breast milk; its active metabolite, fexofenadine, was excreted in limited amounts.

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)
2. Lucas BD, *et al.* Terfenadine pharmacokinetics in breast milk in lactating women. *Clin Pharmacol Ther* 1995; **57:** 398–402.

Effects on the liver. Three episodes of acute hepatitis with jaundice occurred in a patient taking terfenadine intermittently over a period of 17 months.[1] Liver function tests returned to normal after the drug was stopped. Two further cases[2] of cholestatic hepatitis associated with terfenadine have been reported. Again, liver function tests returned to normal after drug withdrawal. A study[3] by the Boston Collaborative Drug Surveillance Program of 210 683 patients who had received prescriptions for terfenadine concluded that the use of terfenadine was rarely associated with important idiopathic liver disease. The investigators found only 3 cases of acute liver disease where a causal connection to terfenadine could not be ruled out; all these patients had also received a hepatotoxic drug and had made a full recovery.

1. Larrey D, *et al.* Terfenadine and hepatitis. *Ann Intern Med* 1985; **103:** 634.
2. Sahai A, Villeneuve JP. Terfenadine-induced cholestatic hepatitis. *Lancet* 1996; **348:** 552–3.
3. Myers MW, Jick H. Terfenadine and risk of acute liver disease. *Br J Clin Pharmacol* 1998; **46:** 251–3.

Effects on the nervous system. Non-sedating effects on the CNS have been reported after a single dose of terfenadine;[1] these have included anxiety, palpitations, and insomnia. The UK manufacturers commented that clinical studies suggest that the incidence of such effects is similar to that seen after placebo.[2]

Workers who had described a generalised tonic-clonic seizure in a patient taking terfenadine[3] later reported that the patient had subsequently had a second unprovoked seizure[4] and now considered that terfenadine may not have been the cause of his original seizure. Convulsions have been reported after overdosage with terfenadine (see under Arrhythmias, above).

The sedative effects of the older antihistamines and the lack of such effects with the non-sedating antihistamines including terfenadine are discussed under Sedation on p.562.

1. Napke E, Biron P. Nervous reactions after first dose of terfenadine in adults. *Lancet* 1989; **ii:** 615–16.
2. Masheter HC. Nervous reactions to terfenadine. *Lancet* 1989; **ii:** 1034.
3. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 241.
4. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 736.

Hypersensitivity. Terfenadine use was associated with 108 reports of skin reactions, including rashes, urticaria, angioedema, photosensitivity reactions and peeling of the skin of the hands or feet.[1]

1. Stricker BHCh, *et al.* Skin reactions to terfenadine. *BMJ* 1986; **293:** 536.

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

Interactions

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

Terfenadine should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the triazole and imidazole antifungals such as itraconazole and ketoconazole, the macrolide antibacterials including clarithromycin, erythromycin, josamycin, and troleandomycin, the streptogramin antibacterial quinupristin/dalfopristin, the serotonin reuptake inhibitors citalopram, fluoxetine, fluvoxamine, nefazodone, and paroxetine, the HIV-protease inhibitors, the NNRTIs delavirdine and efavirenz, and zileuton. The metabolism of terfenadine may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, probucol, pentamidine isetionate, and the beta blocker sotalol should be avoided as should diuretics that cause electrolyte imbalances especially hypokalaemia. The use of terfenadine and astemizole together is not recommended.

◊ General references.

1. Kivistö KT, *et al.* Inhibition of terfenadine metabolism: pharmacokinetic and pharmacodynamic consequences. *Clin Pharmacokinet* 1994; **27:** 1–5.

Antibacterials. Pharmacokinetic studies have shown that the macrolide antibiotics *erythromycin*[1] and *clarithromycin*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with erythromycin[3] or *troleandomycin*.[4]

1. Honig PK, *et al.* Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; **52:** 231–8.
2. Honig P, *et al.* Effect of erythromycin, clarithromycin and azithromycin on the pharmacokinetics of terfenadine. *Clin Pharmacol Ther* 1993; **53:** 161.
3. Biglin KE, *et al.* Drug-induced torsades de pointes: a possible interaction of terfenadine and erythromycin. *Ann Pharmacother* 1994; **28:** 282.
4. Fournier P, *et al.* Une nouvelle cause de torsades de pointes: association terfenadine et troleandomycine. *Ann Cardiol Angeiol (Paris)* 1993; **42:** 249–52.

Antidepressants. Cardiac abnormalities have been reported in 2 patients taking *fluoxetine* with terfenadine.[1,2] Similarly, the use of *nefazodone* with terfenadine has resulted in prolongation of the QT interval.[3]

1. Swims MP. Potential terfenadine-fluoxetine interaction. *Ann Pharmacother* 1993; **27:** 1404–5.
2. Marchiando RJ, Cook MD. Probable terfenadine-fluoxetine-associated cardiac toxicity. *Ann Pharmacother* 1995; **29:** 937–8.
3. Abernethy DR, *et al.* Loratadine and terfenadine interaction with nefazodone: both antihistamines are associated with QTc prolongation. *Clin Pharmacol Ther* 2001; **69:** 96–103.

Antiepileptics. For reference to an interaction between terfenadine and *carbamazepine*, see p.475.

Antifungals. Pharmacokinetic studies have shown that *itraconazole*[1] and *ketoconazole*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with ketoconazole[3] or itraconazole.[1,4] While there has been a pharmacokinetic study[5] that suggested that the interaction between terfenadine and *fluconazole* might not be clinically significant, as the mechanism of the interaction appeared to involve the metabolite of terfenadine and did not lead to accumulation of the cardiotoxic parent compound, this may not always be the case. Studies in a small group of patients who had abnormal patterns of terfenadine metabolism found increases in terfenadine concentrations associated with ECG abnormalities when terfenadine was given with high doses of fluconazole.[6]

1. Pohjola-Sintonen S, *et al.* Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. *Eur J Clin Pharmacol* 1993; **45:** 191–3.
2. Honig PK, *et al.* Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. *JAMA* 1993; **269:** 1513–18.
3. Monahan BP, *et al.* Torsades de pointes occurring in association with terfenadine use. *JAMA* 1990; **264:** 2788–90.
4. Crane JK, *et al.* Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. *Am J Med* 1993; **95:** 445–6.
5. Honig PK, *et al.* The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin Pharmacol Ther* 1993; **53:** 630–6.
6. Cantilena LR, *et al.* Fluconazole alters terfenadine pharmacokinetics and electrocardiographic pharmacodynamics. *Clin Pharmacol Ther* 1995; **57:** 185.

Calcium-channel blockers. For reference to an interaction between terfenadine and *nifedipine*, see p.1353.

Grapefruit juice. A study[1] in healthy subjects given terfenadine and grapefruit juice for 7 days found raised plasma-terfenadine concentrations and prolongation of the QT interval. These effects were less pronounced when terfenadine was given 2 hours before grapefruit juice, but were nevertheless quantifiable in some subjects. In another study QT interval changes were not found in healthy subjects given single doses of terfenadine and grapefruit juice.[2] However, the highly variable pharmacokinetics between individuals led the authors to conclude that prolongation of the QT interval was possible following single doses. The probable mechanism of the interaction is inhibition of the metabolism of terfenadine by the cytochrome P450 isoenzyme CYP3A4.

1. Benton RE, *et al.* Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. *Clin Pharmacol Ther* 1996; **59:** 383–8.
2. Rau SE, *et al.* Grapefruit juice-terfenadine single-dose interaction: magnitude, mechanism, and relevance. *Clin Pharmacol Ther* 1997; **61:** 401–9.

Pharmacokinetics

Terfenadine is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are achieved within about 2 hours. It is a prodrug and undergoes extensive first-pass metabolism in the liver to its active metabolite the carboxylic acid derivative fexofenadine (p.579). The other main metabolite is an inactive piperidine-carbinol derivative. About 97% of terfenadine is bound to plasma proteins; fexofenadine is reported to be less extensively bound. Terfenadine does not appear to cross the blood-brain barrier to a significant extent; limited amounts of fexofenadine, but not the parent drug, have been detected in breast milk. An elimination half-life of 16 to 23 hours has been reported for terfenadine. The metabolites, and traces of unchanged drug, are excreted in the urine and the faeces.

◊ References.

1. Eller MG, *et al.* Pharmacokinetics of terfenadine in healthy elderly subjects. *J Clin Pharmacol* 1992; **32:** 267–71.

Uses and Administration

Terfenadine, a piperidine derivative, is a non-sedating antihistamine. It does not have significant antimuscarinic actions. It is used for the symptomatic relief of allergic conditions including rhinitis (p.565) and conjunctivitis (p.564) and skin disorders such as urticaria (p.565).

The maximum oral dose of terfenadine is 120 mg daily given either as 60 mg twice daily or 120 mg in the morning; a starting dose of 60 mg daily in a single dose or in two divided doses is recommended for rhinitis and conjunctivitis. Children who are over 12 years of age and weigh more than 50 kg may receive the usual adult dosage.

For dosage in renal impairment see below.

Administration in renal impairment. Half the usual oral daily dose of terfenadine has been suggested for patients with creatinine clearance less than 40 mL/minute.

Preparations

BP 2008: Terfenadine Oral Suspension; Terfenadine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Terfemax†; ***Cz.:*** Lotanax†; Tergal†; Teridin†; ***Denm.:*** Teldanex†; Tenadin†; Terfin†; ***Ger.:*** Hisfedin†; Terfedura†; Terfemundin†; ***Hong Kong:*** Fenason†; Hisdane†; Histafen; Tamagon; Vida Fenadine†; ***India:*** Trexyl†; ***Indon.:*** Alpenaso; Histastop; Terfin; ***Ital.:*** Allerzil†; ***Malaysia:*** Neutramine†; Tamagon†; ***Mex.:*** Teldanet†; ***Norw.:*** Teldanex†; ***Port.:*** Triludan†; ***S.Afr.:*** Fendin; Triludan†; ***Spain:*** Cyater; Rapidal†; Ternadin; ***Swed.:*** Teldanex†; ***Turk.:*** Teradin; ***Venez.:*** Terfanil†; Tetram†; Tirfen†.

Multi-ingredient: ***Arg.:*** Cortaler Novo†; Cortistamin NF†; Sinlergia†; Terfenadina DG†; Vixidone T†; ***India:*** Alpha-Zedex†; Teguphen†; Tusant†; ***Indon.:*** Rhinofed; ***Malaysia:*** Trexydin†; ***Mex.:*** Teldane D†; ***Venez.:*** Rinodrina†; Rinotirfen†.

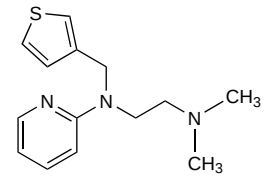
Thenyldiamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tenildiamina; Thényldiamine, Chlorhydrate de; Thenyldiamini Hydrochloridum; Thenyldiaminium Chloride. *NN*-Dimethyl-*N*′-(2-pyridyl)-*N*′-(3-thenyl)ethylenediamine hydrochloride.

Тенилдиамина Гидрохлорид

$C_{14}H_{19}N_3S,HCl$ = 297.8.

CAS — 91-79-2 (thenyldiamine); 958-93-0 (thenyldiamine hydrochloride).



(thenyldiamine)

Profile

Thenyldiamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p.561). It is given by mouth as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** NTR.

Thiethylperazine *(BAN, USAN, rINN)*

Thiéthylpérazine; Thiethylperazinum; Tietilperazina; Tietylperazin; Tietyyliperatsiini. 2-Ethylthio-10-[3-(4-methylpiperazin-1-yl)-propyl]phenothiazine.

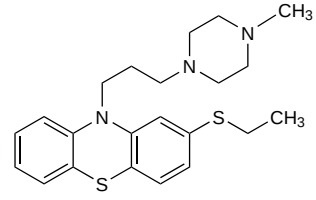
Тиэтилперазин

$C_{22}H_{29}N_3S_2$ = 399.6.

CAS — 1420-55-9.

ATC — R06AD03.

ATC Vet — QR06AD03.



Thiethylperazine Malate *(BANM, rINNM)*

Malato de tietilperazina; Thiéthylpérazine, Malate de; Thiethylperazini Malas.

Тиэтилперазина Малат

$C_{22}H_{29}N_3S_2,2C_4H_6O_5$ = 667.8.

CAS — 52239-63-1.

ATC — R06AD03.

ATC Vet — QR06AD03.