

Dyflon (BAN)

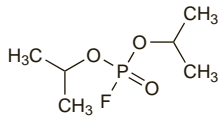
DFF; Difluorophate; Di-isopropyl Fluorophosphate; Di-isopropylfluorophosphonate; Fluostigmine; Isoflurofate; Isoflurophate. Di-isopropyl phosphorofluoridate.

$C_6H_{14}FO_3P = 184.1$.

CAS — 55-91-4.

ATC — S01EB07.

ATC Vet — QS01EB07.

**Pharmacopoeias.** In *US*.

USP 31 (Isoflurophate). 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.

Profile

Dyflon is an irreversible inhibitor of cholinesterases with actions similar to those of ecothiopate iodide (below). It has been used mainly in the treatment of open-angle glaucoma, particularly in aphakic patients and when other drugs have proved inadequate; it has usually been given as a 0.025% ophthalmic ointment. It was also used in the diagnosis and management of accommodative convergent strabismus.

Handling. The vapour of dyflon is very toxic. The eyes, nose, and mouth should be protected when handling dyflon, and contact with the skin should be avoided. Dyflon 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.

Preparations

USP 31: Isoflurophate Ophthalmic Ointment.

Ecothiopate Iodide (BAN, rINN)

Ecothiopate Iodide; Ecostigmine Iodide; Écothiopate, Iodure d'; Ecothiopatī Iodidum; Ekotiopaattijodidi; Ekotiopatjodid; Ioduro de ecotiopato; M1-217. (2-Diethoxyphosphinythioethyl)trimethylammonium iodide.

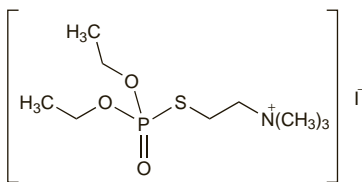
Экотиопата Йодид

$C_9H_{23}INO_3PS = 383.2$.

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

ATC — S01EB03.

ATC Vet — QS01EB03.

**Pharmacopoeias.** In *Jpn* and *US*.

USP 31 (Ecothiopate Iodide). A white, crystalline, hygroscopic solid having a slight mercaptan-like odour. Soluble 1 in 1 of water, 1 in 25 of dehydrated alcohol, and 1 in 3 of methyl alcohol; practically insoluble in other organic solvents. Its solutions in water have a pH of about 4. Store in airtight containers preferably at a temperature below 0°. Protect from light.

Adverse Effects

As for Neostigmine, p.631. For adverse effects of miotics, see also Pilocarpine, p.1885.

Ecothiopate is an irreversible cholinesterase inhibitor; its action, and hence its adverse effects, may be prolonged.

Plasma and erythrocyte cholinesterases may be reduced by treatment with eye drops of ecothiopate or other long-acting anticholinesterases, and systemic toxicity occurs more frequently than with shorter-acting miotics. Acute iritis, retinal detachment, or precipitation of acute glaucoma may occasionally occur, and iris cysts (especially in children) or lens opacities may develop on prolonged treatment.

Treatment of Adverse Effects

To treat the systemic effects of poisoning, atropine sulfate may be given parenterally with pralidoxime chloride as for intoxication with organophosphorus insecticides (see p.1460); subcon-

junctival injection of pralidoxime has been used to reverse severe ocular adverse effects. Supportive treatment, including assisted ventilation, should be given as necessary.

To prevent or reduce development of iris cysts in patients receiving ecothiopate eye drops, phenylephrine eye drops may be given simultaneously.

Precautions

As for Neostigmine, p.632. For precautions of miotics, see also under Pilocarpine, p.1885. In general, as with other long-acting anticholinesterases, ecothiopate should be used only where therapy with other drugs has proved ineffective. Ecothiopate iodide should not be used in patients with iodine hypersensitivity.

Interactions

As for Neostigmine, p.632. The possibility of an interaction remains for a considerable time after stopping long-acting anticholinesterases such as ecothiopate.

Uses and Administration

Ecothiopate is an irreversible inhibitor of cholinesterase; its actions are similar to those of neostigmine (p.632) but much more prolonged. Its miotic action begins within 1 hour of its application and may persist for 1 to 4 weeks; it causes a reduction in intra-ocular pressure, which is maximal after 24 hours and may persist for days or weeks.

Ecothiopate iodide is used mainly in the treatment of open-angle glaucoma (p.1873), particularly in aphakic patients and when other drugs have proved inadequate. It is given as drops of a 0.03 to 0.25% ophthalmic solution. Licensed product information states that 2 daily doses are preferred to allow for diurnal variations in intra-ocular pressure, although it has also been given once daily or on alternate days. It is advisable to give the single dose or one of the 2 daily doses at bedtime.

Ecothiopate iodide eye drops are also used in the diagnosis and management of accommodative convergent strabismus (p.1874).

Preparations

USP 31: Ecothiopate Iodide for Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Austral: Phospholine Iodide†; **Austria:** Phospholinjodid†; **USA:** Phospholine Iodide†.

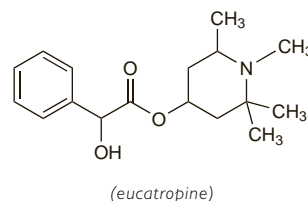
Eucatropine Hydrochloride (BANM, rNNM)

Clorhidrato de Eufalmina; Eucatropine, Chlorhydrate d'; Eucatropini Hydrochloridum; Eucatropinum Chloride; Hidrocloruro de eucatropina. 1,2,2,6-Tetramethyl-4-piperidyl mandelate hydrochloride.

Эукатропина Гидрохлорид

$C_{17}H_{25}NO_3.HCl = 327.8$.

CAS — 100-91-4 (eucatropine); 536-93-6 (eucatropine hydrochloride).

**Pharmacopoeias.** In *US*.

USP 31 (Eucatropine Hydrochloride). A white, odourless, granular powder. Very soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Profile

Eucatropine hydrochloride is a tertiary amine antimuscarinic that has been used as a mydriatic. It has little or no effect on accommodation.

Preparations

USP 31: Eucatropine Hydrochloride Ophthalmic Solution.

Homatropine (BAN)

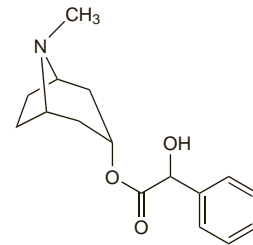
Homatropiini; Homatropin; Homatropina; Homatropinum. (1R,3r,5S)-Tropan-3-yl (RS)-mandelate.

$C_{16}H_{21}NO_3 = 275.3$.

CAS — 87-00-3.

ATC — S01FA05.

ATC Vet — QS01FA05.

**Homatropine Hydrobromide** (BANM)

Homatr. Hydrobrom.; Homatropiinihydrobromidi; Homatropina, hidrobromuro de; Homatropine, bromhydrate d'; Homatropin-hidrobromid; Homatropinhydrobromid; Homatropinhydrobromid; Homatropini hydrobromidum; Homatropinum Bromide; Homatropino hidrobromidas; Homatropinum Bromatum; Homatropiny bromowodorek; Omotropina Bromidrat; Oxtolyltropine Hydrobromide; Tropy Mandelate Hydrobromide.

$C_{16}H_{21}NO_3.HBr = 356.3$.

CAS — 51-56-9.

ATC — S01FA05.

ATC Vet — QS01FA05.

NOTE. HOM is a code approved by the BP 2008 for use on single unit doses of eye drops containing homatropine hydrobromide 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 (Homatropine Hydrobromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Homatropine Hydrobromide). White crystals or a white crystalline powder. Soluble 1 in 6 of water, 1 in 40 of alcohol, and 1 in 420 of chloroform; insoluble in ether. pH of a 2% solution in water is between 5.7 and 7.0. Store in airtight containers. Protect from light.

Homatropine Methylbromide (BANM, rINN)

Homatropiinietylibromidi; Homatropine Methylbromide; Homatropine, métylbromure d'; Homatropini métylbromidum; Homatropin-métylbromid; Homatropin-metilbromid; Homatropinmetilbromid; Homatropine metilbromidas; Methylhomatropinum Bromatum; Methylhomatropinum Bromide; Metilbromuro de homatropina. (1R,3r,5S)-3-[(±)-Mandeloyloxy]-8-methyltropanium bromide.

Гоматропина Метилбромид

$C_{16}H_{21}NO_3.CH_2Br = 370.3$.

CAS — 80-49-9.

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

Ph. Eur. 6.2 (Homatropine Methylbromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.5 to 6.5. Protect from light.

USP 31 (Homatropine Methylbromide). A white, odourless, powder that slowly darkens on exposure to light. Very soluble in water; freely soluble in alcohol and in acetone containing about 20% of water; practically insoluble in acetone and in ether. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Ophthalmic use. Antimuscarinic toxicity (including ataxia, restlessness, excitement, hallucinations) has been reported in children¹ and the elderly^{2,3} given homatropine eye drops.

1. Hoefnagel D. Toxic effects of atropine and homatropine eye drops in children. *N Engl J Med* 1961; **264**: 168–71.
2. Reid D, Fulton JD. Tachycardia precipitated by topical homatropine. *BMJ* 1989; **299**: 795–6.
3. Tune LE, et al. Anticholinergic delirium caused by topical homatropine ophthalmologic solution: confirmation by anticholinergic radioreceptor assay in two cases. *J Neuropsychiatr Clin Neurosci* 1992; **4**: 195–7.

Interactions

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

Uses and Administration

Homatropine is a tertiary amine antimuscarinic with effects similar to those of atropine (p.1219). It is used as the hydrobromide, also a tertiary amine, to produce mydriasis and cycloplegia (p.1874); its actions are more rapid and of shorter duration than those of atropine, but it is less potent and has a relatively weak cycloplegic effect. In general, onset of action is between 30 and 60 minutes, and recovery within 1 to 3 days. Homatropine hydrobromide is generally used as a 1, 2, or 5% ophthalmic solution. For the determination of refraction, instillation may be repeated

if necessary 5 to 10 minutes later. In the treatment of uveitis (p.1515), the eye drops should be instilled two or three times daily, or up to every 3 to 4 hours if required.

The *BNFC* recommends that eye drops containing 0.5% homatropine hydrobromide are used once daily or on alternate days for uveitis in children aged 3 months to 2 years; older children may be given 1 or 2% eye drops twice daily.

Homatropine has also been used as the quaternary ammonium methobromide derivative in the treatment of gastrointestinal spasm and as an adjunct in peptic ulcer disease; homatropine methobromide has also been included in preparations used for the treatment of coughs.

Preparations

BP 2008: Homatropine Eye Drops;

USP 31: Homatropine Hydrobromide Ophthalmic Solution; Homatropine Methylobromide Tablets; Hydrocodone Bitartrate and Homatropine Methylobromide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Antiespasmodico; Dallapasma; Espasmatropin; Paratropina; **Braz.:** Espasmo Flatol; Novotropina; **Gr.:** Nopar; **Malaysia:** Homa†; **Mex.:** Homasedin†; Homogin; Infalfren Simple; Pasmolit; **Spain:** Homatrop; **Venez.:** Litropina.

Multi-ingredient: **Arg.:** Antispaquina; Asestor; Bellatotal; Bibol Leloup; Bilosan Compuesto†; Carbon Tabs; Colistop; Dimaval; Espasmo Ibupirac†; Espasmo Fin; Factor AG Antiespasmodico; Hepatodirectol; Ibupirac Fem; Opoenterol†; Paratropina Antigas; Paratropina Compuesta; Sumal; Zimerol; **Braz.:** Analgosedan†; Asmatron†; Atapec†; Belacodid†; Bromalgin†; Calmazin†; Codeverin†; Dipirol†; Enterobion†; Espasalgon†; Espasmo Colic†; Espasmo Luftal; Etaverol†; Flagass Baby; Marsoni†; Migrane; Naquinto†; Pasmalgin†; Plencodan†; Sedalene; Sedalin; Spasmotropin; Tropinal; Vagoplex†; **Chile:** Codelasa; **Hung.:** Bilagit†; Neo-Bilagit; Ridol†; Troparinum; **India:** Dysfur-M†; **Mex.:** Bontal; Contefur†; Coralzul; Dialgin; Facetin-D; Fuzoty†; Neopecsul; Neoxil; Sultroquin†; Tasakal†; Threcho; Trilor†; Yodozona; **Philipp.:** Creamalin HM; **Spain:** Cortenema; **Thai.:** Polyzyme-†; **USA:** Hycodan; Hydromet; Hydropane; Tussigon; **Venez.:** Frevagt; Metilfedrin†.

Latanoprost (BAN, USAN, rINN)

Latanoprost; Latanoprostum; PhXA-41; XA-41. Isopropyl (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl)-5-heptenoate.

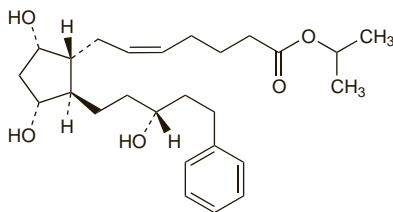
Латанопро́ст

$C_{26}H_{40}O_5 = 432.6$.

CAS — 130209-82-4.

ATC — S01EE01.

ATC Vet — QS01EE01.



Adverse Effects and Precautions

Latanoprost eye drops may produce a gradual increase in the amount of brown pigment in the iris, due to increased melanin content of melanocytes. This change in eye colour is most evident in patients with mixed colour irises, and may be permanent in some patients. The onset of iris pigmentation is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. Darkening, thickening, and lengthening of eye lashes may occur and are reversible upon stopping treatment. Darkening of the palpebral skin has been reported rarely. Ocular irritation, conjunctival hyperaemia, transient punctate epithelial erosions and eyelid oedema may occur; there have also been rare reports of iritis and/or uveitis, and macular oedema. Systemic effects may also occur, see below for further details. Dizziness, headache, arthralgia, and myalgia have also been reported.

Effects on the eyes. Latanoprost has been associated with various adverse effects on the eyes, including case reports of cystoid macular oedema¹ and bilateral optic disc oedema.² Licensed product information states that reports of macular oedema have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with risk factors for cystoid macular oedema such as those with diabetic retinopathy or retinal vein occlusion.

Herpes simplex dendritic keratitis developed in 2 patients during latanoprost therapy.³ The author suggested that the biochemical changes in the cornea caused by latanoprost may predispose to herpes keratitis.

1. Wardrop DRA, Wishart PK. Latanoprost and cystoid macular oedema in a pseudophakic. *Br J Ophthalmol* 1998; **82**: 843–4.
2. Stewart O, et al. Bilateral optic disc oedema associated with latanoprost. *Br J Ophthalmol* 1999; **83**: 1092–3.
3. Ekatomatis P. Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma. *Br J Ophthalmol* 2001; **85**: 1008–9.

Systemic effects. The use of latanoprost eye drops has been associated with systemic adverse reactions. In a case report¹ of 2 patients with latanoprost-associated hypertension the authors mentioned that other events including peripheral and facial oedema, dyspnoea, exacerbation of asthma, tachycardia, and chest pain or angina pectoris had been reported. Another case report² also referred to exacerbation of angina. Although a study³ involving 24 stable asthmatics found that latanoprost eye drops had no effect on pulmonary function or asthma symptoms, UK licensed product information recommends caution in patients with asthma.

1. Peak AS, Sutton BM. Systemic adverse effects associated with topically applied latanoprost. *Ann Pharmacother* 1998; **32**: 504–5.
2. Mitra M, et al. Exacerbation of angina associated with latanoprost. *BMJ* 2001; **323**: 783.
3. Hedner J, et al. Latanoprost and respiratory function in asthmatic patients: randomized, double-masked, placebo-controlled crossover evaluation. *Arch Ophthalmol* 1999; **117**: 1305–9.

Interactions

Paradoxical increases in intra-ocular pressure have been reported after the concomitant ophthalmic use of 2 prostaglandin analogues. UK licensed product information states that the use of 2 or more prostaglandin analogues or derivatives is not recommended.

Uses and Administration

Latanoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) that is used to reduce intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension (p.1873). Reduction of intra-ocular pressure starts about 3 to 4 hours after instillation and is maximal after 8 to 12 hours; pressure reduction lasts for at least 24 hours. A 0.005% ophthalmic solution is instilled once daily, preferably in the evening.

References

1. Patel SS, Spencer CM. Latanoprost: a review of its pharmacological properties, clinical efficacy and tolerability in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 1996; **9**: 363–78.
2. Einarson TR, et al. Meta-analysis of the effect of latanoprost and brimonidine on intraocular pressure in the treatment of glaucoma. *Clin Ther* 2000; **22**: 1502–15.
3. Zhang WY, et al. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001; **85**: 983–90.
4. Feldman RM. An evaluation of the fixed-combination of latanoprost and timolol for use in open-angle glaucoma and ocular hypertension. *Expert Opin Pharmacother* 2004; **5**: 909–21.
5. Bayer A, et al. Clinical predictors of latanoprost treatment effect. *J Glaucoma* 2005; **14**: 260–3.
6. Diestelhorst M, Larsson LI. European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. *Ophthalmology* 2006; **113**: 70–6.
7. Fung AT, et al. Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; **91**: 62–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Glaucostat; Klonaprost; Latanoflax; Louten; Ocuprost†; Paraiop; Tanarof; Xalatan; **Austral.:** Xalatan; **Austria:** Xalatan; **Belg.:** Xalatan; **Braz.:** Xalatan; **Canada.:** Xalatan; **Chile:** Gaax; Latof; Louten; Xalatan; **Cz.:** Xalatan; **Denm.:** Xalatan; **Fin.:** Xalatan; **Fr.:** Xalatan; **Ger.:** Xalatan; **Gr.:** Xalatan; **Hong Kong:** Xalatan; **Hung.:** Xalatan; **India:** 9P†; **Indon.:** Xalatan; **Irl.:** Xalatan; **Israel:** Xalatan; **Ital.:** Xalatan; **Malaysia:** Xalatan; **Mex.:** Gaap Ofteno; Latsol; Xalatan; **Neth.:** Xalatan; **Norw.:** Xalatan; **NZ:** Xalatan; **Philipp.:** Xalatan; **Pol.:** Xalatan; **Port.:** Xalatan; **Rus.:** Xalatan (Ксаластан); **S.Afr.:** Xalatan; **Singapore:** Xalatan; **Spain:** Xalatan; **Swed.:** Xalatan; **Switz.:** Xalatan; **Thai.:** Xalatan; **Turk.:** Xalatan; **UK:** Xalatan; **USA:** Xalatan; **Venez.:** Gaap Ofteno; Laprost; Latanoprest; Xalatan.

Multi-ingredient: **Arg.:** Louten T; Ocuprostim; Xalacom; **Austral.:** Xalacom; **Austria:** Xalacom; **Belg.:** Xalacom; **Braz.:** Xalacom; **Canada.:** Xalacom; **Chile:** Gaax T; Latof-T; Xalacom; **Cz.:** Xalacom; **Denm.:** Xalacom; **Fin.:** Xalacom; **Fr.:** Xalacom; **Ger.:** Xalacom; **Gr.:** Xalacom; **Hong Kong:** Xalacom; **Hung.:** Xalacom; **Indon.:** Xalacom; **Irl.:** Xalacom; **Israel:** Xalacom; **Ital.:** Xalacom; **Malaysia:** Xalacom; **Mex.:** Xalacom; **Neth.:** Xalacom; **Norw.:** Xalacom; **NZ:** Xalacom; **Philipp.:** Xalacom; **Pol.:** Xalacom; **Port.:** Tavu; Xalacom; **Rus.:** Xalacom (Ксааком); **S.Afr.:** Xalacom; **Singapore:** Xalacom; **Spain:** Xalacom; **Swed.:** Xalacom; **Switz.:** Xalacom; **Thai.:** Xalacom; **UK:** Xalacom; **Venez.:** Xalacom.

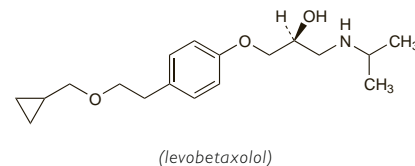
Levobetaxolol Hydrochloride (USAN, rINN) ⊗

AL-1577A (levobetaxolol or levobetaxolol hydrochloride); Hidrocloruro de levobetaxolol; Lévoβétaxolol, Chlorhydrate de; Levobetaxololi Hydrochloridum. (–)-(S)-1-[p-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-isopropylaminopropan-2-ol hydrochloride.

Левобетаксолола Гидрохлорид

$C_{18}H_{29}NO_3 \cdot HCl = 343.9$.

CAS — 93221-48-8 (levobetaxolol); 116209-55-3 (levobetaxolol hydrochloride).



(levobetaxolol)

Profile

Levobetaxolol, the S-isomer of betaxolol (p.1231) is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have no significant membrane-stabilising properties.

Levobetaxolol has been used as the hydrochloride to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Betaxon†.

Levobunolol Hydrochloride

(BANM, USAN, rINN) ⊗

(–)-Bunolol Hydrochloride; l-Bunolol Hydrochloride; Hidrocloruro de levobunolol; Lévoβunolol, Chlorhydrate de; Levobunolol Hidroklorür; Levobunololihydroklorid; Levobunololi Hydrochloridum; Levobunololihydrokloridi; W-7000A. (–)-5-(3-tert-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride.

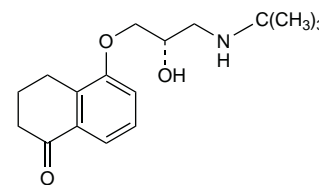
Левобунолола Гидрохлорид

$C_{17}H_{25}NO_3 \cdot HCl = 327.8$.

CAS — 47141-42-4 (levobunolol); 27912-14-7 (levobunolol hydrochloride).

ATC — S01ED03.

ATC Vet — QS01ED03.



(levobunolol)

Pharmacopoeias. In Br and US.

BP 2008 (Levobunolol Hydrochloride). A white or pinkish-white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of between 4.5 and 6.5. Protect from light.

USP 31 (Levobunolol Hydrochloride). A white odourless crystalline powder. Soluble in water and in methyl alcohol; slightly soluble in alcohol and in chloroform. A 5% solution in water has a pH between 4.5 and 6.5.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

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

Pharmacokinetics

Some systemic absorption is reported to occur after topical application to the eye. After oral doses levobunolol is rapidly and almost completely absorbed from the gastrointestinal tract. It is extensively metabolised