cellular hypoxia, and improved blood viscosity and erythrocyte deformability. Calcium-channel blocking activity might have a role, but evidence for the efficacy of other calcium-channel blockers in migraine prophylaxis (see Nifedipine, p.1355) is less convincing than for flunarizine.

Case reports have indicated benefit with flunarizine in the prophylaxis of the rare disorder of alternating hemiplegia in childhood[5,6] but a subsequent study[7] in 12 children did not produce conclusive findings. A later long-term study[8] reported that 7 of 9 children given flunarizine for up to 5 years for hemiplegia showed a reduction in the duration of attacks, and 3 had a reduction in frequency, but only 1 of these obtained a complete cessation of episodes.

The role of antihistamines in general in the management of migraine is discussed briefly on p.564.

1. Todd PA, Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; **38:** 481–99.
2. Andersson K-E, Vinge E. β-Adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. *Drugs* 1990; **3:** 355–73.
3. Soelberg Sørensen P, *et al.* Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; **31:** 650–7.
4. Gawel MJ, *et al.* Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992; **19:** 340–5.
5. Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; **ii:** 579.
6. Curatolo P, Cusmai R. Drugs for alternating hemiplegic migraine. *Lancet* 1984; **ii:** 980.
7. Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics* 1987; **18:** 191–5.
8. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. *Neurology* 1993; **43:** 36–41.

Tourette's syndrome. A small unblinded study[1] involving 7 patients has suggested that flunarizine is more effective than placebo in the treatment of Tourette's syndrome (see Tics, p.954).

1. Micheli F, *et al.* Treatment of Tourette's syndrome with calcium antagonists. *Clin Neuropharmacol* 1990; **13:** 77–83.

Vertigo. Antihistamines are the mainstay of the treatment of vertigo (p.565). However, their antimuscarinic adverse effects may prove troublesome, particularly in the elderly, and they produce central sedation. Flunarizine is devoid of antimuscarinic properties, although it may produce central sedation.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bercetina; Coromert; Flufenal; Mondus; Niflucan; Sibelium; Vasculoflex†; ***Austria:*** Amalium; Flunarium; Sibelium; ***Belg.:*** Flunarimed; Flunatop; Kelamigra; Sibelium; ***Braz.:*** Flunarin; Fluvert; Fluzix; Sibelium; Vertigium; Vertix; ***Canad.:*** Sibelium; ***Chile:*** Flerox; Fluxus; Irrigor; Sibelium; Zentralin; ***Cz.:*** Sibelium; ***Denm.:*** Sibelium; ***Fr.:*** Sibelium; ***Ger.:*** Flunavert; Natil-N; Sibelium; ***Gr.:*** Sibelium; ***Hong Kong:*** Fludan; Sibelium†; ***Hung.:*** Sibelium; ***India:*** Migarid; Nomigrain; ***Indon.:*** Bartolium; Cevadil; Degnium; Dizilium; Frego; Sibelium; Sibenid; Silum; Sinral; Unalium; Xepalium; ***Irl.:*** Sibelium; ***Ital.:*** Flugeral; Flunagen; Fluxarten; Gradient; Issium; Sibelium; Vasculene; ***Malaysia:*** Fludan; Forknow; Migarid; Sibelium; ***Mex.:*** Axilin; Fasolan; Naflurył; Sibelium; ***Neth.:*** Sibelium; ***Philipp.:*** Sibelium; ***Port.:*** Sibelium; Vasilium; Zinasen; ***S.Afr.:*** Sibelium; ***Singapore:*** Forknow; Narizine†; Sibelium†; ***Spain:*** Flerudin; Flurpax; Sibelium; ***Switz.:*** Sibelium; ***Thai.:*** Cedelate†; Finelium†; Floxin; Fludan; Flulium; Flunarium; Flunaza†; Flunazine†; Fluricin; Hexilium; Liberal; Medilium; Poli-Flunarin; Seabell†; Sibelium; Simoyiam; Sobelin; Vanid; Vertilium; Zelium; ***Turk.:*** Sibelium; ***Venez.:*** Fludil; Sibelium.

Multi-ingredient: *Arg.:* Angiolit†; CCK Flunarizina†; Sibelium Plus; ***Braz.:*** Vertizine D.

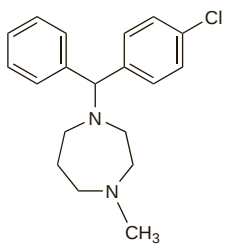
Homochlorcyclizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de homoclorciclizina; Homochlorcyclizine, Chlorhydrate d'; Homochlorcyclizini Hydrochloridum. 1-(4-Chlorobenzhydryl)perhydro-4-methyl-1,4-diazepine dihydrochloride.

Гомохлорциклизина Гидрохлорид

$C_{19}H_{23}ClN_2,2HCl$ = 387.8.

CAS — 848-53-3 (homochlorcyclizine); 1982-36-1 (homochlorcyclizine hydrochloride).



(homochlorcyclizine)

Pharmacopoeias. In *Jpn.*

Profile

Homochlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p.561) with antimuscarinic and moderate sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria (p.565) and rhinitis (p.565), and in pruritic skin disorders (p.565). It is given in oral doses of 10 to 20 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Homoclomin; ***Indon.:*** Homoclomin; ***Jpn:*** Homoclomin; ***Thai.:*** Homoclomin.

Hydroxyzine *(BAN, rINN)*

Hidroxizina; Hydroksitsiini; Hydroxizin; Hydroxyzinum. (*RS*)-2-{2-[4-(*p*-Chloro-α-phenylbenzyl)piperazin-1-yl]ethoxy}ethanol.

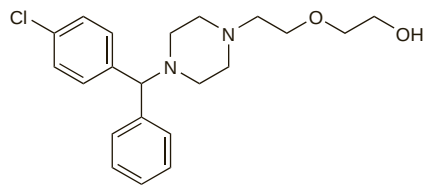
Гидроксизин

$C_{21}H_{27}ClN_2O_2$ = 374.9.

CAS — 68-88-2.

ATC — N05BB01.

ATC Vet — QN05BB01.



Hydroxyzine Embonate *(BANM, rINNM)*

Embonato de hidroxizina; Hydroxyzine, Embonate d'; Hydroxyzine Pamoate; Hydroxyzini Embonas; Pamoato de hidroxizina. 2-{2-[4-(4-Chlorobenzhydryl)piperazin-1-yl]ethoxy}ethanol 4,4′-methylenebis(3-hydroxy-2-naphthoate).

Гидроксизина Эмбонат

$C_{21}H_{27}ClN_2O_2,C_{23}H_{16}O_6$ = 763.3.

CAS — 10246-75-0.

ATC — N05BB01.

ATC Vet — QN05BB01.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Hydroxyzine Pamoate). A light yellow, practically odourless powder. Soluble 1 in more than 1000 of water, of chloroform, and of ether, 1 in 700 of alcohol, 1 in 10 of dimethylformamide, and 1 in 3.5 of 10M sodium hydroxide solution; practically insoluble in methyl alcohol. Store in airtight containers.

Hydroxyzine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidroxizina; Hidroksizin Hidroklorür; Hidroksizino hidrochloridas; Hydroxizin-hidroklorid; Hydroksitsiinihydrokloridi; Hydroxizinhydrokloríd; Hydroxyzin dihydrochlorid; Hydroxyzine, chlorhydrate d'; Hydroxyzini Dihydrochloridum; Hydroxyzini hydrochloridum.

Гидроксизина Гидрохлорид

$C_{21}H_{27}ClN_2O_2,2HCl$ = 447.8.

CAS — 2192-20-3.

ATC — N05BB01.

ATC Vet — QN05BB01.

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

Ph. Eur. 6.2 (Hydroxyzine Hydrochloride). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in acetone. Store in airtight containers. Protect from light.

USP 31 (Hydroxyzine Hydrochloride). A white, odourless, powder. Soluble 1 in 1 of water, 1 in 4.5 of alcohol, and 1 in 13 of chloroform; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Incompatibility. Hydroxyzine hydrochloride has been reported to be incompatible with aminophylline, benzylpenicillin salts, chloramphenicol sodium succinate, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), thioridazine, and some soluble barbiturates.

Stability. A mixture of hydroxyzine hydrochloride, chlorpromazine hydrochloride, and pethidine hydrochloride stored in glass or plastic syringes was found[1] to be stable for 366 days at 4° and 25°.

1. Conklin CA, *et al.* Stability of an analgesic-sedative combination in glass and plastic single-dose syringes. *Am J Hosp Pharm* 1985; **42:** 339–42.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Intramuscular injection of hydroxyzine has been reported to cause marked local discomfort. Intravenous use has been associated with haemolysis.

Amputation. Accidental intra-arterial injection of hydroxyzine has led to necrosis of the extremity requiring amputation of the digits of the affected limb.[1]

1. Hardesty WH. Inadvertent intra-arterial injection. *JAMA* 1970; **213:** 872.

Arrhythmias. ECG abnormalities, particularly alterations in T-waves, were associated with anxiolytic doses of hydroxyzine hydrochloride and were similar to those produced by thioridazine and tricyclic antidepressants.[1]

1. Hollister LE. Hydroxyzine hydrochloride: possible adverse cardiac interactions. *Psychopharmacol Comm* 1975; **1:** 61–5.

Effects on sexual function. A 32-year-old man had prolonged penile erections (priapism) after taking two separate doses of hydroxyzine for a skin rash.[1] It was suggested that the effect might be due to a hydroxyzine metabolite that was found to be structurally similar to a metabolite of trazodone, a drug known to induce penile erections.

1. Thavundayil JX. *et al.* Prolonged penile erections induced by hydroxyzine: possible mechanism of action. *Neuropsychobiology* 1994; **30:** 4–6.

Effects on the skin. Four children given hydroxyzine hydrochloride for restlessness developed a fixed drug eruption of the penis.[1] All recovered on drug withdrawal and subsequently had positive rechallenges.

1. Cohen HA, *et al.* Fixed drug eruption of the penis due to hydroxyzine hydrochloride. *Ann Pharmacother* 1997; **31:** 327–9.

Liver disorders. A study[1] has suggested that hydroxyzine should only be given once daily for the relief of pruritus in patients with primary biliary cirrhosis. The mean serum elimination half-lives of hydroxyzine and its metabolite cetirizine in 8 patients with primary biliary cirrhosis were 36.6 and 25.0 hours respectively.

1. Simons FER, *et al.* The pharmacokinetics and pharmacodynamics of hydroxyzine in patients with primary biliary cirrhosis. *J Clin Pharmacol* 1989; **29:** 809–15.

Porphyria. Hydroxyzine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Hydroxyzine is rapidly absorbed from the gastrointestinal tract and is metabolised. Metabolites include cetirizine (p.570), which has antihistaminic activity. An elimination half-life of about 20 hours has been reported.

◊ References.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.

Liver disorders. For reference to a prolonged half-life of hydroxyzine in patients with primary biliary cirrhosis, see under Adverse Effects and Precautions, above.

Uses and Administration

Hydroxyzine, a piperazine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an antiemetic. Its main use is as an anxiolytic (p.952) but see Anxiety Disorders below. It is also used as an adjunct to pre- and postoperative medication (see Anaesthesia, p.563) and in the management of pruritus (p.565) and urticaria (p.565) and has been used as an adjunct to opioid analgesia in the management of cancer pain (p.5).

Hydroxyzine may be given orally as the hydrochloride or the embonate; doses are expressed in terms of the hydrochloride. Hydroxyzine embonate 170 mg is equivalent to about 100 mg of hydroxyzine hydrochloride.

The usual oral doses in adults are: 50 to 100 mg four times daily for the short-term management of anxiety; for pruritus an initial dose of 25 mg given at night, increased if necessary to 25 mg three or four times daily; and 50 to 100 mg for pre- or postoperative sedation. For pruritus in children over 6 years of age the initial dose is 15 to 25 mg daily increased if necessary to 50 to 100 mg daily in divided doses; for children 6 months to 6 years old the initial dose is 5 to 15 mg daily increased if necessary to 50 mg daily in divided doses.

Alternatively, 1 mg/kg daily may be given in divided doses, to a maximum of 2.5 mg/kg daily in children aged 1 to 6 years, and to a maximum of 2 mg/kg daily in those aged 6 years and over. The pre- or postoperative sedative dose in children is 600 micrograms/kg. Dosage should be reduced in patients with hepatic or renal impairment, see below.

Hydroxyzine hydrochloride may also be given by deep intramuscular injection. For prompt control of anxiety or agitation in adults 50 to 100 mg is injected intramuscularly initially, and the dose may be repeated every four to six hours as required. For other indications when oral dosage is not practical, the intramuscular dose is 25 to 100 mg for adults and 1.1 mg/kg for children. Hydroxyzine should not be given by intravenous injection since haemolysis may result.

Administration in hepatic or renal impairment. In patients with hepatic impairment, UK licensed product information recommends a 33% reduction in the total oral daily dose of hydroxyzine. In patients with moderate or severe renal impairment, a dose reduction of 50% is recommended.

Anxiety disorders. Although hydroxyzine is used in the management of anxiety, there is little evidence to support its efficacy in anxious patients,[1] and the *BNF* considers that use of antihistamines solely for their sedative effect in anxiety is not appropriate.

1. Ballenger JC, *et al.* Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2001; **62** (suppl 11): 53–8. Available at: http://www.psychiatrist.com/private/supplenet/v62s11/v62s1108.pdf (accessed 15/08/08)

Preparations

USP 31: Hydroxyzine Hydrochloride Injection; Hydroxyzine Hydrochloride Syrup; Hydroxyzine Hydrochloride Tablets; Hydroxyzine Pamoate Capsules; Hydroxyzine Pamoate Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Ataraxone; Hidroxina†; Hyderax; ***Austria:*** Atarax; ***Belg.:*** Atarax; ***Braz.:*** Hixizine; Prurizin; ***Canad.:*** Atarax; ***Chile:*** Dalun; Fasarax; Nexit†; ***Cz.:*** Atarax; ***Denm.:*** Atarax; ***Fin.:*** Atarax; ***Fr.:*** Atarax; ***Ger.:*** AH 3 N; Atarax; Elroquil N; ***Gr.:*** Atarax; Iremofar; ***Hong Kong:*** Atarax; Qualidrozine; ***Hung.:*** Atarax; ***India:*** Atarax; ***Indon.:*** Bestalin; Iterax; ***Israel:*** Otarex; ***Ital.:*** Atarax; ***Malaysia:*** Atarax; ***Mex.:*** Atarax; ***Neth.:*** Atarax; Navicalm†; ***Norw.:*** Atarax; ***NZ:*** Serecid; ***Philipp.:*** Iterax; ***Pol.:*** Atarax; ***Port.:*** Atarax; Coraphene; ***Rus.:*** Atarax (Атаракс); ***S.Afr.:*** Aterax; Neurax; ***Singapore:*** Atarax; Hizin; Phymorax†; ***Spain:*** Atarax; ***Swed.:*** Atarax; ***Switz.:*** Atarax; ***Thai.:*** Abacus; Allerax; Antizine; Atano; Atarax; Cerax; Darax†; Drazine; Hadarax; Histan; Hizin; Honsa; Hydroxin†; Katrax; Masarax†; Med-Xyzarax†; Polizine†; Postarax†; R-Rax; Taraxin; Trandrozine; Unamine; ***Turk.:*** Atarax; Validol; ***UK:*** Atarax; Ucerax; ***USA:*** Atarax†; Vistaril; Vistazine†.

Multi-ingredient: ***Austria:*** Diligan; ***Braz.:*** Marax; ***Ger.:*** Diligan†; ***India:*** Marax; ***Port.:*** Diligan†; Vesparax†; ***S.Afr.:*** Geratar; ***Spain:*** Calmoplex; Dolodens; ***USA:*** Hydrophed; Marax; Theomax DF; ***Venez.:*** Marax†.

Isothipendyl Hydrochloride *(BANM, rINNM)*

Hidrocloruro de isotipendil; Isothipendyl, Chlorhydrate d'; Isothipendyli Hydrochloridum. *NN*-Dimethyl-1-(pyrido[3,2-*b*][1,4]benzothiazin-10-ylmethyl)ethylamine hydrochloride.

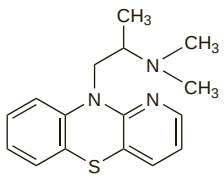
Изотипендила Гидрохлорид

$C_{16}H_{19}N_3S,HCl$ = 321.9.

CAS — 482-15-5 (isothipendyl); 1225-60-1 (isothipendyl hydrochloride).

ATC — D04AA22; R06AD09.

ATC Vet — QD04AA22; QR06AD09.



(isothipendyl)

Profile

Isothipendyl hydrochloride, an azaphenothiazine derivative, is an antihistamine (p.561) that has been applied topically for hypersensitivity and pruritic skin disorders although as with any antihistamine there is a risk of sensitisation. It has also been given orally and by the rectal route.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Actapront; ***Braz.:*** Andantol; ***Fr.:*** Sedermyl; ***Indon.:*** Andantol; ***Israel:*** Thiodantol; ***Ital.:*** Calmogel; ***Mex.:*** Andantol.

Ketotifen Fumarate *(BANM, USAN, rINNM)*

Fumarato de ketotifeno; HC-20511 (ketotifen); Ketotifeenivetyfumaraatti; Ketotifen Hydrogen Fumarate; Kétotifène, Fumarate de; Kétotifène, hydrogénofumarate de; Ketotifen-fumarát; Ketotifén-hidrogén-fumarát; Ketotifeni Fumaras; Ketotifeni hydrogenofumaras; Ketotifeno-vandenilio fumaratas; Ketotifenvätefumarat. 4-(1-Methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophen-10(9*H*)-one hydrogen fumarate.

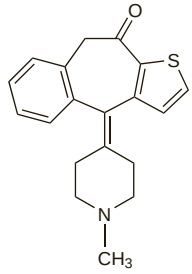
Кетотифена Фумарат

$C_{19}H_{19}NOS,C_4H_4O_4$ = 425.5.

CAS — 34580-13-7 (ketotifen); 34580-14-8 (ketotifen fumarate).

ATC — R06AX17; S01GX08.

ATC Vet — QR06AX17; QS01GX08.



(ketotifen)

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

Ph. Eur. 6.2 (Ketotifen Hydrogen Fumarate; Ketotifen Fumarate BP 2008). A white to brownish-yellow, fine crystalline powder. Sparingly soluble in water; very slightly soluble in acetonitrile; slightly soluble in methyl alcohol.

Adverse Effects and Precautions

As for the antihistamines in general, p.561; drowsiness may be a problem, and dry mouth and dizziness may occur at the beginning of treatment but usually resolve with continued use. Weight gain and CNS stimulation have been reported. Isolated cases of severe skin reactions, cystitis, and hepatitis have been reported. Irritation, pain, and punctate keratitis are commonly reported after topical application to the eye.

For precautions to be observed in asthmatic patients, see Sodium Cromoglicate, p.1136. Ketotifen may take several weeks to exert its full effect; existing anti-asthma treatment should not be abruptly withdrawn after starting ketotifen therapy. It should not be used for the treatment of acute asthma attacks.

Overdosage. Overdoses of ketotifen ranging from 10 to 120 mg were reported in 8 patients.[1] Symptoms included drowsiness, confusion, dyspnoea, bradycardia or tachycardia, disorientation, and convulsions. Gastric lavage was performed in 6 patients, and all 8 recovered within 12 hours after supportive treatment.

In an overview of 21 cases of overdosage (including those reported above) the manufacturers stated that no serious signs or symptoms had been reported with doses below 20 mg, and there had been no fatalities.[2] The most serious effects reported had included unconsciousness, convulsions, bradycardia and tachycardia, and a severe hypotensive reaction. Management is essentially supportive and symptomatic.

1. Jefferys DB, Volans GN. Ketotifen overdose: surveillance of the toxicity of a new drug. *BMJ* 1981; **282:** 1755–6.
2. Le Blaye I, *et al.* Acute ketotifen overdosage: a review of present clinical experience. *Drug Safety* 1992; **7:** 387–92.

Interactions

As for the sedating antihistamines in general, p.563.

A reversible fall in the platelet count has been seen in a few patients receiving ketotifen with oral antidiabetics and it has been suggested that this combination should therefore be avoided.

Pharmacokinetics

Ketotifen fumarate is almost completely absorbed from the gastrointestinal tract after oral doses, but bioavailability is reported to be only about 50% due to hepatic first-pass metabolism. Peak plasma concentrations occur 2 to 4 hours after an oral dose. It is mainly excreted in the urine as inactive metabolites with a small amount of unchanged drug; the terminal elimination half-life is about 21 hours.

Uses and Administration

Ketotifen is a sedating antihistamine (p.563) that also has a stabilising action on mast cells analogous to that of sodium cromoglicate (p.1137). It is used in the treatment of allergic conditions such as rhinitis (p.565) and conjunctivitis (p.564). Ketotifen has also been used in the prophylactic management of asthma, when it may take several weeks to exert its full effect; it should not be used to treat acute asthma attacks.

Ketotifen is given as the fumarate, but doses are expressed in terms of the base; ketotifen fumarate 1.38 mg is equivalent to about 1 mg of ketotifen.

Ketotifen fumarate is taken in oral doses equivalent to 1 mg of ketotifen twice daily with food, increased if necessary to 2 mg twice daily; 0.5 to 1 mg at night may be preferable for the first few days of treatment if drowsiness is likely to be a problem.

Ketotifen fumarate has also been applied topically, as eye drops equivalent to 0.025% ketotifen, used twice daily.

For children's doses, see below.

Action. It has been suggested that the anti-allergic action of ketotifen was independent of its antihistaminic properties.[1] This might be due to its effect on responses to platelet-activating factor (PAF).[2] However, the significance of PAF in the pathogenesis of asthma has been questioned.

1. Greenwood C. The pharmacology of ketotifen. *Chest* 1982; **82** (suppl): 45S–8S.
2. Morley J, *et al.* Effects of ketotifen upon responses to platelet activating factor: a basis for asthma prophylaxis. *Ann Allergy* 1986; **56:** 335–40.

Administration in children. Ketotifen fumarate can be given to children for the treatment of allergic conditions such as rhinitis (p.565) or conjunctivitis (p.564), and has been used in the prophylactic management of asthma. Oral doses equivalent to 1 mg of ketotifen twice daily with food may be used from 3 years of age. A dose equivalent to 500 micrograms ketotifen twice daily has been suggested in children between 6 months and 3 years of age.

Ketotifen fumarate has also been applied topically twice daily, as eye drops equivalent to 0.025% ketotifen, in children from 3 years of age.

Asthma. Results of studies on the effectiveness of ketotifen in the treatment of asthma (p.1108) have been conflicting; although some have found it effective in reducing symptoms[1-4] and in enabling a reduction in use of other anti-asthmatic drugs,[2,4] others have reported no significant benefits,[5,6] and UK guidelines on the management of asthma consider ketotifen to be ineffective.[7] A systematic review[8] found that it was of benefit in improving control of asthma and wheezing in children with mild to moderate disease, but noted that the high prevalence of atopy in several of the studies reviewed meant that the results might not be generalisable to children with asthma in general. A study in children described as 'preasthmatic' (that is, being at high risk of developing asthma) suggested that long-term therapy with ketotifen decreased the risk of asthma onset.[9]

1. Paterson JW, *et al.* Evaluation of ketotifen (HC20-511) in bronchial asthma. *Eur J Clin Pharmacol* 1983; **25:** 187–93.
2. Tinkelman DG, *et al.* A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma. *J Allergy Clin Immunol* 1985; **76:** 487–97.
3. Miraglia Del Giudice M, *et al.* Study of the efficacy of ketotifen treatment in asthmatic children under 3 years of age. *Curr Ther Res* 1986; **40:** 685–93.
4. Rackham A, *et al.* A Canadian multicenter study with Zaditen (ketotifen) in the treatment of bronchial asthma in children aged 5 to 17 years. *J Allergy Clin Immunol* 1989; **84:** 286–96.
5. White MP, *et al.* Ketotifen in the young asthmatic—a double-blind placebo-controlled trial. *J Int Med Res* 1988; **16:** 107–13.
6. Volovitz B, *et al.* Efficacy and safety of ketotifen in young children with asthma. *J Allergy Clin Immunol* 1988; **81:** 526–30.
7. Scottish Intercollegiate Guidelines Network/British Thoracic Society. British guideline on the management of asthma: a national clinical guideline. Revised edition May 2008. Available at: http://www.sign.ac.uk/pdf/sign101.pdf (accessed 23/06/08)
8. Bassler D, *et al.* Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).
9. Bustos GJ, *et al.* Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995; **25:** 568–73.

Conjunctivitis. References.

1. Martín AP, *et al.* The effect of ketotifen on inflammatory markers in allergic conjunctivitis: an open, uncontrolled study. *BMC Ophthalmol* 2003; **3:** 2. Available at: http://www.biomedcentral.com/1471-2415/3/2 (accessed 14/04/08)
2. Kidd M, *et al.* Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *Br J Ophthalmol* 2003; **87:** 1206–11.
3. Ganz M, *et al.* Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Therapy* 2003; **20:** 79–91.
4. Abelson MB, *et al.* Efficacy and safety of single- and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population. *Pediatr Allergy Immunol* 2004; **15:** 551–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Antilerg; Bilozen; Biomira; Ketocev; Ketokid†; Respimex; Zaditen; ***Austral.:*** Zaditen; ***Austria:*** Ketotisan; Zaditen; ***Belg.:*** Zaditen; ***Braz.:*** Asdron; Asmalergin; Asmanon; Asmax; Asmen; Asmifen; Asmofen; Biatos; Broncoten†; Profilasmim-Ped†; Uni Cetotifen†; Zaditen; Zetitec†; ***Canad.:*** Zaditen; Zaditor; ***Chile:*** Ketotisin; Oftaler; Zaditen; ***Cz.:*** Ketof; Zaditen; ***Denm.:*** Zaditen; ***Fin.:*** Zaditen; ***Fr.:*** Zaditen; ***Ger.:*** Astifat†; Ketof; Padiatifen†; Zaditen; Zatofug†; ***Gr.:*** Dovidin; Ecradin; Eucycline; Fental; Frenasma; Isocaren; K-Drops; Kathricol; Klevistamin; Labelphen; Lavoptik; Nostimex†; Noxtor; Orpidix; Pellexeme; Urpem; Zaditen; Zeoklamin; Zethrinal; Zidofen; ***Hong Kong:*** Amitone; Asmafen; Asmaten; Astifen; Dhatifen; Ketifen; Vidatifen; Zaditen; ***Hung.:*** Zaditen; ***India:*** Ketasma; ***Indon.:*** Astifen; Intifen; Nortifen; Prevas; Profilas; Scanditen; Zaditen; ***Irl.:*** Zaditen; ***Israel:*** Profiten; Zaditen; ***Ital.:*** Alleal; Allerket; Bentifen; Chetofen; Ketoftil; Sosefen; Stamifen; Zaditen; ***Malaysia:*** Asmafen; Asumalife; Denerel; Dhatifen; Ketifen; Licoften; Xidanef†; Zaden†; Zaditen; ***Mex.:*** Asmaral-K; Biotifen; Cantel; Kasmal; Kedrop; Keraffler; Ketaxal†; Nemodine; Nomotec; Osaten; Pretifen; Saluket-H1; Ventisol; Zaditen; ***Neth.:*** Bentifen; Zaditen; ***Norw.:*** Zaditen;