Coltsfoot

Coughwort; Fárfara; Huflattich; Tusílago; Tussilage.

Камчужная Трава

Pharmacopoeias. *Chin.* and *Fr.* include Coltsfoot Flower.

Profile

The leaves and flowers of coltsfoot (*Tussilago farfara*) have been used for their demulcent and supposed expectorant properties in the treatment of cough and other mild respiratory disorders. However, there has been some concern about potential hepatotoxicity and carcinogenicity due to the content of pyrrolizidine alkaloids.

◊ A review[1] of the actions and uses of coltsfoot pointed out that given the potential risks of its use long-term or in pregnancy, and the availability of other demulcent herbs, the use of coltsfoot preparations to treat throat irritations can no longer be considered appropriate.

1. Berry M. Coltsfoot. *Pharm J* 1996; **256:** 234–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Arceligasol; Negacne; ***Cz.:*** Perospirt†; Species Pectorales Planta; ***Ital.:*** Lozione Same Urto; ***Pol.:*** Mucosit; Pyrosal; ***Spain:*** Llantusil†; ***UK:*** Antibron; Chesty Cough Relief.

Creosote

Creasote; Creosota; Creosotal (creosote carbonate); Wood Creosote.

Древесный Креозот

CAS — 8021-39-4 (creosote); 8001-59-0 (creosote carbonate).
ATC — R05CA08.
ATC Vet — QR05CA08.

Pharmacopoeias. In *Jpn.*

Profile

Creosote is a liquid consisting of a mixture of guaiacol, cresol, and other phenols obtained from wood tar. It possesses disinfectant properties and has been used as an expectorant. It has also been used as the carbonate and as lactocreosote.

Adverse effects are similar to those of Phenol, p.1656.

Commercial creosote used for timber preservation is obtained from coal tar.

Preparations

Proprietary Preparations (details are given in Part 3)

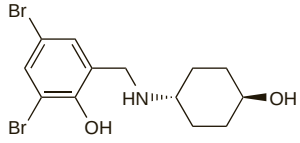
Multi-ingredient: ***Austral.:*** Compound Inhalation of Menthol; ***Austria:*** Famel cum Codein; Famel cum Ephedrin; ***Braz.:*** Rhum Creosotado; ***Hung.:*** Fagifor†; ***India:*** Pulmo-Cod (C & G); ***Ital.:*** Creosoto Composto; Famel†; ***Switz.:*** Famel; ***UK:*** Famel Original.

Dembrexine *(BAN, rINN)*

Dembreksiini; Dembrexin; Dembrexina; Dembrexinum; Dembroxol. *trans*-4-[(3,5-Dibromosalicyl)amino]cyclohexanol.

Дембрексин

$C_{13}H_{17}Br_2NO_2$ = 379.1.
CAS — 83200-09-3 (dembrexine); 52702-51-9 (dembrexine hydrochloride).



Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.
Ph. Eur. 6.2 (Dembrexine Hydrochloride Monohydrate for Veterinary Use; Dembrexine Hydrochloride Monohydrate BP(Vet) 2008). A white or almost white, crystalline powder. Slightly soluble in water and in anhydrous ethanol; freely soluble in methyl alcohol.

Profile

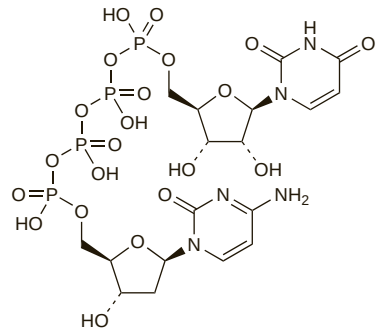
Dembrexine is a mucolytic used as the hydrochloride in veterinary medicine.

Denufosol Tetrasodium *(USAN, rINNM)*

Denufosol tetrasódico; Dénufosol tetrasodique; Denufosolum tetranatricum; INS-37217. 2′-Deoxycytidine(5′)tetraphospho(5′)uridine tetrasodium.

Денуфозол Тетранатрий

$C_{18}H_{23}N_5Na_4O_{21}P_4$ = 861.3.
CAS — 211448-85-0 (denufosol); 318250-11-2 (denufosol tetrasodium).



(denufosol)

Profile

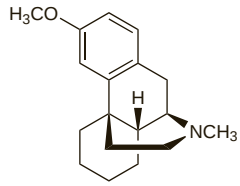
Denufosol tetrasodium is a selective $P2Y_2$-receptor agonist that stimulates chloride and water secretion from respiratory tract epithelial cells, and increases mucosal hydration and mucociliary clearance. An inhaled preparation is under investigation for the treatment of cystic fibrosis.

Dextromethorphan *(BAN, pINN)*

Dekstrometorfaani; Dextrométhorphane; Dextromethorphanum; Dextrometorfan; Dextrometorfano. (+)-3-Methoxy-9a-methylmorphinan; (9*S*,13*S*,14*S*)-6,18-Dideoxy-7,8-dihydro-3-*O*-methylmorphine.

Декстрометорфан

$C_{18}H_{25}NO$ = 271.4.
CAS — 125-71-3.
ATC — R05DA09.
ATC Vet — QR05DA09.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dextromethorphan: Bromage; Brome; Candy; CCC; C-C-C; Dex; Dextro; DM; Drex; DXM; Red Devils; Robo; Rojo; Skittles; Triple C; Triple C's; Tussin; Velvet; Vitamin D.

Pharmacopoeias. In *US.*
USP 31 (Dextromethorphan). A practically white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; freely soluble in chloroform. Store in airtight containers.

Dextromethorphan Hydrobromide *(BANM, pINNM)*

Dekstrometorfaanihydrobromidi; Dekstrometorfan Hidrobromür; Dekstrometorfano hidrobromidas; Dekstrometorfanu bromowodorek; Dextromethorfan-hydrobromid monohydrát; Dextrométhorphane, bromhydrate de; Dextromethorphani hydrobromidum; Dextromethorphani Hydrobromidum Monohydricum; Dextrometorfán-hidrobromid; Dextrometorfanhydrobromid; Hidrobromuro de dextrometorfano. Dextromethorphan hydrobromide monohydrate.

Декстрометорфана Гидробромид

$C_{18}H_{25}NO,HBr,H_2O$ = 370.3.
CAS — 125-69-9 (anhydrous dextromethorphan hydrobromide); 6700-34-1 (dextromethorphan hydrobromide monohydrate).
ATC — R05DA09.
ATC Vet — QR05DA09.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Dextromethorphan Hydrobromide). An almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol. Protect from light.
USP 31 (Dextromethorphan Hydrobromide). Practically white crystals or crystalline powder having a faint odour. Soluble 1 in 65 of water; freely soluble in alcohol and in chloroform; insoluble in ether. pH of a 1% solution in water is between 5.2 and 6.5. Store in airtight containers.

Adverse Effects and Treatment

Adverse effects with dextromethorphan appear to be rare and may include dizziness and gastrointestinal disturbances. Excitation, confusion, and respiratory depression may occur after overdosage. Dextromethorphan has been subject to abuse, but there is little evidence of dependence of the morphine type.

◊ General references.

1. Bem JL, Peck R. Dextromethorphan: an overview of safety issues. *Drug Safety* 1992; **7:** 190–9.

Hypersensitivity. A fixed-drug reaction developed in a patient after ingestion of dextromethorphan 30 mg.[1] Oral provocation with dextromethorphan produced a positive reaction but the results of topical application tests were negative. Urticaria, angioedema, and shortness of breath were reported in another patient;[2] symptoms recurred on oral challenge, but no skin test was performed. Similar symptoms were reported in a third patient;[3] skin testing provoked a positive reaction. On oral rechallenge, the patient developed urticaria initially, followed by generalised erythema and pruritus and decreased blood pressure after a second dose.

1. Stubb S, Reitamo S. Fixed-drug eruption due to dextromethorphan. *Arch Dermatol* 1990; **126:** 970–1.
2. Knowles SR, Weber E. Dextromethorphan anaphylaxis. *J Allergy Clin Immunol* 1998; **102:** 316–17.
3. Robledo T, *et al.* Adverse reaction to dextromethorphan. *Allergy* 2004; **59:** 890.

Overdosage. There have been reports[1-7] of overdosage or accidental poisoning (usually in children) due to dextromethorphan, including rare fatalities. Naloxone may be effective in reversing toxicity. Extrapyramidal reactions were seen in a child who ingested dextromethorphan.[6] Overdosage has also been associated with abuse (see below).

1. Shaul WL, *et al.* Dextromethorphan toxicity: reversal by naloxone. *Pediatrics* 1977; **59:** 117–19.
2. Katona B, Wason S. Dextromethorphan danger. *N Engl J Med* 1986; **314:** 993.
3. Rammer L, *et al.* Fatal intoxication by dextromethorphan: a report on two cases. *Forensic Sci Int* 1988; **37:** 233–6.
4. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; **9:** 237–8.
5. Pender ES, Parks BR. Toxicity with dextromethorphan-containing preparations: a literature review and report of two additional cases. *Pediatr Emerg Care* 1991; **7:** 163–5.
6. Warden CR, *et al.* Dystonic reaction associated with dextromethorphan ingestion in a toddler. *Pediatr Emerg Care* 1997; **13:** 214–15.
7. Roberge RJ, *et al.* Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; **17:** 285–8.

Precautions

Dextromethorphan should not be given to patients at risk of developing respiratory failure. Caution is needed in patients with a history of asthma and it should not be given during an acute attack. Care is also advisable in patients with bronchitis, emphysema, or in other conditions where chronic or persistent cough occurs.

Abuse. Dextromethorphan has been abused,[1-12] alone or with other drugs in over-the-counter preparations or as a powder sold under the name DXM. There have been a few reports of dependence,[1,2,11] but evidence of classical opioid dependence is generally considered to be lacking.

1. Fleming PM. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; **293:** 597.
2. Orrell MW, Campbell PG. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; **293:** 1242–3.
3. Walker J, Yatham LN. Benylin (dextromethorphan) abuse and mania. *BMJ* 1993; **306:** 896.
4. Wolfe TR, Caravati EM. Massive dextromethorphan ingestion and abuse. *Am J Emerg Med* 1995; **13:** 174–6.
5. Nordt SP. DXM: a new drug of abuse? *Ann Emerg Med* 1998; **31:** 794–5.
6. Cranston JW, Yoast R. Abuse of dextromethorphan. *Arch Fam Med* 1999; **8:** 99–100.
7. Price LH, Lebel J. Dextromethorphan-induced psychosis. *Am J Psychiatry* 2000; **157:** 304.
8. Noonan WC, *et al.* Dextromethorphan abuse among youth. *Arch Fam Med* 2000; **9:** 791–2.
9. Banerji S, Anderson IB. Abuse of Coricidin HBP cough and cold tablets: episodes recorded by a poison center. *Am J Health-Syst Pharm* 2001; **58:** 1811–14.
10. Food and Drug Administration. FDA warns against abuse of dextromethorphan (DXM) (issued 20 May 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.html (accessed 16/05/07)
11. Desai S, *et al.* Chronic addiction to dextromethorphan cough syrup: a case report. *J Am Board Fam Med* 2006; **19:** 320–3.
12. Bryner JK, *et al.* Dextromethorphan abuse in adolescence: an increasing trend: 1999-2004. *Arch Pediatr Adolesc Med* 2006; **160:** 1217–22.

Children. For doubts about the use of dextromethorphan as an antitussive in children see Cough, under Uses and Administration, below.

Interactions

Severe and sometimes fatal reactions have been reported after use of dextromethorphan in patients receiving

MAOIs. Dextromethorphan is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6; the possibility of interactions with inhibitors of this enzyme, including amiodarone, haloperidol, propafenone, quinidine, SSRIs, and thioridazine, should be borne in mind.

Antiarrhythmics. *Quinidine* can increase serum concentrations of dextromethorphan markedly, and some patients have experienced symptoms of dextromethorphan toxicity when the two drugs have been used together.[1,2] Based on this interaction, the combination has been studied for its therapeutic effect in amyotrophic lateral sclerosis (see Neurological Disorders, below). *Amiodarone* also appears to be able to increase serum concentrations of dextromethorphan.[3]

1. Zhang Y, *et al.* Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmacol Ther* 1992; **51:** 647–55.
2. Pope LE, *et al.* Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol* 2004; **44:** 1132–42.
3. Funck-Brentano C, *et al.* Influence of amiodarone on genetically determined drug metabolism in humans. *Clin Pharmacol Ther* 1991; **50:** 259–66.

Antibacterials. Serotonin syndrome-like symptoms have occurred when dextromethorphan has been taken with *linezolid*.

Antidepressants. A patient receiving *fluoxetine* experienced visual hallucinations after she began taking dextromethorphan.[1] The hallucinations were similar to those she had had 12 years earlier with lysergide. She had previously taken dextromethorphan alone without any adverse reactions. A serotonin syndrome (p.416) has been reported in a patient who took a cold-remedy containing dextromethorphan while receiving *paroxetine*.[2]

1. Achamallah NS. Visual hallucinations after combining fluoxetine and dextromethorphan. *Am J Psychiatry* 1992; **149:** 1406.
2. Skop BP, *et al.* The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* 1994; **12:** 642–4.

Pharmacokinetics

Dextromethorphan is rapidly absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites including dextrorphan (p.2293), which has some cough suppressant activity.

Genetic polymorphism. The *O*-demethylation of dextromethorphan and the hydroxylation of debrisoquine are under common polymorphic control, involving the cytochrome P450 isoenzyme CYP2D6, and dextromethorphan has been used as an alternative to debrisoquine (p.1256) for the phenotyping of oxidative metabolism.[1,2] Non-invasive determinations can be made using samples of urine or saliva.[3,4] Dextromethorphan has also been suggested as a tool to investigate *N*-demethylation, an alternate metabolic pathway for this drug.[5]

1. Belec L, *et al.* Extensive oxidative metabolism of dextromethorphan in patients with almitrine neuropathy. *Br J Clin Pharmacol* 1989; **27:** 387–90.
2. Streetman DS, *et al.* Dose dependency of dextromethorphan for cytochrome P450 2D6 (CYP2D6) phenotyping. *Clin Pharmacol Ther* 1999; **66:** 535–41.
3. Hildebrand M, *et al.* Determination of dextromethorphan metabolizer phenotype in healthy volunteers. *Eur J Clin Pharmacol* 1989; **36:** 315–18.
4. Hou Z-Y, *et al.* Salivary analysis for determination of dextromethorphan metabolic phenotype. *Clin Pharmacol Ther* 1991; **49:** 410–19.
5. Jones DR, *et al.* Determination of cytochrome P450 3A4/5 activity in vivo with dextromethorphan N-demethylation. *Clin Pharmacol Ther* 1996; **60:** 374–84.

Uses and Administration

Dextromethorphan hydrobromide is a cough suppressant used for the relief of non-productive cough; it has a central action on the cough centre in the medulla. It is also an antagonist of *N*-methyl-D-aspartate (NMDA) receptors. Although structurally related to morphine, dextromethorphan has no classical analgesic properties (but see Pain below) and little sedative activity.

Dextromethorphan hydrobromide is reported to act within half an hour of an oral dose and to exert an effect for up to 6 hours. It is given orally in doses of 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to a usual maximum of 120 mg in 24 hours.

Dextromethorphan polistirex (a dextromethorphan and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release oral preparations. The dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, is the equivalent of 60 mg every 12 hours.

Dextrorphan (p.2293), the *O*-demethylated metabolite of dextromethorphan, also has cough suppressant properties.

For dosage of dextromethorphan in children, see Administration in Children, below.

Administration in children. Although dextromethorphan hydrobromide is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547 and also Cough, below).

In the USA, the following oral doses have been used:

- 2 to 6 years: 2.5 to 5 mg every 4 hours, or 7.5 mg every 6 to 8 hours, to a maximum of 30 mg in 24 hours
- 6 to 12 years: 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours to a maximum of 60 mg in 24 hours

Dextromethorphan polistirex is used in modified-release oral preparations. The following dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, has been given to children:

- 2 to 6 years: 15 mg every 12 hours
- 6 to 12 years: 30 mg every 12 hours

Cough. Equal doses of dextromethorphan hydrobromide and codeine phosphate were of similar efficacy in reducing the frequency of chronic cough (p.1547) in a double-blind crossover study in adults, but dextromethorphan had a greater effect than codeine on cough intensity.[1] However, these drugs were little more effective than placebo in suppressing night-time cough in children.[2-4] The American Academy of Pediatrics has commented[5] that there is no good evidence for the antitussive efficacy of dextromethorphan in children, that dosage guidelines are derived from (possibly inappropriate) extrapolation from effects in adults, and that adverse effects have been reported. Furthermore, in 2008, the FDA and the MHRA advised that over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547).

There is also some evidence that genetic polymorphism in the cytochrome P450 isoenzyme CYP2D6, and hence variations in metabolism, may have a significant influence on the antitussive efficacy of dextromethorphan.[6]

1. Matthys H, *et al.* Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983; **11:** 92–100.
2. Gadomski A, Horton L. The need for rational therapeutics in the use of cough and cold medicine in infants. *Pediatrics* 1992; **89:** 774–6.
3. Taylor JA, *et al.* Efficacy of cough suppressants in children. *J Pediatr* 1993; **122:** 799–802.
4. Paul IM, *et al.* Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004; **114:** e85–e90.
5. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics* 1997; **99:** 918–20. [Re-affirmed October 2006] Also available at: http://pediatrics.aappublications.org/cgi/reprint/99/6/918.pdf (accessed 11/05/07)
6. Wright CE, *et al.* CYP2D6 polymorphism and the anti-tussive effect of dextromethorphan in man. *Thorax* 1997; **52** (suppl 6): A73.

Neurological disorders. Dextromethorphan appears to have anticonvulsant activity and may have neuroprotective effects in cerebral ischaemia.[1] These effects may be related to its activity as an antagonist of *N*-methyl-D-aspartate (NMDA) receptors or to interaction with σ-receptors. It has been studied in Parkinson's disease for treatment[2] or for management of levodopa-induced dyskinesias,[3] and for its potential protective action in stroke and acute brain injury. Dextromethorphan has also been studied for the management of amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) but has not been found to be of benefit.[4-6] A study[7] in which quinidine was given to inhibit the metabolism of dextromethorphan did find the combination to be more effective in controlling pseudobulbar affect (emotional lability) than either drug alone, but also associated with more adverse effects. In the treatment of pseudobulbar affect in multiple sclerosis patients the dextromethorphan and quinidine combination was found to be well tolerated and more effective than placebo.[8] The NMDA-antagonist properties of dextromethorphan have also been investigated for the treatment[9,10] of nonketotic hyperglycinaemia (p.2393).

1. Tortella FC, *et al.* Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends Pharmacol Sci* 1989; **10:** 501–7.
2. Bonuccelli U, *et al.* Dextromethorphan and parkinsonism. *Lancet* 1992; **340:** 53.
3. Verhagen Metman L, *et al.* Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. *Neurology* 1998; **51:** 203–6.
4. Askmark H, *et al.* A pilot trial of dextromethorphan in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1993; **56:** 197–200.
5. Blin O, *et al.* A controlled one-year trial of dextromethorphan in amyotrophic lateral sclerosis. *Clin Neuropharmacol* 1996; **19:** 189–92.
6. Gredal O, *et al.* A clinical trial of dextromethorphan in amyotrophic lateral sclerosis. *Acta Neurol Scand* 1997; **96:** 8–13.
7. Brooks BR, *et al.* Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology* 2004; **63:** 1364–70.
8. Panitch HS, *et al.* Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol* 2006; **59:** 780–7.
9. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97:** 924–6.
10. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132:** 709–13.

Pain. Dextromethorphan has a potential role in the blockade of pain. It has been investigated[1-3] in the management of neuropathic pain with promising results in diabetic neuropathy (p.6), although pain was not reduced in postherpetic neuralgia (p.9). High doses of dextromethorphan may be needed for an effect, or combination with quinidine, which inhibits dextromethorphan metabolism.[4] However, the use of dextromethorphan in diabetic neuropathy remains investigational, and further well-controlled trials are needed.[5]

A systematic review[6] of 28 studies of dextromethorphan as an adjunct for postoperative pain found that despite a tendency for patients to report less pain than with placebo, and to use less opioid analgesia postoperatively, the differences tended to be inconsistent and of questionable clinical significance. There was some suggestion that parenteral dextromethorphan was more effective than oral.

1. Nelson KA, *et al.* High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997; **48:** 1212–18.
2. Sang CN, *et al.* Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology* 2002; **96:** 1053–61.
3. Carlsson KC, *et al.* Analgesic effect of dextromethorphan in neuropathic pain. *Acta Anaesthesiol Scand* 2004; **48:** 328–36.
4. Thisted RA, *et al.* Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study. *Clin Ther* 2006; **28:** 1607–18.
5. Criner TM, Perdun CS. Dextromethorphan and diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 1221–3.
6. Duedahl TH, *et al.* A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* 2006; **50:** 1–13.

Preparations

USP 31: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Dextromethorphan Hydrobromide Syrup; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Dextrotos; Romilar; ***Austral.:*** Benadryl for the Family Dry Forte; Bisolvon Dry; Dexi-Tuss†; Nucosef DM†; Robitussin DX; Robitussin Honey Cough Syrup†; Strepsils Cough Relief; Strepsils Dry Cough†; Tussinol for Dry Coughs†; ***Austria:*** Prontodex; Wick Formel 44; Wick Formel 44 plus Husten-Pastillen; Wick Formel 44 Plus Hustenstiller; ***Belg.:*** Actifed New; Bronchosedal; Dexir; Humex; Nortussine Mono; Notuxal; Romilar Antitussivum; Soludril Antiussivum; Toux-San; Touxium Antitussivum; Tussipect; Tusso Rhinathiol; Vicks Vaposyrup Antitussif; ***Canad.:*** Balminil DM; Benylin DM; Bronchophan DM; Buckley's DM; Calmylin No 1†; Cough Syrup DM; Delsym; DM Children's Cough Syrup; DM Cough Syrup; DM Sans Sucre; Jack & Jill Thin Strips Cough; Koffex DM; Neo Citran Cough; Pharmilin-DM†; Pharminil DM; Robitussin Childrens Cough DM; Robitussin DM CoughGels; Sedatuss DM; Sucrets Cough Control; Syrup DM; Triaminic Cough; Triaminic DM; Triaminic Long Acting Cough; Tussin Antitussive†; Vicks Formula 44; ***Chile:*** Pectobronc; Tusminal; ***Cz.:*** Dr Rentschler Hustenstiller; Humex Pro Deti; Robitussin Antitussicum; Robitussin Junior; Tussidrill; ***Denm.:*** Dexofan; ***Fin.:*** Lagun†; Resilar; ***Fr.:*** Codotussyl Toux Seche; Dexir; Drill toux seche; Ergix; Ergix Toux Seche; Fluditec toux seche; Humex Toux Seche Dextromethorphane; Nodex; Pulmodexane; Tussidane; Tuxium†; Vicks Toux Seche; ***Ger.:*** Arpha Hustensirup†; Em-medical forte†; Hustenstiller; NeoTussan; Silomat DMP; Tuss Hustenstiller†; Wick Formel 44 Husten-Stiller; Wick Formel 44 plus Husten-Pastillen S; ***Gr.:*** Vaposyrup†; ***Hong Kong:*** Balminil DM†; Dextrome; Pusiran; Robitussin Maximum Strength Cough; Robitussin Paediatric Cough; Tussils; ***Hung.:*** Drill; Methor; Rhinathiol; Robitussin Antitussicum; Robitussin Junior; Wick Formula 44 kohogescillapito†; ***India:*** Alex Cough; Lastuss; Lexcof; ***Indon.:*** Bisoltussin; ***Irl.:*** Benylin Non-Drowsy Dry Cough; Delsym; Robitussin Dry Cough; Robitussin Junior; ***Israel:*** Tarodex; ***Ital.:*** Aricodiltosse; Bechilar; Bronchenolo; Broncofama; Formitrol; Honeytuss; Lisomucil Tosse Sedativo; Metorfan; Neo Borocillina Tosse Sciroppo; Sanabronchiol†; Tossoral; Tussycalm; Vicks Tosse Pastiglie; Vicks Tosse Sedativo; ***Malaysia:*** Dexcophan; Metofen Forte†; Nospan; Pusiran; Tussidex Forte†; Tussils; Upha Dextrophan; ***Mex.:*** Atassol; Athos; Balbek; Balsedrina; Bekesina-S; Bekidiba Dex; Bioquidan; Brocolan; Bromelip; Debequin; Dontuxin; Flex Metak; Jarabe Garde; Megal Simple†; Neo-Ulcoid; Numonyl D†; Protan; Quimofan; Romilar; Tosifan; ***Neth.:*** Bisoltussin; Dampo bij droge hoest; Darolan Hoestprikkeldempende; Daromefan; Pectofree; Rami-Dextromethorfan; Romilar; Tussipect; Vicks Hoestsiroop; Vicks Vaposiroop; Vicks Vapotab; ***NZ:*** Benadryl Dry Forte; Robitussin DX; Strepsils Cough; Strepsils Dry Cough; ***Philipp.:*** Cofles; Extendryl DM; Mytusan DM; Pulmodex; Streptuss; Suprekof DM; ***Pol.:*** Acodin; Dexatussin; Robitussin Antitussicum; Robitussin Junior; Tussal Antitussicum; Tussidex; TussiDrill; ***Port.:*** Bisoltussin; Diacol; Drill Tosse Seca; Rhinathiol; Tussilene; Vicks Pastihas; Vicks Xarope Antitussico; ***S.Afr.:*** Benylin Dry Cough; ***Singapore:*** Beathorphan; Dexcophan; Metophan; Nospan; Pusiran; Tussidex†; Tussils; ***Spain:*** Aquitos; Benylin Antitusivo†; Bexatus; Bisolvon Antitusivo; Cinfatos; Formulatus; Frenatus; Ilvitus; Iniston Antitusivo; Parlatos; Pastillas Dr Andreu; Robitussin DM Antitusivo; Romilar; Serratos; Streptuss; Tosrhimatiol†; Tusitinas†; Tusorama; Tussidrill; ***Switz.:*** Astho-Med; Bexine; Calmerphan-L; Calmesine; Emedrin N; Pharmacard Family Toux seche†; Pulmofor; Tussalpront; Vicks Formule 44 Calmine; ***Thai.:*** Cortuss; Dec†; Depan-F; Dex†; Dextramet; Dextroral; Eicof; Icolid; Icolid Plus; Manodextro; MLM-Dex; Polydex; Potussan; Pusiran; Romilar; Strepsils Dry Cough; Throatsil-DEX; Tusco; Tussils; ***UAE:*** Exedexe; Sedofan P; ***UK:*** Adult Dry Cough; Benylin Dry Coughs Non-Drowsy; Dry Cough Syrup; Robitussin for Dry Coughs; Vicks Cough Lozenges with Honey; Vicks Cough Syrup with Honey for Dry Coughs; Vicks Vaposyrup for Dry Coughs; ***USA:*** AeroTuss 12; Benylin Adult†; Benylin Pediatric†; Buckleys

Cough; Creo-Terpin; Creomulsion; Delsym; DexAlone; Diabe-Tuss DM; ElixSure Childrens Cough; Hold DM; Little Colds Cough Formula; PediaCare Childrens Long-Acting Cough; PediaCare Infants Long-Acting Cough; Robitussin Pediatric; Scot-Tussin DM Cough Chasers; Silphen DM; Simply Cough; Sucrets DM; Theraflu Cough; Triaminic Long Acting Cough; Trocal; Vicks 44 Cough Relief; ***Venez.:*** Bromodel†; Detofan†; Hidrofan†; Libolar; Metordex†; Mexobron†; Promedin; Tilodrin.

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

Dimemorfan Phosphate *(rINNM)*

AT-17; Dimémorfane, Phosphate de; Dimemorfani Phosphas; Fosfato de dimemorfano. (+)-3,9a-Dimethylmorphinan phosphate.

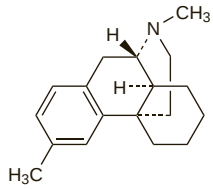
Димеморфана Фосфат

$C_{18}H_{25}N,H_3PO_4$ = 353.4.

CAS — 36309-01-0 (dimemorfan); 36304-84-4 (dimemorfan phosphate).

ATC — R05DA11.

ATC Vet — QR05DA11.



(dimemorfan)

Pharmacopoeias. In *Jpn.*

Profile

Dimemorfan phosphate is a centrally acting cough suppressant used for non-productive cough (p.1547). It is given orally in doses of 10 to 20 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Tusben; ***Spain:*** Dastosin.

Dimethoxanate Hydrochloride *(BANM, rINNM)*

Diméthoxanate, Chlorhydrate de; Dimethoxanati Hydrochloridum; Hidrocloruro de dimetoxanato. 2-(2-Dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate hydrochloride.

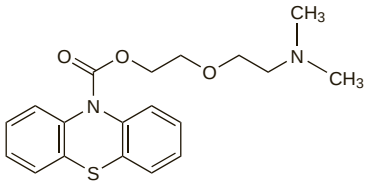
Диметоксаната Гидрохлорид

$C_{19}H_{22}N_2O_3S,HCl$ = 394.9.

CAS — 477-93-0 (dimethoxanate); 518-63-8 (dimethoxanate hydrochloride).

ATC — R05DB28.

ATC Vet — QR05DB28.



(dimethoxanate)

Profile

Dimethoxanate hydrochloride is a centrally acting cough suppressant used for non-productive cough (p.1547). It is given orally in usual doses of 37.5 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Cotrane.

Dornase Alfa *(BAN, USAN, rINN)*

Deoxyribonuclease; Desoxyribonuclease; DNase I; Dornasa alfa; Dornasum Alfa; Dornaz Alfa; rhDNase. Deoxyribonuclease I (human recombinant).

Дорназа Альфа

$C_{1321}H_{1995}N_{339}O_{396}S_9$ = 29249.6.

CAS — 143831-71-4; 132053-08-8.

ATC — B06AA10; R05CB13.

ATC Vet — QB06AA10; QR05CB13.

Description. Dornase alfa is a recombinant enzyme having the same amino acid sequence and glycosylation pattern as human deoxyribonuclease I.

Adverse Effects

Common adverse effects with dornase alfa aerosol include pharyngitis, hoarseness of the voice, and chest pain. Occasionally laryngitis, conjunctivitis, and skin rashes and urticaria have been reported. There may be a transient decline in pulmonary function on beginning therapy with dornase alfa.

Uses and Administration

Dornase alfa acts as a mucolytic by hydrolysing DNA that has accumulated in sputum from decaying neutrophils. It is used as a nebulised solution in patients with cystic fibrosis; in the UK its indication is limited to patients with a forced vital capacity (FVC) greater than 40% of predicted value and to patients over 5 years of age, but in the USA it may also be given for advanced disease (FVC less than 40%) and to younger children. The usual dose is 2500 units (2.5 mg) of dornase alfa given once daily via a jet nebuliser. This dose may be given twice daily to patients over 21 years of age.

Bovine deoxyribonuclease has been used similarly. It has also been used topically, often with fibrinolysin, as a debriding agent for inflammatory and infected lesions. Bovine deoxyribonuclease has also been given by injection.

Administration in children. Although in some countries dornase alfa is not recommended for use in children under 5 years of age, a study[1] to assess the delivery of dornase alfa to the lungs of children with cystic fibrosis aged between 3 months and 5 years, showed that the amounts present in the lower airways were comparable to those in older children. It also appeared to be safe in these younger patients during the 2-week study period.

1. Wagener JS, *et al.* Aerosol delivery and safety of recombinant human deoxyribonuclease in young children with cystic fibrosis: a bronchoscopic study. *J Pediatr* 1998; **133:** 486–91.

Asthma. There are reports of the use of dornase alfa to liquefy mucus plugs and relieve an attack of acute severe asthma (p.1108) in children.[1-3] However, a randomised controlled study[4] found that adding a single dose of nebulised dornase alfa to standard emergency treatment has no benefits in children with moderate to severe acute asthma.

1. Greally P. Human recombinant DNase for mucus plugging in status asthmaticus. *Lancet* 1995; **346:** 1423–4.
2. Patel A, *et al.* Intratracheal recombinant human deoxyribonuclease in acute life-threatening asthma refractory to conventional treatment. *Br J Anaesth* 2000; **84:** 505–7.
3. Durward A, *et al.* Resolution of mucus plugging and atelectasis after intratracheal rhDNase therapy in a mechanically ventilated child with refractory status asthmaticus. *Crit Care Med* 2000; **28:** 560–2.
4. Boogaard R, *et al.* Recombinant human deoxyribonuclease for the treatment of acute asthma in children. *Thorax* 2008; **63:** 141–6.

Chronic obstructive pulmonary disease. A large phase III study in patients hospitalised for acute exacerbations of chronic bronchitis (p.1112) was halted prematurely because of a non-significant trend to increased mortality in patients given dornase alfa.[1]

1. Hudson TJ. Dornase in treatment of chronic bronchitis. *Ann Pharmacother* 1996; **30:** 674–5.

Cystic fibrosis. There is good evidence that inhalation therapy with dornase alfa can produce modest but useful improvement in lung function in some patients with cystic fibrosis (p.166). Most studies have concentrated on patients with mild or moderate disease (forced vital capacity at least 40% of the predicted value) in whom FEV_1 and forced vital capacity have shown improvements generally of the order of 5 to 10%,[1-3] and in whom more prolonged therapy (24 weeks) has been shown to reduce the risk of exacerbations of respiratory infections, and hence the need for intravenous antibacterial therapy.[3] There is also evidence that benefit may occur in patients with more severe disease.[4] A systematic review[5] of studies concluded that there is evidence to show that dornase alfa therapy over a 1-month period is associated with improved lung function. Furthermore, a randomised, multicentre, placebo-controlled study[6] in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a period of 96 weeks. However, only a minority of patients, perhaps about one-third,[7] benefit from the drug, and at present there is no way of identifying those who will respond other than by a therapeutic trial.[8,9]

Given the high cost of therapy, which is not entirely recouped by savings in acute care, there has been some controversy about the appropriate use of dornase alfa:[10-13] it seems to be generally felt that it should be reserved for specialist use in cystic fibrosis clinics, but that patients should not be denied a trial where appropriate. Most responders with mild to moderate impairment of lung function will show improvements within 2 weeks, although in more severely affected patients a 6-week trial is advocated.[8] A review of the use of dornase alfa in cystic fibrosis concluded that dosing on alternate days would be as effective as daily dosing, and would reduce costs and treatment time.[14]

1. Ramsey BW, *et al.* Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis* 1993; **148:** 145–51.
2. Ranasinha C, *et al.* Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993; **342:** 199–202.
3. Fuchs H, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994; **331:** 637–42.
4. McCoy K, *et al.* Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996; **110:** 889–95.
5. Jones AP, *et al.* Dornase alpha for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 15/07/08).
6. Quan JM, *et al.* A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001; **139:** 813–20.
7. Davis PB. Evolution of therapy for cystic fibrosis. *N Engl J Med* 1994; **331:** 672–3.
8. Conway SP, Littlewood JM. rhDNase in cystic fibrosis. *Br J Hosp Med* 1997; **57:** 371–2.
9. Ledson MJ, *et al.* Targeting of dornase alpha therapy in adult cystic fibrosis. *J R Soc Med* 1998; **91:** 360–4.
10. Anonymous. Dornase alfa for cystic fibrosis. *Drug Ther Bull* 1995; **33:** 15–16.
11. Spencer D, Weller P. Dornase-alfa for cystic fibrosis. *Lancet* 1995; **345:** 1307.
12. Bush A, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; **310:** 1533.
13. Robert G, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; **311:** 813.
14. Suri R. The use of human deoxyribonuclease (rhDNase) in the management of cystic fibrosis. *BioDrugs* 2005; **19:** 135–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Pulmozyme; ***Austral.:*** Pulmozyme; ***Austria:*** Pulmozyme; ***Belg.:*** Pulmozyme; ***Braz.:*** Pulmozyme; ***Canad.:*** Pulmozyme; ***Chile:*** Viscozyme; ***Cz.:*** Pulmozyme; ***Denm.:*** Pulmozyme; ***Fin.:*** Pulmozyme; ***Fr.:*** Pulmozyme; ***Ger.:*** Pulmozyme; ***Gr.:*** Pulmozyme; ***Hung.:*** Pulmozyme; ***Irl.:*** Pulmozyme; ***Israel:*** Pulmozyme; ***Ital.:*** Pulmozyme; ***Mex.:*** DNSM; Pulmozyme; ***Neth.:*** Pulmozyme; ***Norw.:*** Pulmozyme; ***NZ:*** Pulmozyme; ***Pol.:*** Pulmozyme; ***Port.:*** Pulmozyme; ***Rus.:*** Pulmozyme (Пульмозим); ***S.Afr.:*** Pulmozyme; ***Spain:*** Pulmozyme; ***Swed.:*** Pulmozyme; ***Switz.:*** Pulmozyme; ***Turk.:*** Pulmozyme; ***UK:*** Pulmozyme; ***USA:*** Pulmozyme.

Multi-ingredient: ***Arg.:*** Clorfibrase; ***Austria:*** Fibrolan; ***Braz.:*** Cauterex; Dermofibrin C†; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino-Cauterex; Gino-Fibrase; Procutan†; ***Chile:*** Elase; ***Cz.:*** Fibrolan; ***Fr.:*** Elase; ***Ger.:*** Fibrolan†; ***Hung.:*** Fibrolan; ***Ital.:*** Elase†; ***Malaysia:*** Elase; ***Mex.:*** Fibrase; Fibrase SA; Ridasa; ***Pol.:*** Fibrolan; ***Switz.:*** Fibrolan.

Dropropizine *(BAN, rINN)*

Dropropitsiini; Dropropizin; Dropropizina; Dropropizinum; UCB-1967. 3-(4-Phenylpiperazin-1-yl)propane-1,2-diol.

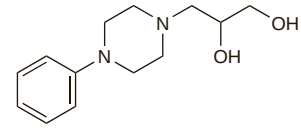
Дропропизин

$C_{13}H_{20}N_2O_2$ = 236.3.

CAS — 17692-31-8.

ATC — R05DB19.

ATC Vet — QR05DB19.



Levodropropizine *(BAN, rINN)*

DF-526; Levdropropizine; Levodropropitsiini; Levodropropizin; Levodropropizina; Levodropropizinas; Lévodropropizine; Levodropropizinum. The (–)-(*S*)-isomer of dropropizine.

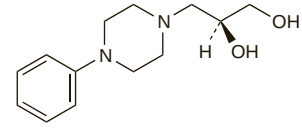
Леводропропизин

$C_{13}H_{20}N_2O_2$ = 236.3.

CAS — 99291-25-5.

ATC — R05DB27.

ATC Vet — QR05DB27.



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

Ph. Eur. 6.2 (Levodropropizine). A white or almost white powder. Slightly soluble in water and in alcohol; freely soluble in dilute acetic acid and in methyl alcohol. A 2.5% solution in water has a pH of 9.2 to 10.2. Protect from light.

Profile

Dropropizine is a cough suppressant reported to have a peripheral action in non-productive cough (p.1547). It is given orally usually in a dose of 30 mg three or four times daily. Levodropropiz-