nol; Syndol; Tensopyn; Vicks Medinite; Xerotens†; ***Spain:*** Cariban; Medinait; Vicks Medinait†; ***Switz.:*** Vicks Medinait; ***Turk.:*** Vicks MediNait; ***UK:*** Painex; Propain Plus; Syndol; Vicks Medinite; ***USA:*** Alka-Seltzer Plus Night-Time Cold; All-Nite Cold Formula; Genite; Night Time Cold/Flu Relief; Nite Time Cold Formula; NyQuil Hot Therapy; NyQuil Nighttime Cold/Flu; Nytcold Medicine; Vicks NyQuil LiquiCaps; Vicks NyQuil Multi-Symptom Cold Flu Relief; Vicks NyQuil Sinus; ***Venez.:*** Mercindol.

Ebastine *(BAN, USAN, rINN)*

Ebastiini; Ebastin; Ebastina; Ebastinas; Ébastine; Ebastinum; LAS-W-090; W-090. 4′-*tert*-Butyl-4-[4-(diphenylmethoxy)piperidino]butyrophenone.

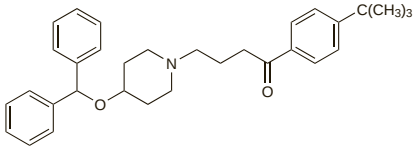
Эбастин

$C_{32}H_{39}NO_2$ = 469.7.

CAS — 90729-43-4.

ATC — R06AX22.

ATC Vet — QR06AX22.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Ebastine). A white or almost white crystalline powder. M.p. about 86°. Practically insoluble in water; very soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

Profile

Ebastine, a piperidine derivative, is a non-sedating antihistamine (p.561) with a long duration of action. It does not have significant sedative or antimuscarinic actions.

Ebastine is given for the symptomatic relief of allergic conditions including rhinitis (p.565) and in pruritic skin disorders (p.565). The usual oral dose is 10 to 20 mg daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

◊ References.

1. Luria X. Comparative clinical studies with ebastine: efficacy and tolerability. *Drug Safety* 1999; **21** (suppl 1): 63–7.
2. Hurst M, Spencer CM. Ebastine: an update of its use in allergic disorders. *Drugs* 2000; **59:** 981–1006.
3. Lasseter KC, *et al.* Pharmacokinetics and safety of ebastine in patients with impaired hepatic function compared with healthy volunteers: a phase I open-label study. *Clin Pharmacokinet* 2004; **43:** 121–9.
4. Noveck RJ, *et al.* Pharmacokinetics and safety of ebastine in healthy subjects and patients with renal impairment. *Clin Pharmacokinet* 2007; **46:** 525–34.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ebastel†; ***Belg.:*** Estivan; ***Braz.:*** Ebastel; ***Chile:*** Ebastel†; ***Cz.:*** Kestine†; ***Denm.:*** Kestine; ***Fin.:*** Kestine; ***Fr.:*** Kestin; ***Ger.:*** Ebastel; ***Gr.:*** Kestine; ***Hong Kong:*** Kestine; ***Ital.:*** Clever; Kestine; ***Jpn:*** Ebastel; ***Mex.:*** Evastel; ***Neth.:*** Kestine; Netan; ***Norw.:*** Kestine; ***Philipp.:*** Aleva; ***Port.:*** Estivan; Kestine; ***Rus.:*** Kestine (Кестин); ***S.Afr.:*** Kestine; ***Singapore:*** Kestine; ***Spain:*** Bactil; Busidril†; Ebastel; ***Swed.:*** Kestine; ***Venez.:*** Ebastel.

Multi-ingredient: ***Arg.:*** Ebastel D†; ***Braz.:*** Ebastel D; ***Mex.:*** Evastel-D; ***Spain:*** Rino Ebastel; Rinobactil.

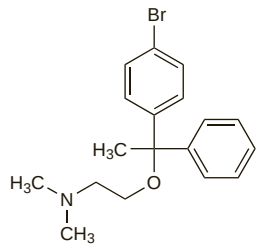
Embramine Hydrochloride *(BANM, rINNM)*

Embramine, Chlorhydrate d'; Embramini Hydrochloridum; Embraminium Chloratum; Hidrocloruro de embramina; Mebrophenhydramine Hydrochloride; Mebrophenhydraminium Chloratum. 2-(4-Bromo-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

Эмбрамина Гидрохлорид

$C_{18}H_{22}BrNO,HCl$ = 384.7.

CAS — 3565-72-8 (embramine); 13977-28-1 (embramine hydrochloride); 21661-63-2 (embramine teoclate).



(embramine)

Profile

Embramine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p.561). Embramine hydrochloride and embramine teoclate have been given orally for their antihistamine and antiemetic properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Medrin; ***India:*** Mebryl.

Emedastine Fumarate *(BANM, rINNM)*

AL-3432A; Emedastiinidifumaraatti; Emedastin difumarát; Emedastin Fumarat; Emedastindifumarat; Emedastine Difumarate *(USAN)*; Émédastine, difumarate d'; Émédastine, Fumarate d'; Emedastini difumaras; Emedastini Fumaras; Emedastyny difumaran; Fumarato de emedastina; KB-2413; KG-2413; LY-188695. 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)benzimidazole fumarate (1:2).

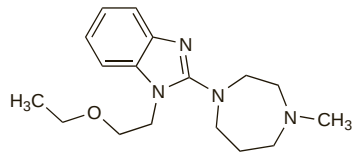
Эмедастина Фумарат

$C_{17}H_{26}N_4O,2C_4H_4O_4$ = 534.6.

CAS — 87233-61-2 (emedastine); 87233-62-3 (emedastine fumarate).

ATC — S01GX06.

ATC Vet — QS01GX06.



(emedastine)

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

Ph. Eur. 6.2 (Emedastine Difumarate). A white or yellowish powder. It exhibits polymorphism. Soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 0.2% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 31 (Emedastine Difumarate). A white to faintly yellow crystalline powder. Soluble in water. pH of a 0.2% solution in water is between 3.0 and 4.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the antihistamines in general, p.561.

Ocular corneal infiltrates, local irritation, photophobia, rhinitis, and headaches have been reported after use of emedastine eye drops. Treatment should be stopped if corneal infiltrates develop.

Pharmacokinetics

Emedastine is absorbed from the gastrointestinal tract, peak plasma concentrations being attained about 3 hours after an oral dose. It is mainly metabolised in the liver to two primary metabolites 5- and 6-hydroxyemedastine which are excreted in the urine along with a small amount of unchanged drug. Small amounts of emedastine are absorbed after application to the eye. The elimination half-life is reported to be 7 hours after an oral dose and 10 hours following topical use.

Uses and Administration

Emedastine is an antihistamine. It is instilled twice daily as the fumarate as eye drops containing the equivalent of 0.05% of emedastine for the symptomatic relief of allergic conjunctivitis (p.564). It is also given orally in usual doses of 2 to 4 mg of the fumarate daily in two divided doses for allergic rhinitis (p.565), urticaria (p.565), and pruritic skin disorders (p.565).

Preparations

USP 31: Emedastine Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Austria: Emadine; ***Belg.:*** Emadine; ***Braz.:*** Emadine; ***Canad.:*** Emadine; ***Cz.:*** Emadine; ***Denm.:*** Emadine; ***Fin.:*** Emadine; ***Fr.:*** Emadine; ***Ger.:*** Emadine; ***Gr.:*** Emadine; ***Hong Kong:*** Emadine; ***Hung.:*** Emadine; ***Irl.:*** Emadine; ***Israel:*** Emadine; ***Ital.:*** Emadine; ***Jpn:*** Daren; Remicut; ***Malaysia:*** Emadine; ***Neth.:*** Emadine; ***Norw.:*** Emadine; ***Pol.:*** Emadine; ***Port.:*** Emadine; ***S.Afr.:*** Emadine; ***Spain:*** Emadine; ***Swed.:*** Emadine; ***Switz.:*** Emadine; ***Thai.:*** Emadine; ***Turk.:*** Emadine; ***UK:*** Emadine; ***USA:*** Emadine.

Epinastine Hydrochloride *(rINNM)*

Épinastine, Chlorhydrate d'; Epinastine, chlorhydrate d'; Epinastini hydrochloridum; Hidrocloruro de epinastina; WAL-801-Cl. 3-Amino-9,13b-dihydro-1*H*-dibenz[*c,f*]imidazo[1,5-*a*]azepine hydrochloride.

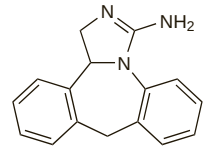
Эпинастина Гидрохлорид

$C_{16}H_{15}N_3,HCl$ = 285.8.

CAS — 80012-43-7 (epinastine).

ATC — R06AX24; S01GX10.

ATC Vet — QR06AX24; QS01GX10.



(epinastine)

Profile

Epinastine hydrochloride is an antihistamine (p.561) reported to have no significant sedative activity. It has been given orally in the management of allergic rhinitis and pruritic skin disorders. It is also used twice daily as eye drops, usually in a concentration of 0.05%, in the symptomatic relief of allergic conjunctivitis.

◊ References.

1. Sarashina A, *et al.* Population pharmacokinetics of epinastine, a histamine H receptor antagonist, in adults and children. *Br J Clin Pharmacol* 2005; **59:** 43–53.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Alket; Flurinol; ***Belg.:*** Relestat; ***Braz.:*** Talerc; ***Chile:*** Flurinol; ***Cz.:*** Purivist; ***Fr.:*** Purivist; ***Ger.:*** Relestat; ***Gr.:*** Relestat; ***Hung.:*** Relestat; ***Irl.:*** Relestat; ***Ital.:*** Relestat; ***Jpn:*** Alesion; ***Mex.:*** Flurinol; ***Neth.:*** Relestat; ***Pol.:*** Relestat; ***Port.:*** Relestat; ***Spain:*** Relestat; ***Swed.:*** Relestat; ***Switz.:*** Relestat; ***UK:*** Relestat; ***USA:*** Elestat; ***Venez.:*** Flurinol.

Multi-ingredient: ***Arg.:*** Flurinol D; ***Mex.:*** Flurinol D.

Fexofenadine Hydrochloride

(BANM, USAN, rINNM)

Feksofenadiinihydrokloridi; Feksofenadin Hidroklorür; Fexofénadine, chlorhydrate de; Fexofenadinhydroklorid; Fexofenadini hydrochloridum; Hidrocloruro de fexofenadina; MDL-16455A; Terfenadine Carboxylate Hydrochloride. (±)-*p*-{1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-piperidino]butyl}-α-methylhydratropic acid hydrochloride.

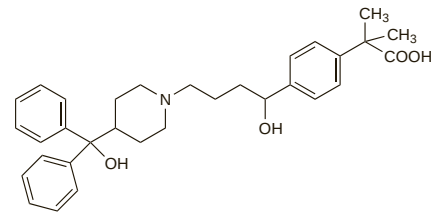
Фексофенадина Гидрохлорид

$C_{32}H_{39}NO_4,HCl$ = 538.1.

CAS — 138452-21-8.

ATC — R06AX26.

ATC Vet — QR06AX26.



(fexofenadine)

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

Ph. Eur. 6.2 (Fexofenadine Hydrochloride). A white or almost white powder. Slightly soluble in water; freely soluble in methyl alcohol; very slightly soluble in acetone. It exhibits polymorphism.

USP 31 (Fexofenadine Hydrochloride). Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

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

Arrhythmias. A 67-year-old man suffered syncope after taking fexofenadine 180 mg daily for 2 months.[1] His ECG showed an abnormally prolonged QT interval which shortened once fexofenadine was stopped, although the interval tended to be long even without drug therapy. Nonetheless rechallenge was positive. The manufacturers of fexofenadine have commented[2] that the patient was at risk of developing arrhythmias before taking the drug.

The ECG effects of fexofenadine have been studied[3] in normal subjects and doses of up to 480 mg daily [4 times the recommended dose for seasonal allergic rhinitis] did not prolong the QT interval. See also p.562.

1. Pinto YM, *et al.* QT lengthening and life-threatening arrhythmias as associated with fexofenadine. *Lancet* 1999; **353:** 980.
2. Giraud T. QT lengthening and arrhythmias associated with fexofenadine. *Lancet* 1999; **353:** 2072.
3. Pratt CM, *et al.* Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999; **83:** 1451–4.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving fexofenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

See also under Adverse Effects and Precautions, in Terfenadine, p.590.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Psoriasis. Exacerbation of psoriasis has been reported[1] in association with the use of fexofenadine.

1. Saraswat A, Saraswat M. Pustular exacerbation of psoriasis due to fexofenadine. *Clin Exp Dermatol* 2006; **31:** 477–8.

Interactions

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

Plasma concentrations of fexofenadine have been increased when given with erythromycin or ketoconazole, but, unlike terfenadine, licensed product information states that this was not associated with adverse effects on the QT interval.

Antacids containing aluminium and magnesium hydroxide have reduced the absorption of fexofenadine. Fruit juices including grapefruit may reduce the bioavailability of fexofenadine and use together should be avoided.

◊ References.

1. Dresser GK, *et al.* Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* 2005; **77:** 170–7.

Pharmacokinetics

Fexofenadine is rapidly absorbed after oral doses with peak plasma concentrations being reached in 2 to 3 hours. It is about 60 to 70% bound to plasma proteins. About 5% of the total dose is metabolised, mostly by the intestinal mucosa, with only 0.5 to 1.5% of the dose undergoing hepatic biotransformation by the cytochrome P450 system. Elimination half-life of about 14 hours has been reported although this may be prolonged in patients with renal impairment. Excretion is mainly in the faeces with only 10% being present in the urine. Fexofenadine does not appear to cross the blood-brain barrier.

Fexofenadine is a metabolite of terfenadine and as such has been detected in breast milk after the administration of terfenadine.

◊ References.

1. Russell T, *et al.* Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. *Clin Pharmacol Ther* 1998; **64:** 612–21.

Uses and Administration

Fexofenadine, an active metabolite of terfenadine (p.590), is a non-sedating antihistamine. It does not possess significant sedative or antimuscarinic actions. Fexofenadine is used as the hydrochloride in the symptomatic relief of allergic conditions including seasonal allergic rhinitis (p.565) and chronic urticaria (p.565).

In the UK a dose of fexofenadine hydrochloride 120 mg once daily is given orally in the treatment of seasonal allergic rhinitis; the recommended dose in chronic idiopathic urticaria is 180 mg once daily. US licensed product information suggests a dose of 60 mg twice daily or 180 mg once daily for both indications.

Fexofenadine is also used with a decongestant such as pseudoephedrine hydrochloride.

For doses in children or in patients with renal impairment, see below.

◊ References.

1. Markham A, Wagstaff AJ. Fexofenadine. *Drugs* 1998; **55:** 269–74.
2. Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 2000; **59:** 301–21.
3. Kawashima M, *et al.* Review of fexofenadine in the treatment of chronic idiopathic urticaria. *Int J Dermatol* 2002; **41:** 701–6.
4. Meeves SG, Appajosyula S. [Aventis, USA]. Efficacy and safety profile of fexofenadine HCl: a unique therapeutic option in H1-receptor antagonist treatment. *J Allergy Clin Immunol* 2003; **112** (suppl): S69–S77.
5. Mansfield LE. Once-daily immediate-release fexofenadine and sustained-release pseudoephedrine combination: a new treatment option for allergic rhinitis. *Expert Opin Pharmacother* 2006; **7:** 941–51.

Administration in children. Fexofenadine hydrochloride is used in children for the treatment of seasonal allergic rhinitis in an oral dose of 30 mg twice daily; in the UK it is licensed for use in children aged 6 to 11 years whereas in the USA it may be used in children as young as 2 years.

In the USA, fexofenadine is also licensed for use in paediatric chronic idiopathic urticaria. The dose in children aged 6 months to less than 2 years is 15 mg twice daily; older children may be given 30 mg twice daily.

For suggested doses in children with renal impairment see below.

Administration in renal impairment. US licensed product information recommends that initial oral doses of fexofenadine hydrochloride in adults with renal impairment should be reduced to 60 mg once daily. In children with renal impairment, the initial dose should be reduced to 30 mg once daily in patients aged 2 to 11 years, and to 15 mg once daily in children aged 6 months to less than 2 years.

UK product information advises that fexofenadine should be given with caution to patients with renal impairment; however, it also states that dose adjustment is not considered to be necessary in such patients.

Preparations

USP 31: Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Fexofenadine Hydrochloride Capsules; Fexofenadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alerfedine; Allegra; Fexofen†; ***Austral.:*** Fexotabs; Telfast; Xergic; ***Austria:*** Telfast; ***Belg.:*** Telfast; ***Braz.:*** Allegra; Altiva; ***Canad.:*** Allegra; ***Chile:*** Aerodan; Alexia; Allegra; Fenax; ***Cz.:*** Afexil; Ewofex; Telfast; ***Denm.:*** Telfast; ***Fin.:*** Telfast; ***Fr.:*** Telfast; ***Ger.:*** Telfast; ***Hong Kong:*** Telfast; ***Hung.:*** Altiva; Telfast; ***India:*** Alermex†; Allegra; Fexigra; Fexofen; Fexova; Odifex; ***Indon.:*** Telfast; ***Irl.:*** Telfast; ***Israel:*** Telfast; ***Ital.:*** Kalicet†; Telfast; ***Malaysia:*** Telfast; ***Mex.:*** Allegra; ***Neth.:*** Telfast; ***Norw.:*** Telfast; ***NZ:*** Telfast; Xergic; ***Philipp.:*** Telfast; ***Pol.:*** Telfast; ***Port.:*** Telfast; ***Rus.:*** Fexadin (Фексадин); Telfast (Телфаст); ***S.Afr.:*** Telfast; ***Singapore:*** Telfast; ***Spain:*** Telfast; ***Swed.:*** Telfast; ***Switz.:*** Telfast; ***Thai.:*** Fenafex; Telfast; ***Turk.:*** Fexadyne; Fexofen; Telfast; ***UK:*** Telfast; ***USA:*** Allegra; ***Venez.:*** Allegra; Fexidine; Fexoril; Rinolast.

Multi-ingredient: ***Arg.:*** Alerfedine D; Allegra-D; ***Austral.:*** Telfast Decongestant; ***Braz.:*** Allegra-D; ***Canad.:*** Allegra-D; ***Chile:*** Alexia D; Allegra-D; ***Hong Kong:*** Telfast-D; ***Indon.:*** Telfast Plus; ***Malaysia:*** Altiva-D; Telfast-D; ***Mex.:*** Allegra-D; ***NZ:*** Telfast Decongestant†; ***Singapore:*** Telfast-D; ***USA:*** Allegra-D; ***Venez.:*** Allegra-D; Rinolast D.

Flunarizine Hydrochloride *(BANM, USAN, rINNM)*

Flunaritsiinidihydrokloridi; Flunarizin-dihydrochlorid; Flunarizindihydroklorid; Flunarizine, Chlorhydrate de; Flunarizine, dichlorhydrate de; Flunarizini dihydrochloridum; Flunarizini Hydrochloridum; Flunarizino dihidrochloridas; Hidrocloruro de flunarizina; R-14950. *trans*-1-Cinnamyl-4-(4,4′-difluorobenzhydryl)piperazine dihydrochloride.

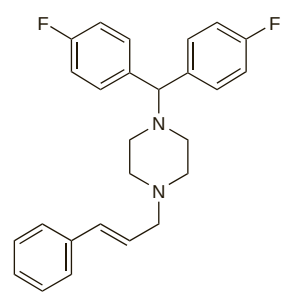
Флунаризина Гидрохлорид

$C_{26}H_{26}F_2N_2.2HCl = 477.4$.

CAS — 52468-60-7 (flunarizine); 30484-77-6 (flunarizine hydrochloride).

ATC — N07CA03.

ATC Vet — QN07CA03.



(flunarizine)

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

Ph. Eur. 6.2 (Flunarizine Dihydrochloride). A white or almost white hygroscopic powder. Slightly soluble in water, in alcohol, and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Adverse effects also seen with flunarizine include weight gain, extrapyramidal symptoms (sometimes associated with depression), and, rarely, galactorrhoea.

Extrapyramidal disorders. Extrapyramidal motor signs (including parkinsonism, orofacial tardive dyskinesia, and akathisia) have been reported in 12 patients given flunarizine 10 to 40 mg daily for between 3 weeks and 15 months; 11 also had mental depression.[1] Partial or complete improvement of symptoms occurred after withdrawal of flunarizine. There have been other reports of similar effects,[2-5] but the association with flunarizine has not always been certain. Some workers have commented that flunarizine is often used in patients at increased risk of depression (migraine and geriatric patients) or extrapyramidal symptoms (geriatric patients)[2,6] or that flunarizine may unmask subclinical idiopathic Parkinson's disease.[6,7]

Extrapyramidal signs, including parkinsonism, have also been associated with the related drug, cinnarizine.[3-5] It has been suggested that such effects may be less likely to occur with cinnarizine than with flunarizine because of its shorter half-life and lower lipophilicity.[3]

1. Chouza C, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; **i:** 1303–4.
2. Meyboom RHB, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; **ii:** 292.
3. Laporte J-R, Capella D. Useless drugs are not placebos: lessons from flunarizine and cinnarizine. *Lancet* 1986; **ii:** 853–4.
4. Laporte J-R, Capella D. Useless drugs are not placebos. *Lancet* 1987; **i:** 1324.
5. Teive HAG, *et al.* Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord* 2004; **10:** 243–5.
6. Amery W. Side-effects of flunarizine. *Lancet* 1986; **i:** 1497.
7. Benvenuti F, *et al.* Side-effects of flunarizine. *Lancet* 1986; **ii:** 464.

Porphyria. Flunarizine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

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

Hepatic enzyme inducers such as carbamazepine, phenytoin, and valproate may interact with flunarizine by increasing its metabolism; an increase in dosage of flunarizine may be required.

Pharmacokinetics

Flunarizine hydrochloride is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. Flunarizine hydrochloride is very lipophilic and is more than 90% bound to plasma proteins. It appears to undergo extensive metabolism; metabolites are excreted principally in the bile. Flunarizine hydrochloride has an elimination half-life of about 18 days.

Uses and Administration

Flunarizine is the difluorinated derivative of cinnarizine. It has antihistamine, sedative, and calcium-channel blocking activity. Flunarizine hydrochloride is used for migraine prophylaxis, for vertigo and vestibular disorders, and for peripheral and cerebral vascular disorders. It has also been used as adjunctive antiepileptic therapy in patients refractory to standard regimens.

Flunarizine is given orally as the hydrochloride although doses are expressed in terms of the base. Flunarizine hydrochloride 11.8 mg is equivalent to about 10 mg of flunarizine. The usual dose is 5 to 10 mg daily, usually given at night to minimise the effects of drowsiness.

Epilepsy. A number of drugs with calcium-channel blocking activity have been investigated as adjuncts in epilepsy (p.465), including flunarizine. Some individual studies have reported benefit, but a systematic review[1] concluded that although flunarizine might have a weak effect on seizure frequency the evidence was not convincing, and the withdrawal rate was significant, probably because of poor tolerability; it should therefore not be recommended as adjunctive antiepileptic therapy. The pharmacokinetic profile of flunarizine may in any case be too complex for clinical use as an antiepileptic.[2]

1. Chaisewikul R, *et al.* Calcium antagonists as an add-on therapy for drug-resistant epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/05).
2. Hoppu K, *et al.* Flunarizine of limited value in children with intractable epilepsy. *Pediatr Neurol* 1995; **13:** 143–7.

Migraine. Flunarizine reduces the frequency of migraine attacks in both adult and paediatric patients and is used for the prophylaxis of migraine (p.616) in some countries. Its effects are comparable with several other prophylactic antimigraine drugs, including the generally preferred propranolol,[1-4] but it is more likely to be reserved for use when first-line drugs have proved to be ineffective or unsuitable. Its mode of action in migraine is unclear; possible mechanisms are inhibition of vasospasm induced by mediators such as serotonin and prostaglandins, inhibition of