Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dimetindene Maleate). A white to almost white, crystalline powder. Slightly soluble in water; soluble in methyl alcohol. Protect from light.

Profile
Dimetindene maleate, an alkylamine derivative, is a sedating antihistamine (p.561); it is mildly sedative and is reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565) and rhinitis (p.565), and in pruritic skin disorders (p.565). It is also used in compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

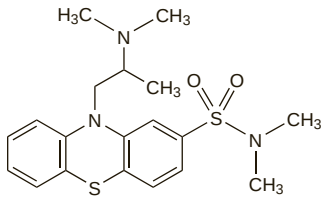
Dimetindene maleate is given in an oral dose of 1 to 2 mg three times daily; modified-release preparations are also available. It may also be given by the intravenous route. Dimetindene maleate is applied topically as a 0.1% gel or lotion although, as with other antihistamines, there is a risk of sensitisation. It is used in a strength of 0.025% in compound nasal preparations.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Fenistil; ***Belg.:*** Fenistil; ***Cz.:*** Fenistil; ***Ger.:*** Fenistil; ***Gr.:*** Fenistil; ***Hung.:*** Fenistil; ***India:*** Foristal; ***Indon.:*** Fenistil; ***Israel:*** Fenistil; ***Ital.:*** Fenistil; ***Neth.:*** Fenistil; ***Norw.:*** Fenistil†; ***Philipp.:*** Fenistil; ***Pol.:*** Fenistil; ***Port.:*** Fenistil; Neostil; ***Rus.:*** Fenistil (Фенистил); ***Spain:*** Fenistil; ***Switz.:*** Fenistil; ***Thai.:*** Fenistil; ***Turk.:*** Fenistil; ***Venez.:*** Fenistil†.

Multi-ingredient: ***Arg.:*** Vibragel; ***Austria:*** Trimedil; Vibrocil; ***Belg.:*** Vibrocil; ***Braz.:*** Gripen; Trimedal; ***Cz.:*** Vibrocil; ***Ger.:*** Vibrocil†; ***Gr.:*** Vibrocil-S; ***Hong Kong:*** Vibrocil†; ***Hung.:*** Otrivin Allergia; Vibrocil; ***Israel:*** Vibrocil; ***Ital.:*** Vibrocil; ***Pol.:*** Otrivin Allergy; ***Port.:*** Vibrocil; ***Rus.:*** Vibrocil (Виброцил); ***S.Afr.:*** Vibrocil; Vibrocil-S; ***Switz.:*** Vibrocil.

Dimetotiazine Mesilate *(BANM, rINNM)*
Dimethothiazine Mesylate; Dimétotiazine, Mésilate de; Dimetotiazini Mesilas; Fonazine Mesylate *(USAN)*; IL-6302 (dimetotiazine); Mesilato de dimetotiazina; 8599-RP (dimetotiazine). 10-(2-Dimethylaminopropyl)-*NN*-dimethylphenothiazine-2-sulphonamide methanesulphonate.

Диметотиазина Мезилат
$C_{19}H_{25}N_3O_2S_2,CH_3SO_3H$ = 487.7.
CAS — 7456-24-8 (dimetotiazine); 7455-39-2 (dimetotiazine mesilate).
ATC — N02CX05.
ATC Vet — QN02CX05.



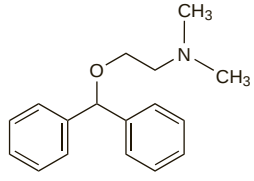
(dimetotiazine)

Profile
Dimetotiazine mesilate, a phenothiazine derivative, is a sedating antihistamine (p.561). It has been used for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders, and in the management of headaches including migraine.

Preparations
Proprietary Preparations (details are given in Part 3)
Indon.: Migristene; ***Mex.:*** Migristene.

Diphenhydramine *(BAN, rINN)*
Benzhydramine; Difenhidramina; Difenhydramiini; Difenhydramin; Diphénhydramine; Diphenhydraminum. 2-Benzhydryloxy-*NN*-dimethylethylamine.

Дифенгидрамин
$C_{17}H_{21}NO$ = 255.4.
CAS — 58-73-1.
ATC — D04AA32; R06AA02.
ATC Vet — QD04AA32; QR06AA02.



Pharmacopoeias. In *Jpn.*

Diphenhydramine Citrate *(BANM, rINNM)*
Benzhydramine Citrate; Citrato de difenhidramina; Diphénhydramine, Citrate de; Diphenhydramini Citras.

Дифенгидрамина Цитрат
$C_{17}H_{21}NO,C_6H_8O_7$ = 447.5.
CAS — 88637-37-0.
ATC — D04AA32; R06AA02.
ATC Vet — QD04AA32; QR06AA02.

Pharmacopoeias. In *US.*
USP 31 (Diphenhydramine Citrate). Store in airtight containers. Protect from light.

Diphenhydramine Di(acefyllinate) *(rINNM)*
Benzhydramine Di(acefyllinate); Bietanautine; Di(acefilinato) de difenhidramina; Diphénhydramine Diacéfylline; Diphenhydramine Di(acephyllinate); Diphenhydramini Diacefyllinas. Diphenhydramine bis(theophyllin-7-ylacetate).

Дифенгидрамина Диацефиллинат
$C_{17}H_{21}NO,2C_9H_{10}N_4O_4$ = 731.8.
CAS — 6888-11-5.
ATC — D04AA32; R06AA02.
ATC Vet — QD04AA32; QR06AA02.

NOTE. The name Etanautine has been applied both to diphenhydramine monoacefyllinate and to ethylbenzhydramine, an antimuscarinic formerly used in the symptomatic treatment of parkinsonism.

Diphenhydramine Hydrochloride *(BANM, rINNM)*
Benzhydramine Hydrochloride; Difenhidramin Hidroklorür; Difenhidramin-hidroklorid; Difenhidramino hidrochloridas; Difenhydramiinihydrokloridi; Difenhydramin-hydrochlorid; Difenhydraminhydroklorid; Difenhydraminy chlorowodorek; Dimedrolum; Diphénhydramine, chlorhydrate de; Diphenhydramini hydrochloridum; Diphenhydraminium Chloride; Hidrocloruro de difenhidramina.

Дифенгидрамина Гидрохлорид
$C_{17}H_{21}NO,HCl$ = 291.8.
CAS — 147-24-0.
ATC — D04AA32; R06AA02.
ATC Vet — QD04AA32; QR06AA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn,* and *US.*
Jpn also includes Diphenhydramine Tannate.
Ph. Eur. 6.2 (Diphenhydramine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 4.0 to 6.0. Protect from light.
USP 31 (Diphenhydramine Hydrochloride). A white, odourless, crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 50 of acetone; very slightly soluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Incompatibility. Diphenhydramine hydrochloride has been reported to be incompatible with amphotericin B, cefmetazole sodium, cefalotin sodium, hydrocortisone sodium succinate, some soluble barbiturates, some contrast media, and solutions of alkalis or strong acids.

Adverse Effects and Precautions
As for the sedating antihistamines in general, p.561.

Abuse. Reports of the abuse of diphenhydramine hydrochloride.

1. Anonymous. Is there any evidence that Benylin syrup is addictive? *BMJ* 1979; **1:** 459.
2. Smith SG, Davis WM. Nonmedical use of butorphanol and diphenhydramine. *JAMA* 1984; **252:** 1010.
3. Feldman MD, Behar M. A case of massive diphenhydramine abuse and withdrawal from use of the drug. *JAMA* 1986; **255:** 3119–20.
4. de Nesnera AP. Diphenhydramine dependence: a need for awareness. *J Clin Psychiatry* 1996; **57:** 136–7.
5. Dinndorf PA, *et al.* Risk of abuse of diphenhydramine in children and adolescents with chronic illnesses. *J Pediatr* 1998; **133:** 293–5.

Extrapyramidal disorders. Reports of dystonic extrapyramidal reactions to diphenhydramine.

1. Lavenstein BL, Cantor FK. Acute dystonia: an unusual reaction to diphenhydramine. *JAMA* 1976; **236:** 291.
2. Santora J, Rozek S. Diphenhydramine-induced dystonia. *Clin Pharm* 1989; **8:** 471.
3. Roila F, *et al.* Diphenhydramine and acute dystonia. *Ann Intern Med* 1989; **111:** 92–3.

Overdosage. In an evaluation of 136 cases, one fatal, of intoxication with diphenhydramine, the plasma concentration was correlated with frequency or extent of symptoms.[1] The most common symptom was impaired consciousness; psychosis, seizures, antimuscarinic symptoms such as mydriasis, tachycardia, and tachyarrhythmias, and respiratory failure were also observed. The positive association between dose and frequency and severity of symptoms was confirmed in a more recent study;[2] it was also found that severe symptoms were more likely to occur when 1 g or more of diphenhydramine had been taken.

There have been reports[3,4] of rhabdomyolysis as an effect of oral diphenhydramine overdosage. The liberal application of a lotion containing diphenhydramine produced acute delirium with visual and auditory hallucinations in a 9-year-old boy[5] and similar effects were seen in 3 children with varicella-zoster infection following the topical application of diphenhydramine (2 of these children also received oral diphenhydramine).[6]

1. Köppel C, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. *Clin Toxicol* 1987; **25:** 53–70.
2. Radovanovic D, *et al.* Dose-dependent toxicity of diphenhydramine overdose. *Hum Exp Toxicol* 2000; **19:** 489–95.
3. Hampel G, *et al.* Myoglobinuric renal failure due to drug-induced rhabdomyolysis. *Hum Toxicol* 1983; **2:** 197–203.
4. Haas CE, *et al.* Rhabdomyolysis and acute renal failure following an ethanol and diphenhydramine overdose. *Ann Pharmacother* 2003; **37:** 538–42.
5. Filloux F. Toxic encephalopathy caused by topically applied diphenhydramine. *J Pediatr* 1986; **108:** 1018–20.
6. Chan CYJ, Wallander KA. Diphenhydramine toxicity in three children with varicella-zoster infection. *DICP Ann Pharmacother* 1991; **25:** 130–2.

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

Pregnancy. A pregnant woman who was receiving diphenhydramine hydrochloride 150 mg daily for a pruritic rash gave birth to an infant who developed diarrhoea and generalised tremulousness 5 days later.[1] The delay in appearance of withdrawal symptoms was considered to be due to reduced activity of glucuronyl conjugating enzymes in the first few days of life.
For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between inguinal hernia or genito-urinary malformations and diphenhydramine exposure, see p.563. See also under Interactions, below, for a report of perinatal death possibly associated with temazepam and diphenhydramine.

1. Parkin DE. Probable Benadryl withdrawal manifestations in a new-born infant. *J Pediatr* 1974; **85:** 580.

Interactions
As for the sedating antihistamines in general, p.563. Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 that is partly responsible for the metabolism of some beta blockers including metoprolol and the antidepressant venlafaxine.

Benzodiazepines. There has been a report[1] suggesting that a reduction in *temazepam* metabolism caused by diphenhydramine may have contributed to perinatal death after ingestion of these drugs by the mother.

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; **313:** 1417–18.

Pharmacokinetics
Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations are achieved about 1 to 4 hours after oral doses. Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly bound to plasma proteins. Metabolism is extensive. Diphenhydramine is excreted mainly in the urine as metabolites; little is excreted as unchanged drug. The elimination half-life has been reported to range from 2.4 to 9.3 hours.

◊ References.

1. Glazko AJ, *et al.* Metabolic disposition of diphenhydramine. *Clin Pharmacol Ther* 1974; **16:** 1066–76.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97. (includes studies indicating a correlation between plasma concentrations and both antihistaminic and sedative effects).
3. Simons KJ, *et al.* Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol* 1990; **30:** 665–71.
4. Scavone JM, *et al.* Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. *J Clin Pharmacol* 1998; **38:** 603–9.

Uses and Administration
Diphenhydramine, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative properties. It 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 is also used for its antiemetic properties in the treatment of nausea and vomiting (p.564), particularly in the prevention and treatment of motion sickness (when