

**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; **Ger.:** Fenistil; **Gr.:** Fenistil; **Hung.:** Fenistil; **India:** Foristol; **Indon.:** Fenistil; **Israel:** Fenistil; **Ital.:** Fenistil; **Neth.:** Fenistil; **Norw.:** Fenistil; **Philipp.:** Fenistil; **Pol.:** Fenistil; **Port.:** Fenistil; **Rus.:** Fenistil (Фенистил); **Spain:** Fenistil; **Switz.:** Fenistil; **Thai.:** Fenistil; **Turk.:** Fenistil; **Venez.:** Fenistil.

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

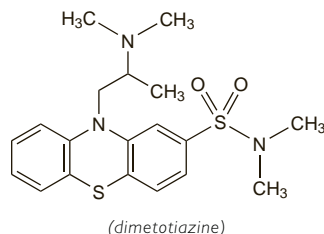
Диметотиазина Мезилат

$C_{19}H_{25}N_3O_3S_2 \cdot CH_3SO_3H = 487.7$ .

**CAS** — 7456-24-8 (dimetotiazine); 7455-39-2 (dimetotiazine mesilate).

**ATC** — N02CX05.

**ATC Vet** — QN02CX05.



### 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; Difenhydramini; Difenhydramin; Diphénhydramine; Diphenhydraminum. 2-Benzhydryloxy-NN-dimethylethylamine.

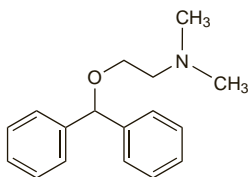
Дифенгидрамин

$C_{17}H_{21}NO = 255.4$ .

**CAS** — 58-73-1.

**ATC** — D04AA32; R06AA02.

**ATC Vet** — QD04AA32; QR06AA02.



**Pharmacopoeias.** In *Jpn.*

The symbol † denotes a preparation no longer actively marketed

### Diphenhydramine Citrate (BANM, rINNM)

Benzhydramine Citrate; Citrato de difenhidramina; Diphénhydramine, Citrate de; Diphenhydramini Citras.

Дифенгидрамина Цитрат

$C_{17}H_{21}NO \cdot C_6H_8O_7 = 447.5$ .

**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(acefyllinato) de difenhidramina; Diphénhydramine Diacefylline; Diphenhydramine Di(acefyllinate); Diphenhydramini Diacefyllinas. Diphenhydramine bis(theophyllin-7-ylacetate).

Дифенгидрамина Диацифиллинат

$C_{17}H_{21}NO \cdot 2C_9H_{10}N_4O_4 = 731.8$ .

**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 hidrokloridas; Difenhydraminihidroklorid; Difenhydramin-hydrochlorid; Difenhydraminhydroklorid; Difenhydraminy chlorowodorek; Dime-drolum; Diphénhydramine, chlorhydrate de; Diphenhydramini hydrochloridum; Diphenhydraminium Chloride; Hidrocloruro de difenhidramina.

Дифенгидрамина Гидрохлорид

$C_{17}H_{21}NO \cdot HCl = 291.8$ .

**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.<sup>1</sup> 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;<sup>2</sup> 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<sup>3,4</sup> 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<sup>5</sup> 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).<sup>6</sup>

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.<sup>1</sup> 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<sup>1</sup> 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<sub>1</sub>-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

it should be given at least 30 minutes before travelling), and in the treatment of vertigo of various causes (p.565). Diphenhydramine is used for its antimuscarinic properties in the control of parkinsonism (p.791) and drug-induced extrapyramidal disorders (p.971) (although the possibility that diphenhydramine itself may cause extrapyramidal symptoms should be remembered). Diphenhydramine has pronounced central sedative properties and may be used as a hypnotic in the short-term management of insomnia (p.564). It is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p.564). However, such preparations should be used with caution in children, and generally avoided in those under 2 years of age (see p.562). It may also be given in combination preparations containing analgesics, particularly paracetamol. Diphenhydramine may be used parenterally as an adjunct in the emergency treatment of anaphylactic shock (p.563) or when oral therapy is not feasible.

For most indications, diphenhydramine hydrochloride is given in usual oral doses of 25 to 50 mg three or four times daily. The dose for children is 6.25 to 25 mg three or four times daily, or a total daily dose of 5 mg/kg may be given in divided doses. The maximum dose in adults and children is about 300 mg daily. A dose of 20 to 50 mg may be used as a hypnotic in adults and children over 12 years old.

When oral therapy is not feasible, diphenhydramine hydrochloride may be given by deep intramuscular injection or by intravenous injection using concentrations of 1% or 5%. Usual doses are 10 to 50 mg, although doses of 100 mg have been given. No more than 400 mg should be given in 24 hours. Children may be given 5 mg/kg daily in divided doses to a maximum of 300 mg in 24 hours. Diphenhydramine hydrochloride is applied topically, usually in preparations containing 1 to 2% although, as with other antihistamines, there is a risk of sensitisation.

Diphenhydramine citrate is given orally in a dose of 76 mg at night in combination preparations for its hypnotic action. Diphenhydramine di(acefyllinate) is given as an antiemetic for the prevention and treatment of motion sickness. The usual oral dose is 90 to 135 mg, which may be repeated if necessary at intervals of at least 6 hours, to a maximum of 540 mg daily. Other diphenhydramine salts that have been used include the polistirex, the salicylate, and the tannate by mouth, the methylbromide rectally, and the metilsulfate applied topically.

Dimenhydrinate (p.576) is diphenhydramine teoclate and mefenidramium metilsulfate is diphenhydramine methylsulfomethylate.

## Preparations

**BP 2008:** Diphenhydramine Oral Solution;

**USP 31:** Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Diphenhydramine and Pseudoephedrine Capsules; Diphenhydramine Hydrochloride Capsules; Diphenhydramine Hydrochloride Elixir; Diphenhydramine Hydrochloride Injection.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Almerina; Amodyn; Benadryl; Benadryl Antiallergico; Caladryl D; Drepattil; Fabologer; Histaler; Klonadryl; Mudantos H; **Austral.:** Snuzaid; Unison; **Austria:** Calmaben; Dermodyn; Dibondrin; Histaxin; Noctor; Sleepat; **Belg.:** Azaron; Benyl; Diphamine; Nuicalm; Nustasium; R Calm; **Braz.:** Difendrin; **Canada:** Aller-Aide; Allerdy; Allergy Caplets; Allergy Elixir; Allergy Formula; Allernix; Benadryl; Calmax; Children's Allergy Formula; Dormex; Dormphen; Isomnal; Jack & Jill Bedtime; Jack & Jill Thin Strips Cough & Cold; Neo Citran Nighttime Cough; Nyctol; Simply Sleep; Sleep Aid; Sleep-Eze D; Somnax; Triaminic Thin Strips Nighttime Cough & Runny Nose; Unison; **Chile:** Jaquedryl; Pasient; Somol; **Cz.:** Benadryl N; Psilo-Balsam; **Fr.:** Butix; Nautamine; **Ger.:** Benadryl N; Betadorm D; Dolestan; Dormult N; Emesax; Halbmund; Hevert-Dorm; Moradorm; nervo OPT N; ratioAllerg; S8; Sedativum-Hevert; Sediad; Sedopretten; Sleepat; Vivinox Sleep; **Gr.:** Sleepat; **Hong Kong:** Benadryl; Calox; Hydramine Cream; Unison; **Hung.:** Psilo-Balsam; **India:** Benadryl; Cofryl; Diminil; **Indon.:** Arcodyl; Benadryl; Oteda; Paradyl; Recodyl; Sidiadryl; **Israel:** Nyctol; **Ital.:** Aliserin; Allergan; Nyctol; **Mex.:** Benadryl; Bionaryl; Bonanot; Drafen; Glcodril; Histadryl; Indumir; Lurispain; Nyctol; Tzoali; **Ulcoid.:** Unison; **NZ:** Unison; **Philipp.:** Allerlin AH; Benadryl Antihistamine; Benaxil; Dramelin; **Port.:** Benaderma; Benergina; Codleryl; Nyctol; **Rus.:** Psilo-Balsam (Псило-Бальзам); **S.Afr.:** Betasleep; Sleepzee-PM; **Singapore:** Benocent; Paxidorm; **Spain:** Benadryl; Neosayonol; Nyctol; Sonodor; **Swed.:** Desentol; **Switz.:** Bedorma; Benocent; Comprimes somniferes "S"; Dobacent; **Thai.:** Benadryl; **Turk.:** Allenik; Allerlin; Benison; Fenotral; **UAE:** Amydramine II; **UK:** Adult Chesty Cough; Child Chesty Cough; Dreemon; Histergan; Mandaly Paediatric; Nightcalm; Nyctol; Paxi-

dorm; Sleep Aid; Sleepzee; **USA:** 40 Winks; Aler-Dryl; AllerMax; Altaryl Children's Allergy; Banophen Allergy; Ben-Tann; Benadryl; Benadryl Allergy; Benadryl Children's Allergy; Benadryl Itch; Children's PediaCare Nighttime Cough; Compoz Night-time Sleep Aid; Dermamycin; Diphen AF; Diphenhist; Dormin; Dyttus; Genahist; Maximum Strength Sleepgels; Maximum Strength Unison SleepGels; Miles Nervine; MouthKote P/R; Nyctol; Scot-Tussin Allergy; Siladryl; Silphen; Simply Sleep; Sleep-Ettes D; Sleepwell 2-nite; Snooze Fast; Somnax; Triaminic Cough & Runny Nose; Tusstat; Twi-lite; **Venez.:** Benadryl; Di-Fedril; Ystajl.

**Multi-ingredient:** numerous preparations are listed in Part 3.

## Diphenylpyraline Hydrochloride (BANM, rINNM)

Diphenylpyraline, Chlorhydrate de; Diphenylpyralini Hydrochloridum; Hidrocloruro de difenilpiralina. 4-Benzhydryloxy-1-methylpiperidine hydrochloride.

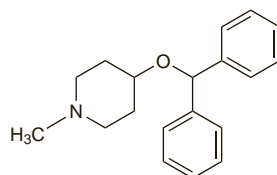
Дифенилпиралина Гидрохлорид

$C_{15}H_{23}NO \cdot HCl = 317.9$ .

CAS — 147-20-6 (diphenylpyraline); 132-18-3 (diphenylpyraline hydrochloride).

ATC — R06AA07.

ATC Vet — QR06AA07.



(diphenylpyraline)

**Pharmacopoeias.** In Br.

**BP 2008** (Diphenylpyraline Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether.

## Adverse Effects and Precautions

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

## Interactions

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

## Pharmacokinetics

◇ References.

- Graham G, Bolt AG. Half-life of diphenylpyraline in man. *J Pharmacokin Biopharm* 1974; **2**: 191–5 (ranged from 24 to 40 hours).

## Uses and Administration

Diphenylpyraline hydrochloride, a piperidine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties.

It has been given for the symptomatic relief of allergic conditions including rhinitis (p.565), and in pruritic skin disorders (p.565). It has also been used in compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

Diphenylpyraline hydrochloride has been given in an oral dose of up to 6 mg daily in 3 or 4 divided doses. Diphenylpyraline and diphenylpyraline hydrochloride have been applied topically although, as with other antihistamines, there is a risk of sensitisation.

Diphenylpyraline teoclate is piprinhydrinate (p.588).

## Preparations

**Proprietary Preparations** (details are given in Part 3)

**Ger.:** Arbid N†.

**Multi-ingredient:** **Austria:** Arbid; Astronautal; Eucillin; Prurimix; Tropoderm; **Belg.:** Bicol; Rhini-San; **Braz.:** Ornatrol†; **Canada:** Creo-Rectal; Vito Bronches†; **Cz.:** Proctospre†; Prurimix†; **Ger.:** Perdiphen†; Proctospre†; Tempil N; **Hong Kong:** Phenahist; **India:** Eskold Expectorant†; Eskold†; **Mex.:** Flumil; **S.Afr.:** Actophlem; Eskomade; Solphylex; Theophen Comp; **Switz.:** Arbid.

## Doxylamine Succinate (BANM, rINNM)

Doksilamin Süksinat; Doksilamino-vandenilio süksinatas; Doksylamiinivetyuksinaatti; Doksilamin-hidrogén-szukcinát; Doxylamine Hydrogen Succinate; Doxylamine, hydrogenosuccinate de; Doxylamine, Succinate de; Doxylamin-hydrogen-sukcinát; Doxylamini hydrogenosuccinas; Doxylamini Succinas; Doxylaminium Succinate; Doxylaminvatesuccinat; Histadoxylamine Succinate; Succinato de doxilamina. NN-Dimethyl-2-[α-methyl-α-(2-pyridyl)benzyloxy]ethylamine hydrogen succinate.

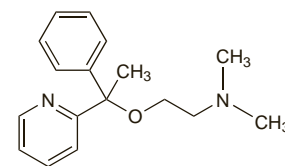
Доксиламин Суксинат

$C_{17}H_{22}N_2O_4 \cdot C_4H_6O_4 = 388.5$ .

CAS — 469-21-6 (doxylamine); 562-10-7 (doxylamine succinate).

ATC — R06AA09.

ATC Vet — QR06AA09.



(doxylamine)

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

**Ph. Eur. 6.2** (Doxylamine Hydrogen Succinate; Doxylamine Succinate BP 2008). A white or almost white powder. Very soluble in water; freely soluble in alcohol.

**USP 31** (Doxylamine Succinate). A white or creamy-white powder having a characteristic odour. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 370 of ether; very slightly soluble in benzene. Protect from light.

## Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. The controversy surrounding the use in pregnancy of combination products of doxylamine is discussed on p.563.

**Overdosage.** In an evaluation of 109 cases of intoxication with doxylamine,<sup>1</sup> no correlation was found between the amount ingested or plasma concentration and the frequency or extent of symptoms. The most common symptom was impaired consciousness. Psychotic behaviour, seizures, and antimuscarinic symptoms such as tachycardia and mydriasis were also observed. Rhabdomyolysis occurred in one patient and was accompanied by transient impairment of renal function. The same group commented<sup>2</sup> that rhabdomyolysis had been noted in 7 of 442 cases of doxylamine overdosage, with an associated rise in plasma creatine kinase and myoglobinuria, and suggested that doxylamine has a direct toxic effect on striated muscle.

- Köppel C, *et al.* Poisoning with over-the-counter doxylamine preparations: an evaluation of 109 cases. *Hum Toxicol* 1987; **6**: 355–9.
- Köppel C, *et al.* Rhabdomyolysis in doxylamine overdose. *Lancet* 1987; **i**: 442–3.

## Interactions

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

## Pharmacokinetics

After oral doses of doxylamine succinate peak plasma concentrations occur after 2 to 3 hours. An elimination half-life of about 10 hours has been reported.

◇ References.

- Friedman H, *et al.* Clearance of the antihistamine doxylamine: reduced in elderly men but not in elderly women. *Clin Pharmacokin* 1989; **16**: 312–16.

## Uses and Administration

Doxylamine succinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative effects.

Doxylamine succinate is given for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders (p.565), as a hypnotic in the short-term treatment of insomnia (p.564), and as an ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p.564).

In general it is no longer used in the management of nausea and vomiting of early pregnancy (see p.563 for the controversy that has surrounded the use in pregnancy of combination products of doxylamine).

Oral doses of up to 25 mg of doxylamine succinate have been given every 4 to 6 hours to a maximum of 150 mg daily. The usual hypnotic dose is 25 mg orally at night.

## Preparations

**USP 31:** Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Doxylamine Succinate Syrup; Doxylamine Succinate Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Austral.:** Dozile; Restavit; **Canada:** Unison-2; **Chile:** Calmax; Dorminotil; Nocpaz; Trimepaz†; Zarcop; **Cz.:** Hoggar N†; **Fr.:** Donormyl; Lidene; Nocyl; **Ger.:** Gittalun; Hewedormir; doxyl intens†; Hoggar Night; Mereprine; Munlett†; SchlafTabs; Sedaplus; **India:** Rest-Aid; **Israel:** Sleep Aid; Unison; **NZ:** Dozile; **Philipp.:** Unison; **Port.:** Dormidina; **S.Afr.:** Equi-Sleep†; Restwel; **Spain:** Dormidina; **Switz.:** Sanalepsi N; **Turk.:** Unison; **USA:** Aldex AN; Unison SleepTabs.

**Multi-ingredient:** **Austral.:** Analgesic/Calmativ; Codalgil Plus; Dimetapp Cold, Cough & Flu; Dolased Analgesic Calmativ; Dolased Day/Night Pain Relief; Fiorinal; Mersyndol; Ordov Migradol†; Panadeine Plus; **Belg.:** Pholco-Mereprine; **Braz.:** Broncolex†; EMS Expectorante; Hytos Plus; Revenil; Revenil Dospan; Revenil Expectorante; Silencium; Silomat Plus†; **Canada:** Dalmacol; Diclectin; Mersyndol with Codeine; Neo Citran Cold & Flu†; Nighttime; Nighttime Cold & Flu; Nyquil Sinus; NyQuil†; ratio-Calmidone; Regular Strength Sinus Medication; Tylenol Sinus (Nighttime Relief); Vicks Nyquil Cold & Flu; **Cz.:** Wick Medinait†; **Fr.:** DolirhumePro; **Ger.:** Paedisup; Wick Medinait†; **India:** Doxinate; Vornate; **Indon.:** Dexamolex; Siladex; **Ir.:** Syndol; **Ital.:** Vicks Medinait; **NZ:** Dimetapp Cold, Cough & Flu Day & Night†; Mersyndol; Pryndette†; **Pol.:** Tabcin Impact†; **Port.:** Nauseflex; **S.Afr.:** Abflex; Acurate; Adco-Dol; Adco-B; D-Dol; Betapain; Cepacol; Codoxol; Doxsyn; Forpyn†; Lenapain; Nethaprin Dospan; Nethaprin Expectorant; Nomopain; Paxidal; Pyncler†; Pynstop; Sedapain; Sedi-