

Profile

Clomilast is a phosphodiesterase type-4 inhibitor that has been investigated in the treatment of chronic obstructive pulmonary disease.

Clenbuterol Hydrochloride (BANM, rINNM) \otimes

Clenbuterol, chlorhydrate de; Clenbuteroli hydrochloridum; Hidrorodoru de clenbuterol; Klenbuterol hydrochlorid; Klenbuterol-hidroklorid; Klenbuterolhidroklorid; Klenbuterolihydroklorid; Klenbuterolio hidrochloridas; NAB-365 (clenbuterol). 1-(4-Amino-3,5-dichlorophenyl)-2-tert-butylaminoethanol hydrochloride.

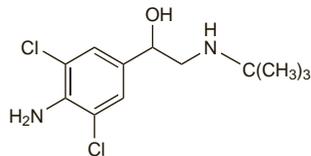
Кленбутерола Гидрохлорид

$C_{12}H_{18}Cl_2N_2O \cdot HCl = 313.7$.

CAS — 37148-27-9 (clenbuterol); 21898-19-1 (clenbuterol hydrochloride).

ATC — R03AC14; R03CC13.

ATC Vet — QR03AC14; QR03CC13.



(clenbuterol)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of clenbuterol:

Angel Dust;
Clen.

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

Ph. Eur. 6.2 (Clenbuterol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 7.0.

Profile

Clenbuterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta₂ receptors (a beta₂ agonist). It has properties similar to those of salbutamol (p.1131). It is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) and in certain patients with chronic obstructive pulmonary disease (p.1112). A usual oral dose is 20 micrograms twice daily; doses of up to 40 micrograms twice daily have occasionally been given. Clenbuterol hydrochloride has also been given by inhalation. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, clenbuterol indicates deterioration of asthma control and the need for review of therapy.

Abuse. Clenbuterol has been used illicitly in animal feeds in an attempt to promote weight gain and to increase muscle to lipid mass. Adverse effects typical of sympathomimetic activity have been attributed to such misuse both in farmers perpetrating such acts¹ and in innocent persons consuming meat products from affected animals.²⁻⁵ Clenbuterol has been abused by sportsmen for its anabolic effects,⁶ although it is doubtful as to whether it enhances performance.⁷ Myocardial infarction was described in an otherwise healthy 17-year-old bodybuilder after abuse of clenbuterol.⁸ Coronary artery spasm and/or temporary thrombosis were suggested as possible explanations for this adverse effect. Contamination of illicit heroin with clenbuterol has also been reported.⁹

- Dawson J. β Agonists put meat in the limelight again. *BMJ* 1990; **301**: 1238-9.
- Martínez-Navarro JF. Food poisoning related to consumption of illicit β -agonist in liver. *Lancet* 1990; **336**: 1311.
- Maistro S, et al. Beta blockers to prevent clenbuterol poisoning. *Lancet* 1995; **346**: 180.
- Brambilla G, et al. Food poisoning following consumption of clenbuterol-treated veal in Italy. *JAMA* 1997; **278**: 635.
- Ramos F, et al. Proposed guidelines for clenbuterol food poisoning. *Am J Med* 2004; **117**: 362.
- Anonymous. Muscling in on clenbuterol. *Lancet* 1992; **340**: 403.
- Spann C, Winter ME. Effect of clenbuterol on athletic performance. *Ann Pharmacother* 1995; **29**: 75-7.
- Kierzkowska B, et al. Myocardial infarction in a 17-year-old body builder using clenbuterol. *Circ* J 2005; **69**: 1144-6.
- CDC. Atypical reactions associated with heroin use: five states, January-April 2005. *MMWR* 2005; **54**: 793-6. Correction. *ibid.*; 852.

Urinary incontinence. A systematic review of the use of adrenergic agonists, including clenbuterol, in urinary incontinence, found that there was weak evidence to suggest that their use was better than placebo.¹ Although only minor adverse effects were reported, the authors noted that there was still potential for rare but serious adverse effects reported elsewhere in the literature.

- Alhasso A, et al. Adrenergic drugs for urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 15/01/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bronq-C; Clembumar; Oxibron; **Austria:** Spiropent; **Chile:** Airum; Asmeren; Broncosolif; **Cz.:** Spiropent; **Ger.:** Contraspasmin; Spiropent; **Gr.:** Spiropent; **Hong Kong:** Clenasma; **Hung.:** Spiropent; **Indon.:** Spiropent; **Ital.:** Clenasma; Monores; Prontovent; Spiropent; **Jpn.:** Spiropent; **Mex.:** Novegas; Oxyflux; Spiropent; **Philipp.:** Spiropent; **Port.:** Broncoterol; Cesbron; **Spain:** Spiropent; Ventolase; **Venez.:** Brodilan; Brodilin; Bucien; Clenbutal; Risopent.

Multi-ingredient Arg.: Mucosolvan Compositum; Oxibron NF; **Austria:** Mucospas; **Ger.:** Spasmo-Mucosolvan; **Mex.:** Ambodil-C; Balsibron-C; Brogal Compositum; Bronolban-M; Brosolan G; Broxof; Compuesto; Broxol Plus; Broxilim-C; Ebromin P; Fludexol-CL; Loxorol; Mucosolvan Compositum; Mucovibrol C; Sekretovit; Ex; Septacin Ex; Seraxol; Serbol; **Port.:** Clembroxol; Mucospas; Ventoliber; **Venez.:** Ambromuco Compositum; Arbixil; Clenbutoxol; Litusix Compositum; Mucolin; Mucosolvan Compositum.

Diprophylline (BAN, rINN)

Dihydroxypropyltheophyllinum; Diprofilina; Diprofilinas; Diprofilin; Diprofilin; Diprofilini; Diprofilin; Diprophyllinum; Dyphylline; Glyphyllinum; Hyphylline. 7-(2,3-Dihydroxypropyl)-1,3-dimethylxanthine; 7-(2,3-Dihydroxypropyl)theophylline.

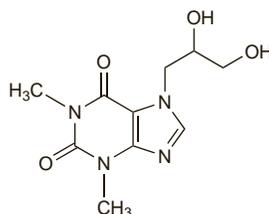
Дипрофиллин

$C_{10}H_{14}N_4O_4 = 254.2$.

CAS — 479-18-5.

ATC — R03DA01.

ATC Vet — QR03DA01.



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

Ph. Eur. 6.2 (Diprophylline). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Dyphylline). A white, odourless, amorphous or crystalline solid. Freely soluble in water; sparingly soluble in alcohol and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140. Diprophylline is primarily excreted unchanged in the urine and should therefore be used with caution in patients with renal impairment; dose adjustments may be required. However, unlike theophylline, plasma concentrations of diprophylline are not greatly affected by changes in liver function or hepatic enzyme activity such as those produced by smoking or age.

Breast feeding. In a study of 20 women given diprophylline by intramuscular injection,¹ diprophylline was found to concentrate in breast milk, with a milk to serum concentration ratio of about 2. However, it was felt that the quantity of diprophylline a breastfed infant would ingest was unlikely to produce any pharmacological action unless the child was very sensitive. The American Academy of Pediatrics² also considers that the use of diprophylline is usually compatible with breast feeding.

- Jarboe CH, et al. Dyphylline elimination kinetics in lactating women: blood to milk transfer. *J Clin Pharmacol* 1981; **21**: 405-10.
- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776-89. Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 19/03/08)

Interactions

Since diprophylline does not undergo metabolism by hepatic microsomal cytochrome P450 it does not exhibit the numerous interactions seen with theophylline (p.1142). However, the possibility of synergistic effects should be borne in mind if it is prescribed with other xanthines.

Probenecid. Probenecid has been reported to decrease the clearance of diprophylline thus prolonging its half-life.¹⁻³

- May DC, Jarboe CH. Inhibition of clearance of dyphylline by probenecid. *N Engl J Med* 1981; **304**: 791.
- May DC, Jarboe CH. Effect of probenecid on dyphylline elimination. *Clin Pharmacol Ther* 1983; **33**: 822-5.
- Acara M, et al. Probenecid inhibition of the renal excretion of dyphylline in chicken, rat and man. *J Pharm Pharmacol* 1987; **39**: 526-30.

Pharmacokinetics

Diprophylline is rapidly absorbed from the gastrointestinal tract and from the site of intramuscular injections. Diprophylline is not converted to theophylline in the body. It is largely excreted

unchanged in the urine with an elimination half-life of about 2 hours. Diprophylline is distributed into breast milk.

Uses and Administration

Diprophylline is a theophylline derivative which is used similarly to theophylline (p.1146) as a bronchodilator in reversible airways obstruction.

The usual oral dose of diprophylline is up to 15 mg/kg every 6 hours. It has also been given intramuscularly. Diprophylline is also an ingredient of preparations that have been promoted for coughs.

Action. Improvements in measurements of lung function after diprophylline in oral doses of 15 and 20 mg/kg were only one-third to one-half those obtained after oral theophylline 6 mg/kg.¹

- Furukawa CT, et al. Diphyllyne versus theophylline: a double-blind comparative evaluation. *J Clin Pharmacol* 1983; **23**: 414-18.

Preparations

USP 31: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Dyphylline Elixir; Dyphylline Injection; Dyphylline Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Austrophyllin; **Gr.:** Silbephyllin; **Hong Kong:** Syneophylline; **Ital.:** Katasma; **Port.:** Neufil; **Turk.:** Difilin; **USA:** Dilort; Dylx; Lufyllin.

Multi-ingredient Fr.: Ozothine a la Diprophylline; **Israel:** Philinat; Philinet; **Ital.:** Cort-Inal; **Spain:** Alergical Expect; Bronsal; Novofilin; **UK:** Noradran; **USA:** Difili-G; Dilex-G; Dy-G; Dyflex-G; Dyline GG; Dyphylline-GG; Jay-Phyl; Lufyllin-EPG; Lufyllin-GG; Panfil G.

Doxofylline (USAN, rINN)

ABC 12/3; Doxofilina; Doxofyllinum. 7-(1,3-Dioxolan-2-ylmethyl)theophylline.

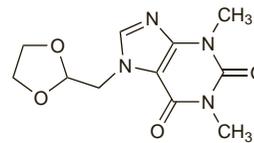
Доксофиллин

$C_{11}H_{14}N_4O_4 = 266.3$.

CAS — 69975-86-6.

ATC — R03DA11.

ATC Vet — QR03DA11.

**Profile**

Doxofylline is a theophylline derivative (p.1140) which is used as a bronchodilator in reversible airways obstruction. It is given in oral doses of up to 1200 mg daily. It may also be given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Ansimar; **Mex.:** Axofin; **Philipp.:** Ansimar; **Thai.:** Puroxan.

Etamiphylline Camsilate (BANM, rINNM)

Camsilato de etamifilina; Diétamiphylline Camposulfonate; Étamiphylline, Camsilate d'; Étamiphylline Camsylate; Etamiphyllini Camsilas; Etamiphyllin Camsylate. 7-(2-Diethylaminoethyl)-1,3-dimethylxanthine camphor-10-sulphonate; 7-(2-Diethylaminoethyl)theophylline camphor-10-sulphonate.

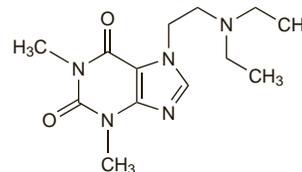
Этамифиллина Камзилат

$C_{23}H_{37}N_5O_6S = 511.6$.

CAS — 314-35-2 (etamiphylline); 19326-29-5 (etamiphylline camsilate).

ATC — R03DA06.

ATC Vet — QR03DA06.



(etamiphylline)

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Etamiphylline Camsilate). A white or almost white powder. Very soluble in water; soluble in alcohol and in chloroform; very slightly soluble in ether. A 10% solution in water has a pH of 3.9 to 5.4.

Profile

Etamiphylline camsilate is a derivative of theophylline (p.1140) and has been used as a bronchodilator in reversible airways ob-