

in the liver; the principal metabolite, dihydrolevobunolol, is reported to possess beta-blocking activity. The metabolites and some unchanged drug are excreted in the urine.

Uses and Administration

Levobunolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Levobunolol is used as the hydrochloride to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension (p.1873). It begins to act 1 hour after instillation with maximal effect seen between 2 and 6 hours; the effect may be maintained for up to 24 hours. Levobunolol hydrochloride is usually used as a 0.5% ophthalmic solution instilled once or twice daily; alternatively a 0.25% solution may be instilled twice daily.

Preparations

BP 2008: Levobunolol Eye Drops;
USP 31: Levobunolol Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Betagan; **Levunolol:** Betagan; **Austria:** Vistagan; **Belg.:** Betagan; **Braz.:** B-Tablock; Betagan; **Canad.:** Betagan; Ophtho-Bunolol†; **Chile:** Betagen; **Cz.:** Vistagan; **Denm.:** Betagan; **Fr.:** Betagan; **Ger.:** Vistagan; **Gr.:** Pentila†; Vistagan; **Hong Kong:** Betagan; **Hung.:** Vistagan; **Irl.:** Betagan; **Israel:** Betagan; **Ital.:** Vistagan; **Malaysia:** Betagan†; **Mex.:** Betagan; **Neth.:** Betagan; **NZ:** Betagan; **Port.:** Betagan; **S.Afr.:** Betagan; **Singapore:** Betagan; **Spain:** Betagan; **Switz.:** Vistagan; **Thai.:** Betagan; **Turk.:** Betagan; **UK:** Betagan; **USA:** Ak-Beta; Betagan; **Venez.:** Vistagan.

Multi-ingredient: **Canad.:** Probeta†.

Methazolamide (BAN, rINN) ⊗

Metazolamidum; Méthazolamide; Methazolamidum. *N*-(4-Methyl-2-sulphamoyl-Δ²-1,3,4-thiadiazolin-5-ylidene)acetamide.

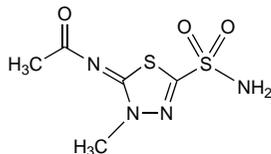
Метазолами́д

C₅H₈N₄O₃S₂ = 236.3.

CAS — 554-57-4.

ATC — S01EC05.

ATC Vet — QS01EC05.



Pharmacopoeias. In US.

USP 31 (Methazolamide). A white or faintly yellow crystalline powder with a slight odour. Very slightly soluble in water and in alcohol; slightly soluble in acetone; soluble in dimethylformamide. Protect from light.

Adverse Effects and Precautions

As for Acetazolamide, p.1875.

Hypersensitivity. Cholestatic hepatitis with jaundice, rash, and subsequent pure red cell aplasia was associated with methazolamide in a patient.¹ Drug-induced hypersensitivity was suspected as the cause of the reaction.

1. Krivoy N, *et al.* Methazolamide-induced hepatitis and pure RBC aplasia. *Arch Intern Med* 1981; **141**: 1229–30.

Pharmacokinetics

Methazolamide is absorbed from the gastrointestinal tract more slowly than acetazolamide. It has been reported not to be extensively bound to plasma protein, and to have a half-life of about 14 hours. About 15 to 30% of the dose is excreted in the urine; the fate of the remainder is unknown.

Uses and Administration

Methazolamide is an inhibitor of carbonic anhydrase with actions similar to those of acetazolamide (p.1876). It is used in the treatment of glaucoma (p.1873) in oral doses of 50 to 100 mg two or three times daily. Its action is less prompt but of longer duration than that of acetazolamide, lasting for 10 to 18 hours.

The diuretic activity of methazolamide is less pronounced than that of acetazolamide.

Preparations

USP 31: Methazolamide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Glaumeta†; **Canad.:** Neptazane†; **Israel:** Neptazane†; **Thai.:** Neptazane†; **USA:** GlaucoTabs†; MZM†.

Metipranolol (BAN, USAN, rINN) ⊗

BMOI-004; Methipranolol; Métipranolol; Metipranololum; VUAB-6453 (SPOFA); VUFB-6453. 1-(4-Acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol; 4-(2-Hydroxy-3-isopropylaminopropoxy)-2,3,6-trimethylphenyl acetate.

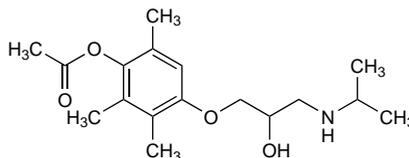
Метипранолол

C₁₇H₂₇NO₄ = 309.4.

CAS — 22664-55-7.

ATC — S01ED04.

ATC Vet — QS01ED04.



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

Pharmacopoeias. In Br.

BP 2008 (Metipranolol). A white crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; dissolves in dilute mineral acids. The filtrate of a 2.5% suspension in water has a pH of 9.0 to 10.0. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Conjunctivitis, conjunctival leucoplakia, transient stinging, as well as other ocular adverse effects have been reported with metipranolol eye drops. Granulomatous anterior uveitis has been reported rarely; a high incidence reported in the UK may have been associated with changes induced by radiation sterilisation of metipranolol eye drops in their final container, but this preparation is no longer available.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Uses and Administration

Metipranolol is a non-cardioselective beta blocker (p.1225). It is reported to be largely lacking in intrinsic sympathomimetic activity and membrane-stabilising properties.

Metipranolol is used to reduce raised intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p.1873). Eye drops usually containing metipranolol 0.1 or 0.3% are used twice daily.

Metipranolol has also been used by mouth in the management of cardiovascular disorders.

Preparations

BP 2008: Metipranolol Eye Drops.

Proprietary Preparations (details are given in Part 3)

Austria: Beta-Optiole; **Belg.:** Beta-Optiole; **Cz.:** Trimepranol; **Ger.:** Betamann; **Ital.:** Turoptin; **Malaysia:** Beta-Optiole†; **Neth.:** Beta-Optiole; **Philipp.:** Beta-Optiole; **Pol.:** Betamann; **Port.:** Beta-Optiole; **S.Afr.:** Beta-Optiole; **Singapore:** Beta-Optiole†; **Switz.:** Turoptin†; **Thai.:** Beta-Optiole†; **Turk.:** Turoptin; **USA:** OptiPranolol.

Multi-ingredient: **Austria:** Betacarpin; **Belg.:** Normoglaucou; **Cz.:** Tri-mecryton†; **Ger.:** Normoglaucou; **Torlat†; Tri-Torlat†; Gr.:** Beta Optiole; **Ripix†; Hong Kong:** Torlat†; **Ital.:** Ripix; **Malaysia:** Normoglaucou†; **Neth.:** Normoglaucou; **Pol.:** Normoglaucou; **Port.:** Normoglaucou; **Singapore:** Normoglaucou†; **Switz.:** Ripix; **Thai.:** Normoglaucou†.

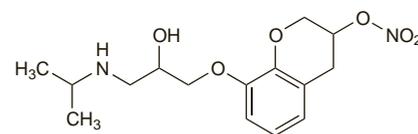
Nipradilol (rINN) ⊗

K-351; Nipradilolum; Nipradolol. 8-[2-Hydroxy-3-(isopropylamino)propoxy]-3-chromanol 3-nitrate.

Нипрадилол

C₁₅H₂₂N₂O₆ = 326.3.

CAS — 81486-22-8.



Profile

Nipradilol is a non-cardioselective beta blocker (p.1225). It is also reported to have direct vasodilating activity. It is used in the management of glaucoma and ocular hypertension (p.1873); eye drops containing nipradilol 0.05% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Hypadil.

Paraoxon

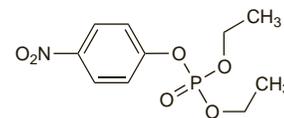
E-600. Diethyl *p*-nitrophenyl phosphate.

C₁₀H₁₄NO₆P = 275.2.

CAS — 311-45-5.

ATC — S01EB10.

ATC Vet — QS01EB10.



Profile

Paraoxon is a potent inhibitor of cholinesterase activity that has been used with other miotics in the treatment of glaucoma. It is the active metabolite of the organophosphorus insecticide parathion (p.2048) and therefore produces similar toxicity but with a faster onset.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Ital.:** Mios.

Physostigmine (BAN)

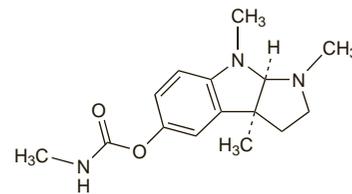
Eserine; Fisostigmina; Fysostigmiini; Fysostigmin; Physostigminum. (3a,5,8aR)-1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl methylcarbamate.

C₁₅H₂₁N₃O₂ = 275.3.

CAS — 57-47-6.

ATC — S01EB05; V03AB19.

ATC Vet — QA03AX90; QA03FA90; QS01EB05; QV03AB19.



Description. An alkaloid obtained from the calabar bean (ordeal bean; chopnut), the seed of *Physostigma venenosum* (Leguminosae).

Pharmacopoeias. In US.

USP 31 (Physostigmine). An alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum* (Leguminosae). It is a white, odourless, microcrystalline powder which acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals. M.p. not lower than 103°. Slightly soluble in water; freely soluble in alcohol; very soluble in chloroform and in dichloromethane; soluble in fixed oils and in benzene. Store in airtight containers. Protect from light.

Physostigmine Salicylate (BANM)

Eserine Salicylate; Ésérine, salicylate d'; Eserini salicylas; Ezerino salicilatas; Fisostigmina, salicilato de; Fiszostigmino salicilatas; Fiszostigminy salicylan; Fiszostigmin-szalicilát; Fyszostigmiinisalicylaatti; Fyszostigminsalicylat; Fyszostigmin-salicylát; Physostig. Sal.; Physostigmine Monosalicylate; Physostigmini salicylas.

C₁₅H₂₁N₃O₂·C₇H₆O₃ = 413.5.

CAS — 57-64-7.

ATC — S01EB05; V03AB19.

ATC Vet — QS01EB05; QV03AB19.

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; Fiszostigmina, sulfato de; Fiszostigmino sulfatas; Fiszostigmin-szulfát; Fysostigmiinisulfaatti; Fysostigminsulfat; Fysostigmin-sulfát; Physostig. Sulph.; Physostigmine Sulphate (*BANM*); Physostigmini sulfas.

$(C_{15}H_{21}N_3O_2)_2 \cdot H_2SO_4 = 648.8$.

CAS — 64-47-1.

ATC — *S01EB05*; *V03AB19*.

ATC Vet — *Q501EB05*; *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

- Cumming G, *et al.* Treatment and recovery after massive overdosage of physostigmine. *Lancet* 1968; **ii**: 147-9.
- 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 pre-systemic metabolism.¹⁻³ Oral bioavailability ranged from 5.2 to 11.7% in 3 of 5 subjects.³

In a study⁴ 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 com-

parison 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 study⁵ 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.

- Gibson M, *et al.* Physostigmine concentrations after oral doses. *Lancet* 1985; **i**: 695-6.
- Sharpless NS, Thal LJ. Plasma physostigmine concentrations after oral administration. *Lancet* 1985; **i**: 1397-8.
- Whelpton R, Hurst P. Bioavailability of oral physostigmine. *N Engl J Med* 1985; **313**: 1293-4.
- 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.
- 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 poisoning¹ and its use can lead to severe cardiac^{2,3} and respiratory effects^{2,3} and to convulsions.^{3,4}

- Aquilonius S-M, Hedstrand U. The use of physostigmine as an antidote in tricyclic anti-depressant intoxication. *Acta Anaesthesiol Scand* 1978; **22**: 40-5.
- Caine ED. Anticholinergic toxicity. *N Engl J Med* 1979; **300**: 1278.
- Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA* 1975; **231**: 941-3.
- 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

- Rodriguez-Budelli MM, *et al.* Action of physostigmine on inherited ataxias. *Adv Neurol* 1978; **21**: 195-202.
- Aschoff JC, *et al.* Physostigmin in der Behandlung von Kleinhirnataxien. *Nervenarzt* 1996; **67**: 311-18.
- 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 study² 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.

- 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).
- 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:** Antilinum.

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

Pilocarpine (*BAN*)

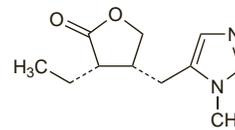
Pilocarpina; Pilocarpinum; Pilocarpiini; Pilocarpin. (3S,4R)-3-Ethyl-dihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]furan-2(3H)-one.

$C_{11}H_{16}N_2O_2 = 208.3$.

CAS — 92-13-7.

ATC — *N07AX01*; *S01E01*.

ATC Vet — *QN07AX01*; *QS01E01*.



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.

$C_{11}H_{16}N_2O_2 \cdot xB_2O_3$.

CAS — 16509-56-1.

ATC — *N07AX01*; *S01E01*.

ATC Vet — *QN07AX01*; *QS01E01*.

Pilocarpine Hydrochloride (*BANM*)

Pilocarp. Hydrochlor.; Pilocarpina, hidrocloruro de; Pilocarpine, chlorhydrate de; Pilocarpine Monohydrochloride; Pilocarpini Chloridum; Pilocarpini hydrochloridum; Pilocarpinum Chloratum; Pilocarpiinihydroklorid; Pilocarpin Hydroklorür; Pilocarpin-hydroklorid; Pilocarpin-hydrochlorid; Pilocarpinhydroklorid; Pilocarpino hidrochloridas; Pilocarpiny chlorowodorek.

$C_{11}H_{16}N_2O_2 \cdot HCl = 244.7$.

CAS — 54-71-7.

ATC — *N07AX01*; *S01E01*.

ATC Vet — *QN07AX01*; *QS01E01*.

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 found¹ to be stable for 60 days at 25° and for 90 days at 4°.

- 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; Pilocarpiini Nitras; Pilocarpinium Nitricum; Pilocarpiini nitraatti; Pilocarpinnitrat; Pilocarpin-nitrat; Pilocarpino nitratas.

$C_{11}H_{16}N_2O_2 \cdot HNO_3 = 271.3$.

CAS — 148-72-1.

ATC — *N07AX01*; *S01E01*.

ATC Vet — *QN07AX01*; *QS01E01*.

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.