

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<sup>5,6</sup> but a subsequent study<sup>7</sup> in 12 children did not produce conclusive findings. A later long-term study<sup>8</sup> 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.

- Todd PA, Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; **38**: 481–99.
- Andersson K-E, Vinge E.  $\beta$ -Adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. *Drugs* 1990; **3**: 355–73.
- 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.
- 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.
- Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; **ii**: 579.
- Curatolo P, Cusmai R. Drugs for alternating hemiplegic migraine. *Lancet* 1984; **ii**: 980.
- Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics* 1987; **18**: 191–5.
- 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<sup>1</sup> involving 7 patients has suggested that flunarizine is more effective than placebo in the treatment of Tourette's syndrome (see Tics, p.954).

- 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:** Amaliun; Flunarium; Sibelium; **Belg.:** Flunarimed; Flunatorp; Kelamigra; Sibelium; **Braz.:** Flunarini; Fluvart; Fluzix; Sibelium; Vertigium; Vertix; **Canada:** Sibelium; **Chile:** Flerox; Fluxus; Imigor; Sibelium; Zentrulin; **Cz.:** Sibelium; **Denm.:** Sibelium; **Fr.:** Sibelium; **Ger.:** Flunavert; Natil-N; Sibelium; **Gr.:** Sibelium; **Hong Kong:** Fludan; Sibelium; **Hung.:** Sibelium; **India:** Migard; Nomigrain; **Indon.:** Bartolium; Cevadil; Degrium; Sibelium; Frego; Sibelium; Siberid; Silum; Sinral; Unaliun; Xepalium; **Irl.:** Sibelium; **Ital.:** Flugler; Flunagen; Fluxarten; Gradient; Issium; Sibelium; Vasculene; **Malaysia:** Fludan; Forknow; Migard; Sibelium; **Mex.:** Axilin; Fasolan; Nafury; Sibelium; **Neth.:** Sibelium; **Philipp.:** Sibelium; **Port.:** Sibelium; Vasiliun; Zinasen; **S.Afr.:** Sibelium; **Singapore:** Forknow; Nanzine†; Sibelium†; **Spain:** Flerudin; Flurpax; Sibelium; **Switz.:** Sibelium; **Thal.:** Cedelate†; Finelium†; Floxin; Fludan; Flulium; Flunarium; Flunaza†; Flunazine†; Fluricin; Hexilium; Liberal; Medilium; Poli-Flunarini; Seabell†; Sibelium; Simoyiam; Sobelin; Vanid; Vertilium; Zelum; **Turk.:** Sibelium; **Venez.:** Fludil; Sibelium.

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

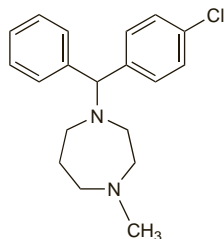
## Homochlorcyclizine Hydrochloride (BANM, rINNM)

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

Гомохлорциклизина Гидрохлорид

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

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



(homochlorcyclizine)

**Pharmacopoeias.** In *Jpn.*

The symbol † denotes a preparation no longer actively marketed

## 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:** Homocloamin; **Indon.:** Homocloamin; **Jpn.:** Homocloamin; **Thal.:** Homocloamin.

## Hydroxyzine (BAN, rINN)

Hidroksizina; Hidroksizini; Hydroxyzin; Hydroxyzinum. (R<sub>S</sub>)-2-[2-[4-(p-Chloro- $\alpha$ -phenylbenzyl)]piperazin-1-yl]ethoxyethanol.

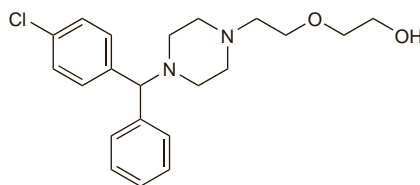
Гидроксизин

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

CAS — 68-88-2.

ATC — N05BB01.

ATC Vet — QN05BB01.



## Hydroxyzine Embonate (BANM, rINNM)

Embonato de hidroksizina; Hydroxyzine, Embonate d'; Hydroxyzine Pamoate; Hydroksizini Embonas; Pamoato de hidroksizina. 2-[2-[4-(4-Chlorobenzhydryl)]piperazin-1-yl]ethoxyethanol 4,4'-methylenebis(3-hydroxy-2-naphthoate).

Гидроксизина Эмбонат

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

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 hidroksizina; Hidroksizin Hidroklorür; Hidroksizino hidrokloridas; Hidroksizin-hidroklorid; Hidroksizinihidroklorid; Hydroksizinihydrochlorid; Hydroksizinihydrochlorid; Hydroksizini dihydrochlorid; Hydroxyzine, chlorhydrate d'; Hydroksizini Dihydrochloridum; Hydroksizini hydrochloridum.

Гидроксизина Гидрохлорид

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

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<sup>1</sup> to be stable for 366 days at 4° and 25°.

- 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.<sup>1</sup>

- 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.<sup>1</sup>

- 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.<sup>1</sup> 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.

- 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.<sup>1</sup> All recovered on drug withdrawal and subsequently had positive rechallenges.

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

**Liver disorders.** A study<sup>1</sup> 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.

- 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.

- Paton DM, Webster DR. Clinical pharmacokinetics of H<sub>1</sub>-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.