick sympathetic neurons via presynaptic alpha 2-adrenoceptors: insights into the role of N- and L-type calcium channels. *Brain Res* 1996; 721(1-2):101-10.
7. Hua-Yu H, Cheng-Wen Z, Yu-Liang S. Toosendanin facilitates [3H]noradrenaline release from rat hippocampal slices. *Nat Toxins* 1996; 492:92-5.
8. 3,4-diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol* 1996; 11(6):458-61.
9. Bever CT Jr, Anderson PA, Leslie J, 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(6):1457-62.
10. Molgo J, Guglielmi JM. 3,4-Diaminopyridine, an orphan drug, in the symptomatic treatment of Lambert-Eaton myasthenic syndrome. *Pflugers Arch* 1996; 431(6 Suppl 2):R295-6.
11. Smith AG, Wald J. Acute ventilatory failure in Lambert-Eaton myasthenic syndrome and its response to 3,4-diaminopyridine. *Neurology* 1996; 46:1143-5.
12. Aisen ML, Sevilla D, Edelstein L, et al. A double-blind placebo-controlled study of 3,4-diaminopyridine in amyotrophic lateral sclerosis patients on a rehabilitation unit. *J Neurol Sci* 1996; 138(1-2):93-6.
13. Bernheim L, Liu JH, Hamann M, et al. Contribution of a non-inactivating potassium current to the resting membrane potential of fusion-competent human myoblasts. *J Physiol Lond* 1996; 493 (Pt 1):129-41.
14. Argov Z, Shapira Y, Averbuch-Heller L, et al. Lambert-Eaton myasthenic syndrome (LEMS) in association with lymphoproliferative disorders. *Muscle Nerve* 1995; 18(7):715-9.
15. Bishop A, Paz MA, Gallop PM, et al. Inhibition of redox cycling methoxatin (PQQ), and of superoxide release by phagocytic white cells. *Free Radic Biol Med* 1995; 18(3):617-20.
16. Shi Y, Xu Y, Xu K. Selective inhibition of the slow K⁺ current motor nerve ending by plasma from a myasthenia gravis patient. *J Neurol Sci* 1995 130(2):165-70.

17. Hu W, Toral J, Cervoni P, et al. Depolarization-induced 86Rb^+ efflux in CHO cells expressing a recombinant potassium channel. *J Pharmacol Toxicol Methods* 1995; 34(1):1-7.
18. Trevett AJ, Laloo DG, Nwokolo NC, et al. Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (*Oxyuranus scutellatus canni*). *Trans R Soc Trop Med Hyg*, 1995; 89(4):444-6.
19. Kamali F, Nicholson E. Determination of 3,4-diaminopyridine in human plasma by high-performance liquid chromatography. *J Pharm Biomed Anal* 1995; 13(6):791-4.
20. Russell JW, Windebank AJ, Harper CM Jr. Treatment of stable chronic demyelinating polyneuropathy with 3,4-diaminopyridine. *Mayo Clin Proc* 1995; 70(6):532-9.
21. Boerma CE, Rommes JH, van Leeuwen RB, 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(3):249-51.
22. Aisen ML, Sevilla D, Gibson G, et al. 3,4-diaminopyridine as a treatment for amyotrophic lateral sclerosis. *J Neurol Soc* 1995; 129(1):21-4.
23. Felts PA, Smith KJ. The use of potassium channel blocking agents in the therapy of demyelinating diseases [letter; comment] [see comments]. *Ann Neurol* 1994; 36(3):454.
24. Polman CH, Bertelsmann FW, de Waal R, et al. 4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis. *Arch Neurol* 1994; 51(11):1136-9.
25. Tamura R, Mano Y, Takayanagi T, et al. 3,4-diaminopyridine in demyelinating peripheral neuropathies [letter; comment]. *Ann Neurol* 1994; 36(3):453.
26. Bever CT Jr. the current status of studies of aminopyridines in patients with multiple sclerosis. *Ann Neurol* 1994; 36 Suppl:S118-21.
27. Cooke JD, Hefter H, Brown SH, et al. Lambert-Eaton myasthenic syndrome: evaluation of movement performance following drug therapy. *Electromyogr Clin Neurophysiol* 1994; 34(2):87-93.
28. Tsuchiya N, Sato M, Uesaka Y, et al. Lambert-Eaton myasthenic syndrome associated with Sjogren's syndrome and discoid lupus erythematosus. *Scand J Rheumatol* 1993; 22(6):302-4.
29. Moretti M, Marchioni CF, Bisetti A. Efficacy and tolerability of brodimoprim in respiratory tract infections. *J Chemother* 1993; 5(6):517-20.
30. Lundh H, Nilsson O, Rosen I, et al. Practical aspects of 3,4-diaminopyridine treatment of the Lambert-Eaton myasthenic syndrome. *Acta Neurol Scand* 1993; 88(20):136-40.
31. Bergin PS, Miller DH, Hirsch NP, et al. Failure of 3,4-diaminopyridine to reverse conduction block in inflammatory demyelinating neuropathies [see comments]. *Ann Neurol* 1993;34(3):406-9.
32. Sanders DB, Howard JF Jr, Massey JM. 3,4-Diaminopyridine in Lambert-Eaton myasthenic syndrome and myasthenia gravis. *Ann N Y Acad Sci* 1993; 681:588-90.
33. Noseworthy JH. Clinical trials in multiple sclerosis. *Curr Opin Neurol Neurosurg* 1993; 6(2):209-15.
34. Peterson C. Changes in calcium's role as a messenger during aging in neuronal and nonneuronal cells. *Ann N Y Acad Sci* 1992; 663:279-93.

35. Davis LE, Johnson JK, Bicknell JM, et al. Human type A botulism and treatment with 3,4-diaminopyridine. *Electromyogr Clin Neurophysiol* 1992; 32(7-8):379-83.
36. van der Horst A, de Goede PN, van Dieman HA, et al. Determination of 4-aminopyridine in serum by solid-phase extraction and high-performance liquid chromatography. *J Chromatogr* 1992; 574(91):166-9.
37. Jost WH, Mielke U, Schimrigk K. therapeutic approaches to Lambert-Eaton myasthenic syndrome in the intra-individual comparison. *Wien Klin Wochenschr* 1991; 54(12):629-32.
38. Palace J, Wiles CM, Newsome-Davis J. 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. *J Neurol Neurosurg Psychiatry* 1991; 54(12):1069-72
39. Telford RJ, Hollway TE. The myasthenic syndrome: anaesthesia in a patient treated with 3,4-diaminopyridine. *Br J Anaesth* 1990; 64(3):363-6.
40. Manji H, Schwartz MS, McKeran RO. Lambert Eaton syndrome: autonomic neuropathy and inappropriate antidiuretic hormone secretion in a patient with small cell carcinoma of the lung. *J Neurol* 1990; 237(5):324-5.
41. Chalk CH, Murray NM, Newsome-Davis J, et al. Response of the Lambert-Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. *Neurology* 1990; 40(10):1552-6.
42. Bever CT Jr, Leslie J, Camenga DL, et al. Preliminary trial of 3,4-diaminopyridine in patients with multiple sclerosis. *Ann Neurol* 1990; 27(4):421-7.