Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US*.
Ph. Eur. 6.2 (Physostigmine Salicylate). Colourless or almost colourless crystals. It becomes red on exposure to air and light; the colour develops more quickly in the presence of moisture. Sparingly soluble in water; soluble in alcohol. A 0.9% solution in water has a pH of 5.1 to 5.9. Store in airtight containers. Protect from light. Aqueous solutions are unstable.
USP 31 (Physostigmine Salicylate). White, shining, odourless, crystals or white powder. It acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 75 of water, 1 in 16 of alcohol, 1 in 6 of chloroform, and 1 in 250 of ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Stability. See below.

Physostigmine Sulfate

Ésérine, sulfate d'; Eserine Sulphate; Eserini Sulfas; Ezerino sulfatas; Fisostigmina, sulfato de; Fizostigmino sulfatas; Fizosztigminszulfát; Fysostigmiinisulfaatti; Fysostigminsulfat; Fysostigmin-sulfát; Physostig. Sulph.; Physostigmine Sulphate *(BANM)*; Physostigmini sulfas.

$(C_{15}H_{21}N_3O_2)_2,H_2SO_4$ = 648.8.
CAS — 64-47-1.
ATC — S01EB05; V03AB19.
ATC Vet — QS01EB05; QV03AB19.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Physostigmine Sulphate). A white or almost white, hygroscopic crystalline powder. It becomes red on exposure to air and light; the colour develops more quickly in the presence of moisture. Very soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 3.5 to 5.5. Store in well-filled airtight glass containers. Protect from light. Aqueous solutions are unstable.
USP 31 (Physostigmine Sulfate). A white, odourless, microcrystalline powder. It is deliquescent in moist air, and acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 4 of water, 1 in 0.4 of alcohol, and 1 in 1200 of ether. Store in airtight containers. Protect from light.

Stability. In aqueous solutions physostigmine is hydrolysed to eseroline and subsequently oxidised to the red compound rubreserine and other coloured products. Solutions for injection or ophthalmic use should not be used if more than slightly discoloured.

Adverse Effects, Treatment, and Precautions

Systemic effects as for Neostigmine, p.631, although usually more severe. Physostigmine crosses the blood-brain barrier and may therefore produce CNS effects.

For adverse effects and precautions for topical miotics see also under Pilocarpine, p.1885. Physostigmine is not well tolerated when used in the eyes for long periods and may produce follicles in the conjunctiva; hypersensitivity reactions are also common. Prolonged use of ophthalmic ointments containing physostigmine may cause depigmentation of the lid margins in dark-skinned patients.

Overdosage. Symptomatic and supportive treatment, including the use of diazepam and atropine where necessary, is generally recommended for systemic toxicity due to physostigmine. However, in an early report, the use of atropine in a patient who had taken 1 g of physostigmine had to be abandoned after it produced tachycardia and multifocal ventricular ectopic beats.[1] In a similar case of severe poisoning a slow intravenous injection of propranolol 5 mg reduced the high pulse rate and controlled pulse irregularities despite frequent intravenous doses of atropine.[2]

1. Cumming G, *et al.* Treatment and recovery after massive overdosage of physostigmine. *Lancet* 1968; **ii:** 147–9.
2. Valero A. Treatment of severe physostigmine poisoning. *Lancet* 1968; **ii:** 459–60.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Physostigmine is readily absorbed from the gastrointestinal tract, subcutaneous tissues, and mucous membranes. It is largely destroyed in the body by hydrolysis of the ester linkage by cholinesterases; a parenteral dose is claimed to be destroyed within 2 hours. It crosses the blood-brain barrier. Little is excreted in the urine.

◊ Small studies suggest marked interindividual differences in the absorption and metabolism of physostigmine salicylate after doses of up to 4 mg by mouth, perhaps because of saturable presystemic metabolism.[1-3] Oral bioavailability ranged from 5.2 to 11.7% in 3 of 5 subjects.[3]

In a study[4] of a single application of a physostigmine (base) transdermal system in 6 subjects, the mean absolute bioavailability was 36% (range 12.6 to 53.2%); the interindividual variability in absolute bioavailability was decreased by about 30% in comparison with an oral solution of physostigmine salicylate. There was continued absorption of physostigmine after removal of the transdermal system, indicating a drug reservoir in the skin.

In a study[5] of 9 patients with Alzheimer's disease, a mean elimination half-life for physostigmine of 16.4 minutes was reported with intravenous physostigmine salicylate. Cholinesterase inhibition was more prolonged than suggested by its elimination half-life.

1. Gibson M, *et al.* Physostigmine concentrations after oral doses. *Lancet* 1985; **i:** 695–6.
2. Sharpless NS, Thal LJ. Plasma physostigmine concentrations after oral administration. *Lancet* 1985; **i:** 1397–8.
3. Whelpton R, Hurst P. Bioavailability of oral physostigmine. *N Engl J Med* 1985; **313:** 1293–4.
4. Walker K, *et al.* Pharmacokinetics of physostigmine in man following a single application of a transdermal system. *Br J Clin Pharmacol* 1995; **39:** 59–63.
5. Asthana S, *et al.* Clinical pharmacokinetics of physostigmine in patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; **58:** 299–309.

Uses and Administration

Physostigmine is a reversible tertiary amine inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632). Physostigmine has been used, alone or more usually with other miotics such as pilocarpine, to decrease intraocular pressure in glaucoma (p.1873). It is a more potent miotic than pilocarpine but is rarely tolerated for prolonged periods. When it is used in glaucoma physostigmine has usually been given as eye drops containing 0.25 or 0.5% of the salicylate or as an ophthalmic ointment containing 0.25% of the sulfate.

Physostigmine crosses the blood-brain barrier and has been used to reverse the central as well as the peripheral effects of agents with antimuscarinic actions after overdosage but such treatment is not usually recommended. Physostigmine is also under investigation in the management of Alzheimer's disease (see Dementia, below).

Antimuscarinic poisoning. As physostigmine penetrates the blood-brain barrier it has been used to reverse the central effects of poisoning with agents that have antimuscarinic actions including tricyclic antidepressants, antihistamines, some antiemetics, some antiparkinsonian drugs, and phenothiazines. However, reviewers agree that in general such use is inappropriate and hazardous. Physostigmine does not appear to affect the mortality rate in tricyclic antidepressant poisoning[1] and its use can lead to severe cardiac[2,3] and respiratory effects[2,3] and to convulsions.[3,4]

1. Aquilonius S-M, Hedstrand U. The use of physostigmine as an antidote in tricyclic anti-depressant intoxication. *Acta Anaesthesiol Scand* 1978; **22:** 40–5.
2. Caine ED. Anticholinergic toxicity. *N Engl J Med* 1979; **300:** 1278.
3. Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA* 1975; **231:** 941–3.
4. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.

Baclofen overdosage. For references to the use of physostigmine in the treatment of baclofen overdosage, see p.1888.

Cerebellar ataxias. Double-blind controlled studies indicate that physostigmine[1,2] can produce symptomatic improvement in some patients with cerebellar ataxia including those with hereditary forms of spinocerebellar degeneration such as Friedreich's ataxia. However, another study did not show any significant improvement in patients given physostigmine for cerebellar ataxia.[3]

1. Rodriguez-Budelli MM, *et al.* Action of physostigmine on inherited ataxias. *Adv Neurol* 1978; **21:** 195–202.
2. Aschoff JC, *et al.* Physostigmin in der Behandlung von Kleinhirnataxien. *Nervenarzt* 1996; **67:** 311–18.
3. Wessel K, *et al.* Double-blind crossover study with physostigmine in patients with degenerative cerebellar diseases. *Arch Neurol* 1997; **54:** 397–400.

Dementia. Physostigmine has been studied in the symptomatic management of Alzheimer's disease (see Dementia, p.362). However, a systematic review concluded that the evidence of its effectiveness was limited and the benefits shown were not convincing.[1] Small early studies with oral physostigmine in Alzheimer's disease were inconclusive; a larger multicentre study[2] using controlled-release physostigmine found that it produced some improvement in cognitive and global function, but gastrointestinal adverse effects were common and led to a high dropout rate.

1. Coelho Filho JM, Birks J. Physostigmine for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 17/03/06).
2. Thal LJ, *et al.* A 24-week randomized trial of controlled-release physostigmine in patients with Alzheimer's disease. *Neurology* 1999; **52:** 1146–52.

Preparations

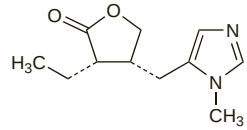
USP 31: Physostigmine Salicylate Injection; Physostigmine Salicylate Ophthalmic Solution; Physostigmine Sulfate Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Austria: Anticholium; ***Cz.:*** Anticholium; ***Ger.:*** Anticholium; ***Gr.:*** Anticholium; ***USA:*** Antilirium.

Multi-ingredient: ***India:*** Bi-Miotic.

Pilocarpine *(BAN)*

Pilocarpina; Pilocarpinum; Pilokarpiini; Pilokarpin. (3*S*,4*R*)-3-Ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]furan-2(3*H*)-one.
$C_{11}H_{16}N_2O_2$ = 208.3.
CAS — 92-13-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.



Description. An alkaloid obtained from the leaves of jaborandi, *Pilocarpus microphyllus* (Rutaceae) and other species of *Pilocarpus*.

Pharmacopoeias. In *US*.
USP 31 (Pilocarpine). A viscous, exceedingly hygroscopic, oily liquid or crystals. M.p. about 34°. Soluble in water, in alcohol, and in chloroform; sparingly soluble in ether and in benzene; practically insoluble in petroleum spirit. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Pilocarpine Borate

Pilocarpina, borato de.
$C_{11}H_{16}N_2O_2,xBH_3O_3$.
CAS — 16509-56-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

Pilocarpine Hydrochloride *(BANM)*

Pilocarp. Hydrochlor.; Pilocarpina, hidrocloruro de; Pilocarpine, chlorhydrate de; Pilocarpine Monohydrochloride; Pilocarpini Chloridum; Pilocarpini hydrochloridum; Pilocarpinium Chloratum; Pilokarpiinihydrokloridi; Pilokarpin Hidroklorür; Pilokarpinhidroklorid; Pilokarpin-hydrochlorid; Pilokarpinhydroklorid; Pilokarpino hidroclorida; Pilokarpiny chlorowodorek.
$C_{11}H_{16}N_2O_2,HCl$ = 244.7.
CAS — 54-71-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

NOTE. PIL is a code approved by the BP 2008 for use on single unit doses of eye drops containing pilocarpine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Pilocarpine Hydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. Very soluble in water and in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.
USP 31 (Pilocarpine Hydrochloride). Colourless, translucent, odourless, hygroscopic crystals. Soluble 1 in 0.3 of water, 1 in 3 of alcohol, and 1 in 360 of chloroform; insoluble in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. Pilocarpine hydrochloride oral solution, prepared from powder or eye drops and buffered at pH 5.5, was found[1] to be stable for 60 days at 25° and for 90 days at 4°.

1. Fawcett JP, *et al.* Formulation and stability of pilocarpine oral solution. *Int J Pharm Pract* 1994; **3:** 14–18.

Pilocarpine Nitrate *(BANM)*

Pilocarp. Nit.; Pilocarpina, nitrato de; Pilocarpine Mononitrate; Pilocarpine, nitrate de; Pilocarpini nitras; Pilocarpinii Nitras; Pilocarpinium Nitricum; Pilokarpiininitraatti; Pilokarpinnitrat; Pilokarpin-nitrát; Pilokarpino nitratas.
$C_{11}H_{16}N_2O_2,HNO_3$ = 271.3.
CAS — 148-72-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

NOTE. PIL is a code approved by the BP 2008 for use on single unit doses of eye drops containing pilocarpine nitrate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Pilocarpine Nitrate). Colourless crystals, or white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Protect from light.
USP 31 (Pilocarpine Nitrate). Shining white crystals. Soluble 1 in 4 of water and 1 in 75 of alcohol; insoluble in chloroform and in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Systemic effects and cautions are as for Neostigmine, p.631.

With the *oral* use of pilocarpine, sweating is a common problem; caution is needed to avoid dehydration in patients who may sweat excessively and who cannot maintain an adequate fluid intake. Paradoxical hypertension and constipation, confusion, and increased urinary frequency have also been reported. Licensed product information states that it should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision or dizziness may affect the performance of skilled tasks including driving. In addition pilocarpine should be given with care to those with cognitive or psychiatric disturbances, with renal calculi or renal impairment, or with biliary-tract disorders. Dosage should be reduced in patients with hepatic impairment (see Administration in Hepatic Impairment, below).

After *ocular* use pilocarpine is usually better tolerated than the anticholinesterases, but in common with other miotics may produce ciliary spasm, ocular pain and irritation, blurred vision, lachrymation, myopia, and browache. Conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage, and increased pupillary block have been reported. Lens opacities have occurred after prolonged use. Treatment with miotics should be stopped if symptoms of systemic toxicity develop.

Miotics are contra-indicated in conditions where pupillary constriction is undesirable such as acute iritis, acute uveitis, anterior uveitis, and some forms of secondary glaucoma. They should be avoided in acute inflammatory disease of the anterior segment of the eye. If possible, treatment with long-acting miotics should be stopped before surgery on the eye as there is an increased risk of hyphaema. Miotics should be used with extreme caution in patients with a history of retinal detachment and in young patients with myopia. Care is also needed in patients with corneal or conjunctival damage. Miosis may cause blurred vision and difficulty with dark adaptation and caution is necessary with night driving or when hazardous tasks are undertaken in poor illumination. Miotics should not be used by patients wearing soft contact lenses.

Asthma. A reminder that topical miotics can precipitate bronchospasm in susceptible patients.[1] However, the severity of the reaction induced by carbachol has been reported to be less than that produced by timolol. Bronchospastic complications are much less likely to occur with pilocarpine but have nevertheless been reported. As inhalations of methacholine are used to induce bronchospasm in the diagnosis of latent asthma, the risk of exacerbating asthma should be considered before methacholine is used in the eye.

1. Prakash UBS, *et al.* Pulmonary complications from ophthalmic preparations. *Mayo Clin Proc* 1990; **65:** 521–9.

Dementia. In patients with dementia of Alzheimer type, CNS symptoms may be induced or exacerbated by the use of pilocarpine eye drops.[1,2]

1. Reyes PF, *et al.* Mental status changes induced by eye drops in dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1987; **50:** 113–15.
2. Fraunfelder FT, Morgan R. The aggravation of dementia by pilocarpine. *JAMA* 1994; **271:** 1742–3.

Glaucoma. Miotics usually lower intra-ocular pressure by decreasing the resistance to outflow of aqueous humour from the anterior chamber through the trabecular network. However, they appear to reduce uveoscleral outflow and this may cause a paradoxical rise in intra-ocular pressure in patients with severely compromised trabecular outflow as was reported in a patient with post-traumatic angle-recession glaucoma.[1] It has been recommended that pilocarpine should be avoided after drainage operations for glaucoma because its miotic effect can increase the occurrence of posterior pupillary synechiae; a topical beta blocker is usually adequate if control of intra-ocular pressure is required.[2] Pilocarpine-induced miosis was shown to cause a significant deterioration in visual field in patients with chronic open-angle glaucoma.[3] It was suggested that this should be an important consideration when choosing therapy for glaucoma, particularly in cases where field loss approaches the permitted legal minimum for driving. Of 53 patients receiving long-term therapy with pilocarpine gel, 15 developed a corneal haze, which persisted for at least 2 years in 13; although the patients remained asymptomatic the long-term effects were unknown.[4] Many patients using the gel also developed superficial punctate keratitis which usually cleared spontaneously during treatment.

1. Bleiman BS, Schwartz AL. Paradoxical intraocular pressure response to pilocarpine: a proposed mechanism and treatment. *Arch Ophthalmol* 1979; **97:** 1305–6.
2. Phillips CI, *et al.* Posterior synechiae after glaucoma operations: aggravation by shallow anterior chamber and pilocarpine. *Br J Ophthalmol* 1987; **71:** 428–32.
3. Webster AR, *et al.* The effect of pilocarpine on the glaucomatous visual field. *Br J Ophthalmol* 1993; **77:** 721–5.
4. Johnson DH, *et al.* Corneal changes during pilocarpine gel therapy. *Am J Ophthalmol* 1986; **101:** 13–15.

Hypersensitivity. Contact urticaria involving the eyelids has been reported[1] in a patient after treatment with pilocarpine eye drops for glaucoma.

1. O'Donnell BF, Foulds IS. Contact allergic dermatitis and contact urticaria due to topical ophthalmic preparations. *Br J Ophthalmol* 1993; **77:** 740–1.

Retinal detachment. The use of miotics has been implicated in numerous reports as a cause of retinal detachment but reviews of the subject have concluded that there is little factual evidence to support the association.[1,2] However, there is circumstantial evidence that retinal detachment is more likely to occur with strong miotics. Furthermore, patients with myopia or pre-existing retinal damage appear to be at greater risk and there is the possibility that even low concentrations of relatively mild miotics such as 1% pilocarpine might precipitate retinal detachment.

1. Alpar JJ. Miotics and retinal detachment: a survey and case report. *Ann Ophthalmol* 1979; **11:** 395–401.
2. Beasley H, Fraunfelder FT. Retinal detachments and topical ocular miotics. *Ophthalmology* 1979; **86:** 95–8.

Systemic absorption. Systemic adverse effects after the ophthalmic use of pilocarpine are thought to be rare and reports of toxicity mainly involve elderly patients treated for acute angle-closure glaucoma prior to surgery and given relatively high doses.[1,2] It may not be feasible to stop the miotic in these circumstances. In a report of psychotic reaction in such a patient,[2] pilocarpine was continued but the patient was instructed on how to minimise absorption by closing the lachrymal canal; an atypical antipsychotic with minimal antimuscarinic effects (risperidone) was also given.

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
2. Sirois FJ. Pilocarpine psychosis. *Psychosomatics* 2005; **46:** 88.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Mean elimination half-lives for pilocarpine have been reported to be 0.76 and 1.35 hours after repeated oral doses of 5 and 10 mg of the hydrochloride, respectively. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. About 30% of an oral dose is excreted in the urine as pilocarpine and its inactive metabolites, including pilocarpic acid; the fate of the remaining 70% is unknown. Data from *animal* studies indicate that pilocarpine is distributed into breast milk at concentrations similar to those in the plasma.

Uses and Administration

Pilocarpine is a direct-acting tertiary amine parasympathomimetic that has the muscarinic effects of acetylcholine (p.1877). It is used mainly in the treatment of glaucoma (p.1873) and in the treatment of dry eye (p.2140) or dry mouth (below); it has also been used as a diaphoretic in diagnostic tests for cystic fibrosis and leprosy (below). Topical application of pilocarpine to the eye produces miosis (pupil constriction) by contraction of the iris sphincter muscle; contraction of the ciliary muscle results in increased accommodation. Constriction of the pupil also pulls open the trabecular meshwork in the eye and this in turn facilitates drainage of aqueous humour and reduction of intra-ocular pressure. After the use of eye drops, miosis occurs in about 10 to 30 minutes and lasts 4 to 8 hours while peak reduction in intra-ocular pressure occurs within 75 minutes and the reduction usually persists for 4 to 14 hours.

Pilocarpine is used in the treatment of open-angle **glaucoma** (but see also Glaucoma, under Adverse Effects, above) and is commonly given with topical beta blockers or sympathomimetics. It is used as the hydrochloride or the nitrate, usually as 0.5 to 4% eye drops given up to 4 times daily, adjusted according to response. Solutions containing 0.25 to 10% of the hydrochloride may also be available and the higher strengths may sometimes be required in patients with heavily pigmented irides. A modified-release system inserted into the conjunctival sac and releasing 20 or 40 micrograms of pilocarpine per hour for 7 days, and a 4% ophthalmic gel have also been used. Pilocarpine may be used before surgery as part of the emergency treatment of acute attacks of angle-closure glaucoma.

The miotic action of pilocarpine has been used to antagonise the effects of sympathomimetic mydriatics on the eye and in surgical procedures on the eye. Pilocarpine borate has been used similarly in ophthalmology to the hydrochloride and nitrate.

Pilocarpine hydrochloride is used in the treatment of **dry mouth** following radiotherapy for malignant neoplasms of the head and neck. It increases salivary flow only in patients with residual salivary gland function. The initial oral dose is 5 mg three times daily with or immediately after meals, increased gradually if necessary after 4 weeks until an adequate response is obtained, up to a maximum of 10 mg three times daily. Oral doses of 5 mg four times daily are used to treat **dry eye** or mouth in patients with Sjögren's syndrome; this dose may be increased to a maximum of 30 mg daily. Treatment should be stopped if no improvement occurs after 3 months of use. For doses in patients with hepatic impairment, see below.

Administration in hepatic impairment. UK licensed product information recommends that daily doses of *oral* pilocarpine should be reduced in patients with moderate to severe cirrhosis. The dose may gradually be increased to 5 mg three times daily if tolerated.

In the USA, licensed information suggests that the starting oral dose of pilocarpine should be 5 mg twice daily in patients with moderate hepatic impairment (Child-Pugh category B); it is not recommended in those with severe impairment (Child-Pugh category C) because of a lack of pharmacokinetic studies in these patients.

Diagnosis and testing. ***CYSTIC FIBROSIS.*** The fact that individuals with cystic fibrosis have abnormally high concentrations of sodium and chloride in their sweat has been used in the diagnosis of this condition and pilocarpine iontophoresis has been used to promote sweating as part of that test.[1] Despite the fact that neonatal genetic screening for cystic fibrosis-causing mutations is now possible, sweat testing using pilocarpine iontophoresis remains the gold standard for diagnosis, and can help avoid the small likelihood of diagnostic error.[2,3] US guidelines[3] note that sweat electrolytes may be transiently elevated during the first 24 hours of life, but sweat testing may be performed from 48 hours onward if an adequate sample can be obtained.

1. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959; **23:** 545–9.
2. Parad RB, *et al.* Sweat testing infants detected by cystic fibrosis newborn screening. *J Pediatr* 2005; **147** (suppl): S69–S72.
3. LeGrys VA, *et al.* Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. *J Pediatr* 2007; **151:** 85–9.

LEPROSY. The induction of sweat secretion by intradermal injection of pilocarpine nitrate has been used to assess the functional status of dermal nerves in patients with leprotic skin lesions.[1]

1. Joshi PB. Pilocarpine test in assesment of therapeutic efficacy in maculoanaesthetic leprosy. *Lepr India* 1976; **48:** 55–60.

Dry mouth. Pilocarpine is used as a sialogogue in the treatment of dry mouth (p.2140) after radiotherapy of the head and neck,[1,2] although benefit may not be entirely related to preservation of salivation.[3,4] A systematic review[5] based on 3 studies found limited evidence to support such use; although about half of the patients responded to pilocarpine, response did not occur in some for up to 12 weeks and adverse effects were common. Pilocarpine may also be of use in the management of drug-induced oral dryness,[6] and is used as a treatment for dry mouth and dry eye in the auto-immune disease, Sjögren's syndrome.[1,7-10]

1. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. *Drugs* 1995; **49:** 143–55.
2. Taylor SE. Efficacy and economic evaluation of pilocarpine in treating radiation-induced xerostomia. *Expert Opin Pharmacother* 2003; **4:** 1489–97.
3. Gorsky M, *et al.* The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97:** 190–5.
4. Gornitsky M, *et al.* Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98:** 45–52.
5. Davies AN, Shorthose K. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 10/06/08).

6. Götrick B, *et al.* Oral pilocarpine for treatment of opioid-induced oral dryness in healthy adults. *J Dent Res* 2004; **83:** 393–7.
7. Nelson JD, *et al.* Oral pilocarpine for symptomatic relief of keratoconjunctivitis sicca in patients with Sjögren's syndrome. *Adv Exp Med Biol* 1998; **438:** 979–83.
8. Vivino FB, *et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. *Arch Intern Med* 1999; **159:** 174–81.
9. Tsifetaki N, *et al.* Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis* 2003; **62:** 1204–7.
10. Baudouin C, *et al.* Traitements actuels de la xérophtalmie dans le syndrome de Gougerot-Sjögren. *Rev Med Interne* 2004; **25:** 376–82.

Reversal of mydriasis. Pilocarpine has been used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but other miotics may be preferred (see p.1874). It counteracts the mydriatic effects of sympathomimetics, such as phenylephrine and hydroxyamfetamine,[1] but is ineffective against mydriasis produced by antimuscarinics, such as homatropine,[1] and may impair vision further when used with tropicamide.[2] Furthermore, there is also the risk of pilocarpine precipitating angle-closure glaucoma in susceptible patients (see Glaucoma, under Precautions, above and also Glaucoma, in Tropicamide, p.1886).

1. Anastasi LM, *et al.* Effect of pilocarpine in counteracting mydriasis. *Arch Ophthalmol* 1968; **79:** 710–15.
2. Nelson ME, Orton HP. Counteracting the effects of mydriatics: does it benefit the patient? *Arch Ophthalmol* 1987; **105:** 486–9.

Preparations

BP 2008: Pilocarpine Hydrochloride Eye Drops; Pilocarpine Nitrate Eye Drops;
USP 31: Pilocarpine Hydrochloride Ophthalmic Solution; Pilocarpine Nitrate Ophthalmic Solution; Pilocarpine Ocular System.

Proprietary Preparations (details are given in Part 3)
Arg.: Alvis†; Gel Carpina†; Isopto Carpina; Klonocarpina†; Omaclopil; Pilocarpol; Pilomed; Sonadryl; Tensiocap; Wetol; Xao Pil; ***Austral.:*** Isopto Carpine; Pilopt; PV Carpine; ***Austria:*** Pilorcarpin Puroptal; Salagen; ***Belg.:*** Isopto Carpine; Pilo; Salagen; ***Braz.:*** Isopto Carpine; Pilocan; ***Canad.:*** Diocarpine†; Isopto Carpine; Miocarpine†; Pilopine HS; Salagen; ***Chile:*** Pilogel; ***Cz.:*** Pilogel; Pilopos; Pilotonina†; Salagen†; ***Fin.:*** Isopto Carpine; Salagen; ***Fr.:*** Pilo; Salagen; ***Ger.:*** Borocarpin-S; Pilo-Stulln†; Pilocarpol†; Pilomann; Pilomann-Ol; Pilopos; Salagen; Spersacarpin; ***Gr.:*** Cidren; Dispercarpine; Isopto Carpine; Pilocollyre; Pilofar; Pilotina†; Prothenol; Saglion; Salagen; Salivoral; Sumario; Xerocap; ***Hong Kong:*** Isopto Carpine†; Pilogel†; Salagen; Spersacarpine†; ***Hung.:*** Humacarpin; Pilogel†; Salagen; ***India:*** Carpo-Miotic; Locarp; Pilocar; ***Irl.:*** Isopto Carpine†; Pilogel; Salagen; ***Israel:*** Glaucocarpine; Mi-Pilo; Salagen; ***Ital.:*** Dropilton; Pilogel†; Pilotonina; Salagen; ***Malaysia:*** Isopto Carpine; Pilo†; Spersacarpine†; ***Mex.:*** Caliprene; Pil; Pilo; ***Neth.:*** Isopto Carpine†; Pilogel; Salagen; ***Norw.:*** Isopto Carpine; Pilo†; ***NZ:*** Isopto Carpine†; Ocusert; Pilopt; ***Philipp.:*** Isopto Carpine; ***Port.:*** Pilocarcil; Piloplex†; Salagen; ***Rus.:*** Oftan Pilocarpin (Офтан Пилокарпин); ***S.Afr.:*** Isopto Carpine; Pilogel; ***Singapore:*** Isopto Carpine; Pilogel; ***Spain:*** Isopto Carpina; Salagen; ***Swed.:*** Salagen; ***Switz.:*** Salagen; Spersacarpine; ***Thai.:*** Isopto Carpine; Salagen; ***Turk.:*** Pilogel; Pilokarsol; Pilosed; ***UK:*** Pilogel; Salagen; ***USA:*** Adsorbocarpine; Akarpine; Isopto Carpine; Ocu-Carpine; Ocusert†; Pilocar; Pilopine HS; Piloptic; Pilopto-Carpine; Pilostat; Salagen; ***Venez.:*** Isopto Carpina†; Pilocar.

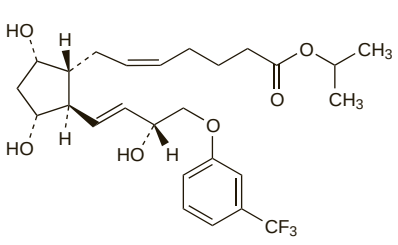
Multi-ingredient: ***Arg.:*** Amplus; Glaucocin†; Glaucotensil; Ofal P†; Pilotim; Timpilo†; ***Austral.:*** Timpilo; ***Austria:*** Betacarpin; Fotil; Normastigmin mit Pilocarpin; Pilostigmin Puroptal; Thiloadren; Timpilo; ***Belg.:*** Carteopil; Normoglaucon; ***Canad.:*** Timpilo†; ***Cz.:*** Fotil; Glauko Biciron†; Ipecarin†; Timpilo†; ***Denm.:*** Fotil; Timpilo†; ***Fin.:*** Fotil; Timpilo†; ***Fr.:*** Carpilo; Pilobloq; Timpilo†; ***Ger.:*** Fotil; Glauko Biciron; Normoglaucon; Syncarpin-N†; Thiloadren N; Timpilo†; TP-Ophtal; ***Gr.:*** Dropiltim; Fotil†; Ripix†; Ryvina†; T+P; Thilocombin†; Timpilo; Yvano; ***Hong Kong:*** Timpilo; ***Hung.:*** Fotil; ***India:*** Bi-Miotic; ***Israel:*** Timpilo; ***Ital.:*** Equiton; Mios; Pilobloc; Pilodren†; Ripix; Timicon; ***Malaysia:*** Normoglaucon†; Timpilo†; ***Neth.:*** Fotil; Normoglaucon; ***Norw.:*** Fotil; Timpilo†; ***NZ:*** Timpilo; ***Philipp.:*** Fotil; ***Pol.:*** Fotil; Normoglaucon; ***Port.:*** Fotil; Normoglaucon; Timoglau Plus; ***Rus.:*** Fotil (Фотил); ***Singapore:*** Normoglaucon†; Timpilo†; ***Swed.:*** Fotil; Timpilo†; ***Switz.:*** Arteopilo; Fotil†; Ripix; Timpilo†; ***Thai.:*** Fotil†; Normoglaucon†; ***USA:*** E-Pilo†; PE†.

Travoprost *(BAN, USAN, rINN)*

AL-6221; Travoprosti; Travoprostum. Isopropyl (*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-{(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl}cyclopentyl)-5-heptenoate.

Травопрост

$C_{26}H_{35}F_3O_6$ = 500.5.
CAS — 157283-68-6.
ATC — S01EE04.
ATC Vet — QS01EE04.



Adverse Effects and Precautions

As for Latanoprost, p.1882.

Effects on the eyes. Severe iritis and corneal oedema developed in an elderly woman 3 weeks after restarting travoprost after eye surgery;[1] rechallenge was positive. The authors commented that the UK MHRA was aware of one other case of uveitis associated with travoprost.

1. Kumarasamy M, Desai SP. Anterior uveitis is associated with travoprost. *BMJ* 2004; **329:** 205.

Uses and Administration

Travoprost is a synthetic analogue of dinoprost (prostaglandin F_2). It is used in the treatment of open-angle glaucoma and ocular hypertension (p.1873), as a 0.004% ophthalmic solution once daily, preferably in the evening. The reduction in pressure starts about 2 hours after instillation and is maximal after 12 hours; the effect is maintained for at least 24 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Arvo; Glaucoprost; Travatan; ***Austral.:*** Travatan; ***Austria:*** Travatan; ***Belg.:*** Travatan; ***Braz.:*** Travatan; ***Canad.:*** Travatan; ***Chile:*** Travatan; ***Cz.:*** Travatan; ***Denm.:*** Travatan; ***Fin.:*** Travatan; ***Fr.:*** Travatan; ***Ger.:*** Travatan; ***Gr.:*** Travatan; ***Hong Kong:*** Travatan; ***Hung.:*** Travatan; ***Indon.:*** Travatan; ***Irl.:*** Travatan; ***Israel:*** Travatan; ***Ital.:*** Travatan; ***Malaysia:*** Travatan; ***Mex.:*** Travatan; ***Neth.:*** Travatan; ***Norw.:*** Travatan; ***NZ:*** Travatan; ***Philipp.:*** Travatan; ***Pol.:*** Travatan; ***Port.:*** Travatan; ***Rus.:*** Travatan (Траватан); ***S.Afr.:*** Travatan; ***Singapore:*** Travatan; ***Spain:*** Travatan; ***Swed.:*** Travatan; ***Switz.:*** Travatan; ***Thai.:*** Travatan; ***Turk.:*** Travatan; ***UK:*** Travatan; ***USA:*** Travatan; ***Venez.:*** Travatan.

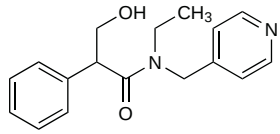
Multi-ingredient: ***Cz.:*** DuoTrav; ***Gr.:*** DuoTrav; ***Hung.:*** DuoTrav; ***NZ:*** DuoTrav; ***Pol.:*** DuoTrav; ***Port.:*** DuoTrav; ***UK:*** DuoTrav.

Tropicamide *(BAN, USAN, rINN)*

Bistropamide; Ro-1-7683; Tropicamida; Tropicamidum; Tropikamid; Tropikamidas; Tropikamidi. *N*-Ethyl-*N*-(4-pyridylmethyl)tropamide; (2*RS*)-*N*-Ethyl-3-hydroxy-2-phenyl-*N*-(pyridin-4-ylmethyl)propanamide.

Тропикамид

$C_{17}H_{20}N_2O_2$ = 284.4.
CAS — 1508-75-4.
ATC — S01FA06.
ATC Vet — QS01FA06.



NOTE. TRO is a code approved by the BP 2008 for use on single unit doses of eye drops containing tropicamide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Tropicamide). A white or almost white, crystalline powder. M.p. 95° to 98°. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.
USP 31 (Tropicamide). A white or practically white crystalline powder, odourless or having not more than a slight odour. M.p. 96° to 100°. Slightly soluble in water; freely soluble in chloroform and in solutions of strong acids. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

◊ References.

1. Vuori M-L, *et al.* Systemic absorption and anticholinergic activity of topically applied tropicamide. *J Ocul Pharmacol* 1994; **10:** 431–7.

Glaucoma. The use of mydriatics is considered liable to provoke an acute attack in patients with glaucoma or a tendency to glaucoma; licensed product information generally contra-indicates their use in such patients. However, a systematic review concluded that in fact a history of open-angle glaucoma did not predispose to acute angle closure under mydriasis, and that mydriasis with tropicamide in particular appeared to be safe and should be recommended in all patients when thorough retinal examination was indicated.[1] In contrast, the use of pilocarpine to reverse mydriatics was potentially harmful.

1. Pandit RJ, Taylor R. Mydriasis and glaucoma: exploding the myth. A systematic review. *Diabet Med* 2000; **17:** 693–9.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Tropicamide is a tertiary amine antimuscarinic with actions similar to those of atropine (p.1219). It is used as eye drops to produce mydriasis and cycloplegia (p.1874). It has a more rapid onset and a shorter duration of effect than atropine: mydriasis is produced within 20 to 40 minutes of use and usually lasts for about 6 hours; cycloplegia is maximal within about 30 minutes and is short-lasting, with complete recovery of accommodation normally within 6 hours. Tropicamide has been reported to be inadequate for cycloplegia in children.

To produce **mydriasis**, a 0.5% solution is instilled 15 to 20 minutes before examination of the eye. To produce **cycloplegia** a 1% solution is used and repeated after 5 minutes; a further instillation may be necessary to prolong the effect after 20 to 30 minutes.

Dementia. Tropicamide has been studied for use in the differential diagnosis of Alzheimer's disease (see Dementia, p.362). Excessive pupil dilatation in response to tropicamide eye drops occurred in patients with signs and symptoms of Alzheimer's disease.[1] However, a double-blind placebo-controlled study[2] in similar patients and healthy subjects indicated that this was not a reliable diagnostic test for Alzheimer's disease.

1. Gómez-Tortosa E, *et al.* Pupil response to tropicamide in Alzheimer's disease and other neurodegenerative disorders. *Acta Neurol Scand* 1996; **94:** 104–9.
2. Graff-Radford NR, *et al.* Tropicamide eyedrops cannot be used for reliable diagnosis of Alzheimer's disease. *Mayo Clin Proc* 1997; **72:** 495–504.

Preparations

BP 2008: Tropicamide Eye Drops;
USP 31: Tropicamide Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Midriaticum†; Mydril; ***Austral.:*** Mydriacyl; ***Austria:*** Mydral; Mydriaticum; ***Belg.:*** Mydriacyl; Tropicol; ***Braz.:*** Ciclomidrin; Mydriacyl; Tropinom; ***Canad.:*** Diotrope†; Mydriacyl; ***Chile:*** Mydriacyl; ***Cz.:*** Mydriacyl†; Mydrum; ***Denm.:*** Mydriacyl; ***Fr.:*** Mydriaticum; ***Ger.:*** Mydriaticum; Mydrum; ***Gr.:*** Tropixal; ***Hong Kong:*** Mydriacyl; Mydriaticum†; ***Hung.:*** Mydrum; ***India:*** Tmide; Tropico; ***Indon.:*** Midric; ***Irl.:*** Mydriacil; ***Israel:*** Mydramide; ***Ital.:*** Tropimil; Visumidriatic; ***Malaysia:*** Mydriacyl; ***Mex.:*** Myriacyl; ***Norw.:*** Mydrian†; ***NZ:*** Mydriacyl; ***Philipp.:*** Mydriacyl; ***Port.:*** Tropicil Top; ***Rus.:*** Mydriacyl (Мидриацил); Mydrum (Мидрум); ***S.Afr.:*** Mydriacyl; Mydriaticum; ***Singapore:*** Mydriacyl; ***Swed.:*** Mydriacyl; ***Switz.:*** Mydriaticum; ***Thai.:*** Mydriacyl; ***Turk.:*** Tropamid; ***UK:*** Mydriacyl; ***USA:*** Mydral; Mydriacyl; Ocu-Tropic; Opticyl; Tropicacyl; ***Venez.:*** Mydriacyl; Mydrox†.

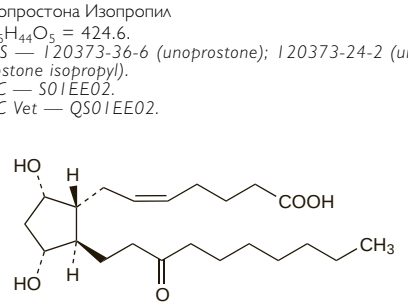
Multi-ingredient: ***Arg.:*** Fotorretin; Sensu; Tropioftal F; ***Canad.:*** Diophenyl-T†; ***Fr.:*** Mydriasert; ***Hong Kong:*** Mydrin-P; ***India:*** Itrop Plus; Tropico Plus; ***Ital.:*** Visumidriatic Fenilefrina; ***Philipp.:*** Sanmyd-P; ***Port.:*** Mydriasert; ***USA:*** Paremyd; ***Venez.:*** Dyfrin†; Fotorretin.

Unoprostone Isopropyl *(rINNM)*

Isopropyl Lunoprostone; Isopropyl Unoprostone; UF-021; Unoprostona de isopropilo; Unoprostone, Isopropyle d'; Unoprostoni Isopropylas. Isopropyl (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate.

Унопростона Изопропил

$C_{25}H_{44}O_5$ = 424.6.
CAS — 120373-36-6 (unoprostone); 120373-24-2 (unoprostone isopropyl).
ATC — S01EE02.
ATC Vet — QS01EE02.



(unoprostone)

Profile

Unoprostone, like latanoprost (p.1882), is a synthetic analogue of dinoprost (prostaglandin F_2). It is used as the isopropyl ester for the treatment of glaucoma and ocular hypertension (p.1873). An ophthalmic solution containing unoprostone isopropyl 0.12 or 0.15% is instilled twice daily.

◊ References.

1. Yamamoto T, *et al.* Clinical evaluation of UF-021 (Rescula; isopropyl unoprostone). *Surv Ophthalmol* 1997; **41** (suppl 2): S99–S103.
2. Eisenberg DL, Camras CB. A preliminary risk-benefit assessment of latanoprost and unoprostone in open-angle glaucoma and ocular hypertension. *Drug Safety* 1999; **20:** 505–14.
3. de Arruda Mello PA, *et al.* Safety of unoprostone isopropyl as mono- or adjunctive therapy in patients with primary open-angle glaucoma or ocular hypertension. *Drug Safety* 2002; **25:** 583–97.
4. Chiba T, *et al.* Comparison of iridial pigmentation between latanoprost and isopropyl unoprostone: a long term prospective comparative study. *Br J Ophthalmol* 2003; **87:** 956–9.
5. Stewart WC, *et al.* The safety and efficacy of unoprostone 0.15% versus brimonidine 0.2%. *Acta Ophthalmol Scand* 2004; **82:** 161–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Rescula; ***Austria:*** Rescula; ***Braz.:*** Rescula; ***Chile:*** Rescula; ***Cz.:*** Rescula; ***Hung.:*** Rescula; ***Jpn:*** Rescula; ***Mex.:*** Rescula; ***Neth.:*** Rescula; ***Philipp.:*** Rescula; ***Singapore:*** Rescula†; ***Switz.:*** Rescula†; ***Thai.:*** Rescula; ***USA:*** Rescula†; ***Venez.:*** Rescula.