2. Kahn A, Blum D. Phenothiazines and sudden infant death syndrome. *Pediatrics* 1982; **70:** 75–8.
3. Kahn A, *et al.* Phenothiazine-induced sleep apneas in normal infants. *Pediatrics* 1985; **75:** 844–7.
4. Cockfield. Phenergan, Theralene, Algotropyl—drugs responsible for the death of new-born babies. *Off J EC* 1986; **29:** C130/25–6.
5. Stanton AN. Sudden infant death syndrome and phenothiazines. *Pediatrics* 1983; **71:** 986–7.

Precautions

As for the sedating antihistamines in general, p.562.

Intravenous injections of promethazine hydrochloride must be given slowly and extreme care must be taken to avoid extravasation or inadvertent intra-arterial injection, because of the risk of severe irritation. Intramuscular injection may be painful, and it should not be given by subcutaneous injection.

False negative and positive results have been reported with some pregnancy tests.

Anaesthesia. In 8 healthy subjects promethazine 25 mg intravenously decreased lower oesophageal sphincter pressure and increased the incidence of gastro-oesophageal reflux.[1] It might, therefore, increase the risk of regurgitation and aspiration of gastric contents during induction of and recovery from anaesthesia. The effect was attributed to the antimuscarinic properties of promethazine.

1. Brock-Utne JG, *et al.* The action of commonly used antiemetics on the lower oesophageal sphincter. *Br J Anaesth* 1978; **50:** 295–8.

Children. A possible association between phenothiazine sedatives and sudden infant death syndrome has been suggested, but has not been confirmed (see under Adverse Effects, above). The current view in the UK and USA is that promethazine should not be given to children under 2 years of age.

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

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p.563.

Renal impairment. Phenothiazine-induced toxic psychosis occurred in a patient with chronic renal failure who had been given promethazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; **10:** 191–5.

Interactions

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

Pharmacokinetics

Promethazine is well absorbed after oral or intramuscular doses. Peak plasma concentrations have been seen 2 to 3 hours after a dose by these routes, although there is low systemic bioavailability after oral doses, due to high first-pass metabolism in the liver. Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Values ranging from 76 to 93% have been reported for plasma-protein binding. Promethazine undergoes extensive metabolism, predominantly to promethazine sulfoxide, and also to *N*-desmethylpromethazine. It is excreted slowly via the urine and bile, chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported.

◊ References.

1. Taylor G, *et al.* Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man. *Br J Clin Pharmacol* 1983; **15:** 287–93.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
3. Stavchansky S, *et al.* Bioequivalence and pharmacokinetic profile of promethazine hydrochloride suppositories in humans. *J Pharm Sci* 1987; **76:** 441–5.
4. Strenkoski-Nix LC, *et al.* Pharmacokinetics of promethazine hydrochloride after administration of rectal suppositories and oral syrup to healthy subjects. *Am J Health-Syst Pharm* 2000; **57:** 1499–1505.

Uses and Administration

Promethazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and some serotonin-antagonist properties. It is usually given as the hydrochloride or teoclate. Promethazine embonate and promethazine maleate have also been given orally. Promethazine dioxide (dioxopromethazine) has been used as the hydrochloride in eye and nasal drops. The antihistamine action has been reported to last for between 4 and 12 hours.

Promethazine hydrochloride is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565). It may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p.563).

Promethazine hydrochloride and promethazine teoclate are used for their antiemetic action in the prevention and treatment of nausea and vomiting in conditions such as motion sickness, drug-induced vomiting, and postoperative vomiting (p.564). They are also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p.565). Promethazine hydrochloride is also employed pre- and postoperatively in surgery and obstetrics for its sedative effects and for the relief of apprehension (see Anaesthesia, p.563); it is often given with pethidine hydrochloride. Promethazine hydrochloride may be used for night-time sedation (see Insomnia, p.564).

Promethazine hydrochloride is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

The following doses have been given **orally**.

- For the treatment of *allergic conditions* promethazine hydrochloride is usually given in a dose of 25 mg at night increased to 25 mg twice daily if necessary; owing to its pronounced sedative effect it is preferably given at night but an alternative dose is 10 to 20 mg two or three times daily.
- Promethazine hydrochloride is given in doses of 20 to 50 mg at night for the short-term management of *insomnia* although its prolonged duration of action can lead to considerable drowsiness the following day.
- For the prevention of *motion sickness* promethazine hydrochloride can be given in a dose of 20 or 25 mg the night before travelling followed by a similar dose the following morning if necessary. The teoclate is used similarly. For the prevention of motion sickness the dose of promethazine teoclate is 25 mg at night or 25 mg one to two hours before travelling.
- For nausea and vomiting arising from causes such as *labyrinthitis* a dose of promethazine teoclate 25 mg at night is usually adequate; this may be increased to 50 or 75 mg at night or to 25 mg two or three times daily if necessary to a maximum of 100 mg daily.
- For *severe vomiting in pregnancy* the *BNF* recommends a dose of promethazine teoclate 25 mg at night, increased if necessary to a maximum of 100 mg.

In *children* the following oral doses of promethazine hydrochloride have been recommended.

- For allergic conditions: 2 to 5 years, 5 to 15 mg daily in one or two divided doses; 5 to 10 years, 10 to 25 mg daily in one or two divided doses.
- For night sedation or premedication: 2 to 5 years, 15 to 20 mg; 5 to 10 years, 20 to 25 mg.
- For the prevention of motion sickness the following doses of promethazine hydrochloride may be given the night before the journey and repeated on the following morning if necessary: 2 to 5 years, 5 mg; 5 to 10 years, 10 mg. Promethazine teoclate may also be given to children aged 5 to 10 years for the prevention of motion sickness in a dose of 12.5 mg daily, starting either on the night before travelling for long journeys or one to two hours before short journeys.
- Children aged 5 to 10 years may also receive promethazine teoclate for nausea and vomiting from causes such as labyrinthitis in a dose of 12.5 to 37.5 mg daily.

Promethazine hydrochloride is also given by the **rectal** route as suppositories. Doses are similar to those given orally.

Promethazine hydrochloride is given **parenterally** by deep intramuscular injection as a solution of 25 or 50 mg/mL. It may also be given by slow intravenous injection or injected into the tubing of a freely running infusion in a concentration of not more than 25 mg/mL, although it is usually diluted to 2.5 mg/mL. The rate of infusion should not exceed 25 mg/minute. The usual parenteral dose for all indications apart from nausea and vomiting is 25 to 50 mg; a dose of 100 mg should not be exceeded. Doses of 12.5 to 25 mg, repeated at intervals of not less than 4 hours, may be given for the treatment of nausea and vomiting, although not more than 100 mg is usually given in 24 hours.

Children aged 5 to 10 years may be given 6.25 to 12.5 mg of promethazine hydrochloride by deep intramuscular injection.

Promethazine has been used **topically** to provide relief in hypersensitivity disorders of the skin and for burns but, as with other antihistamines, it may produce skin sensitisation.

Sedation. For reference to the use of lytic cocktails of chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see under Pethidine, p.115.

Preparations

BP 2008: Promethazine Hydrochloride Tablets; Promethazine Injection; Promethazine Oral Solution; Promethazine Teoclate Tablets;
USP 31: Promethazine Hydrochloride Injection; Promethazine Hydrochloride Suppositories; Promethazine Hydrochloride Syrup; Promethazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Fenergan; ***Austral.:*** Avomine; Gold Cross Antihistamine Elixir†; Insomn-Eze†; Nyal Plus+ Allergy Relief†; Phenergan; ***Belg.:*** Phenergan; ***Braz.:*** Alergiderm; Alergosan†; Fenergan; Pamergan; Profergan; Prometazol; ***Canad.:*** Histantil; Phenergan†; ***Cz.:*** Prothazin; ***Denm.:*** Phenergan; ***Fr.:*** Phenergan; ***Ger.:*** Atosil; Closin; Eusedon mono†; Promethawern†; Proneurin; Prothanon; ***Gr.:*** Phenergan; Titanox; ***Hong Kong:*** Anvomin; Fenazin; Synvomin; ***Hung.:*** Pipolphen; ***India:*** Avomine; Emin; Phenergan; ***Indon.:*** Nufapreg; Phenergan; ***Irl.:*** Phenergan; ***Israel:*** Prothiazine; ***Ital.:*** Allerfen†; Fargan; Farganesse; Fenazil; ***Malaysia:*** Prothazine†; ***Norw.:*** Phenergan; ***NZ:*** Allersoothe; Avomine; Phenergan; ***Philipp.:*** Zinmet; ***Pol.:*** Diphergan; ***Port.:*** Fenergan; ***Rus.:*** Pipolphen (Пипольфен); ***S.Afr.:*** Avomine; Brunazine; Daralix; Lenazine; Phenergan; Prohist; Receptozine; ***Spain:*** Fenergan Topico; Frinova; ***Swed.:*** Lergigan; ***Thai.:*** Meta; Phenergan; Titanox†; ***UAE:*** Histaloc; ***UK:*** Avomine; Phenergan; Sominex; Zir; ***USA:*** Phenadoz; Phenergan; Promethegan; ***Venez.:*** Diven†; Fenergan†.

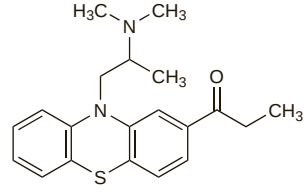
Multi-ingredient: ***Austral.:*** Painstop; Painstop Night-Time Pain Reliever; Panquil; Phensedyl†; Tixylix Nightime; ***Braz.:*** Dorilen; Doriless; Fenergan Expectorante; Lisador; ***Canad.:*** Promatussin DM†; ***Cz.:*** Coldrex Nite; ***Fr.:*** Algotropyl†; Fluisedal; Rhinathiol Promethazine; Transmer†; Tussisedal; ***Ger.:*** Prothazin; ***Hong Kong:*** Dhasedyl; Ephedyl; Fendyl; Marsedyl; Methorsedyl; PEC; Phensedyn; Procodine†; Promethazine Compound Linctus†; Rhinathiol Promethazine; Super Cough†; Tripe P; ***Hung.:*** Tardyl†; ***India:*** Tixylix; ***Indon.:*** Berlifed; Fludexin; Halmezin; Neo Davenol; Phenadex; Prome; Promedex; Promethazine Ikapharmindo; ***Irl.:*** Night Nurse; ***Israel:*** Promethazine Expectorants; Prothiazine Expectorant; ***Ital.:*** Bronconait†; Nuleron; Tachinotte; ***Malaysia:*** Axcel Dextrozine; Dextrodyl; Dextromethorphan Compound; Dhasedyl DM; Hosedyl DM; Mucoease Plus; Phensedyl Dry Cough; Phensedyl†; Promedyl†; Rhinathiol Promethazine; Russedyl Plus; Russedyl†; SCMC Promethazine†; Sedilix DM†; Sedilix†; Tixylix†; ***NZ:*** Phensedyl Dry Family Cough†; Tixylix; ***Rus.:*** Prothiazine Expectorant (Протиазин Экспекторант); ***S.Afr.:*** Acustop; Adco-Kiddipayne; Antipyn†; Ban Pain; Brunacod; Colcaps; Dequa-Coff; Fevapar; Go-Pain; Goldgesic†; Histodor; Infacet; Infapain Forte; Kid-Eeze; Lenazine Forte; Lentogesic; Lesspain†; Medipyn; Megapyn; Mepromol; Painagon; Pedpain; Phensedyl; Propain†; Pynmed; Salterpyn; Stilpane; Stopayne; Tenston; Tixylix; Vacudol; Xeramax†; ***Singapore:*** Beacodyl; Cophadyl; Cophadyl-E; Dhasedyl; Dhasedyl DM; PCL†; Phensedyl†; Procodin; Promedyl†; Rhinathiol Promethazine; Sedilix; Sedilix DM; Unisedyl†; ***Spain:*** Actithiol Antihist; Antihemorroidal†; Fenergan Expectorante; Psicosoma Solucion; ***Swed.:*** Lergigan comp; ***Switz.:*** Linervidol†; Lysedil; Nardyl; Rhinathiol Promethazine; ***Thai.:*** Decos; Nordyl; Nortuss; Phencodin; Phensedyl†; Poly-Cof; Teradyl; ***Turk.:*** Artu; ***UAE:*** Flukit; ***UK:*** Day & Night Nurse; Night Nurse; Pamergan P100; Tixylix Night-Time; ***USA:*** Pentazine VC with Codeine; Phenameth DM; Pherazine DM; Pherazine VC; Pherazine VC with Codeine; Pherazine with Codeine; Prometh VC Plain; Prometh with Dextromethorphan; Promethazine VC with Codeine; ***Venez.:*** Preveral con Codeina; Preveral con Dextrometorfano.

Propiomazine *(BAN, USAN, rINN)*

CB-1678 (propiomazine or propiomazine maleate); Propiomatsiini; Propiomazin; Propiomazina; Propiomazinum; Wy-1359 (propiomazine or propiomazine maleate). 1-[10-(2-Dimethylaminopropyl)phenothiazin-2-yl]propan-1-one.

Пропиомазин

$C_{20}H_{24}N_2OS$ = 340.5.
CAS — 362-29-8.
ATC — N05CM06.
ATC Vet — QN05CM06.



Propiomazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propiomazina; Propiomazine, Chlorhydrate de; Propiomazini Hydrochloridum.

Пропиомазина Гидрохлорид

$C_{20}H_{24}N_2OS,HCl$ = 376.9.
CAS — 1240-15-9.
ATC — N05CM06.
ATC Vet — QN05CM06.

Propiomazine Maleate *(BANM, rINNM)*

CB-1678 (propiomazine or propiomazine maleate); Maleato de propiomazina; Propiomazine Hydrogen Maleate; Propiomazine, Maléate de; Propiomazini Maleas; Wy-1359 (propiomazine or propiomazine maleate).

Пропиомазина Малеат

$C_{20}H_{24}N_2OS,C_4H_4O_4$ = 456.6.
CAS — 3568-23-8.
ATC — N05CM06.
ATC Vet — QN05CM06.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Local irritation may occur at the site of intravenous injection of propiomazine hydrochloride and there may be thrombophlebitis.

Interactions

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

Uses and Administration

Propiomazine, a phenothiazine derivative, is a sedating antihistamine that has been used for its sedative and antiemetic properties in insomnia (p.564) and nausea and vomiting (p.564).

Propiomazine is given as the maleate but doses are expressed in terms of the base; propiomazine maleate 1.3 mg is equivalent to about 1 mg of propiomazine. Doses equivalent to 25 to 50 mg orally at night have been given as a hypnotic.

Propiomazine hydrochloride has been given parenterally.

Preparations

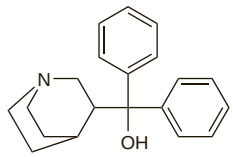
Proprietary Preparations (details are given in Part 3)
Swed.: Propavan.

Quifenadine Hydrochloride *(rINNM)*

Hidrocloruro de quifenadina; Quifénadine, Chlorhydrate de; Quifenadini Hydrochloridum. α,α-Diphenyl-3-quinuclidinemethanol hydrochloride.

Хифенадина Гидрохлорид

$C_{20}H_{23}NO,HCl$ = 329.9.
CAS — 10447-39-9 (quifenadine); 10447-38-8 (quifenadine hydrochloride).



(quifenadine)

Profile

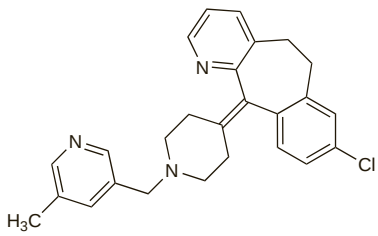
Quifenadine is an antihistamine given orally as the hydrochloride.

Rupatadine *(rINN)*

Rupatadina; Rupatadinum; UR-12592 (rupatadine fumarate). 8-Chloro-6,11-dihydro-11-{1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene}-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

Рупатадин

$C_{26}H_{26}ClN_3$ = 416.0.
CAS — 158876-82-5 (rupatadine); 182349-12-8 (rupatadine fumarate).
ATC — R06AX28.
ATC Vet — QR06AX28.



Profile

Rupatadine is an antihistamine with platelet-activating factor (PAF) antagonist activity that is used for the treatment of allergic rhinitis (p.565) and chronic idiopathic urticaria (p.565). It is given as the fumarate although doses are expressed in terms of the base; rupatadine fumarate 12.8 mg is equivalent to about 10 mg of rupatadine. The usual oral dose is the equivalent of 10 mg once daily of rupatadine.

◊ References.

1. Izquierdo I, *et al.* Rupatadine: a new selective histamine H1 receptor and platelet-activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today* 2003; **39:** 451–68.
2. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007; **67:** 457–74.

Preparations

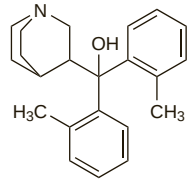
Proprietary Preparations (details are given in Part 3)
Braz.: Rupafin; ***Cz.:*** Tamalis; ***Gr.:*** Rupafin; ***Port.:*** Rinialer; ***Spain:*** Alergoliber; Rinialer; Rupafin.

Sequifenadine *(rINN)*

Bicarphene (sequifenadine or sequifenadine hydrochloride); Bikarfen (sequifenadine or sequifenadine hydrochloride); Sequifenadina; Séquifénadine; Sequifenadinum. α,α-Di-*o*-tolyl-3-quinuclidinemethanol.

Сехифенадин

$C_{22}H_{27}NO$ = 321.5.
CAS — 57734-69-7.



Profile

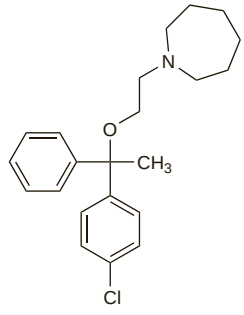
Sequifenadine is an antihistamine used in a wide range of allergic conditions. A usual dose is 50 to 100 mg given orally 2 or 3 times daily. Sequifenadine is reported also to have antiserotonin properties.

Setastine Hydrochloride *(rINNM)*

EGIS-2062; EGYT-2062; Hidrocloruro de setastina; Sétastine, Chlorhydrate de; Setastini Hydrochloridum. 1-{2-[(*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]ethyl}hexahydro-1*H*-azepine hydrochloride.

Сетастина Гидрохлорид

$C_{22}H_{28}ClNO,HCl$ = 394.4.
CAS — 64294-95-7 (setastine).



(setastine)

Profile

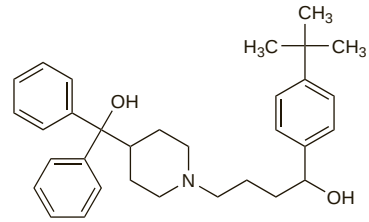
Setastine hydrochloride, a derivative of clemastine, is an antihistamine (p.561) claimed to have no sedative activity. It has been given orally for the symptomatic relief of hypersensitivity disorders.

Terfenadine *(BAN, USAN, rINN)*

MDL-9918; RMI-9918; Terfenadiini; Terfenadin; Terfenadina; Terfenadinas; Terfénadine; Terfenadinum. 1-(4-*tert*-Butylphenyl)-4-[4-(α-hydroxybenzhydryl)piperidino]butan-1-ol.

Терфенадин

$C_{32}H_{41}NO_2$ = 471.7.
CAS — 50679-08-8.
ATC — R06AX12.
ATC Vet — QR06AX12.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Terfenadine). A white or almost white, crystalline powder. It shows polymorphism. Very slightly soluble in water and in dilute hydrochloric acid; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Erythema multiforme and galactorrhoea have also been reported.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with terfenadine, particularly in association with raised blood concentrations (see Arrhythmias, below). To *reduce the risk* of developing such arrhythmias the recommended dose should **not** be exceeded and terfenadine should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of terfenadine, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance is **contra-indicated** (see under Interactions, below). If palpitations, dizziness, syncope, or convulsions occur terfenadine should be withdrawn and the patient investigated for potential arrhythmias.

Alopecia. Hair loss was associated with use of terfenadine in a 24-year-old patient.[1] Regrowth occurred when treatment was stopped.

1. Jones SK, Morley WN. Terfenadine causing hair loss. *BMJ* 1985; **291:** 940.

Arrhythmias. Ventricular arrhythmias including torsade de pointes have occurred with terfenadine at doses greater than those recommended[1] and also at normal doses in patients whose metabolism of terfenadine is impaired by drugs or by liver disease. Generalised convulsions and a quinine-like effect on the ECG have also been reported after a presumed overdose of terfenadine.[2] Consequently a number of recommendations have been made to *reduce the risk* of developing serious arrhythmias (see Adverse Effects and Precautions, above, for details), including those from the UK CSM.[3,4] Terfenadine should be stopped immediately, and the patient evaluated for potential arrhythmias, in those who experience syncope, palpitations, dizziness, or convulsions after taking terfenadine.

Studies[5] have suggested that the ventricular arrhythmias are due to terfenadine itself rather than its active metabolite fexofenadine (p.579). Terfenadine has been shown to inhibit cardiac potassium channels, which results in prolongation of the QT interval, a risk factor for developing arrhythmias, while the non-sedating antihistamines cetirizine, fexofenadine, and loratadine have had no demonstrable effect[5,6] (see also p.562).

1. MacConnell TJ, Stanners AJ. Torsades de pointes complicating treatment with terfenadine. *BMJ* 1991; **302:** 1469.
2. Davies AJ, *et al.* Cardiotoxic effect with convulsions in terfenadine overdose. *BMJ* 1989; **298:** 325.
3. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
4. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
5. Woolsey RL, *et al.* Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993; **269:** 1532–6.
6. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

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

In a study[2] of 4 healthy lactating women given 60 mg of terfenadine every 12 hours for 48 hours, terfenadine was undetected in