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Acefylline Piperazine *(BAN, rINN)*

Acefilina piperazina; Acéfylline Pipérazine; Acefyllinum Piperazinum; Acepifylline; Piperazine Theophylline Ethanoate. Piperazine bis(theophyllin-7-ylacetate) (1:1).

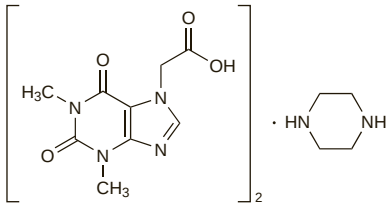
Ацефиллин Пиперазин

$(C_9H_{10}N_4O_4)_2,C_4H_{10}N_2$ = 562.5.

CAS — 18833-13-1; 18428-63-2.

ATC — R03DA09.

ATC Vet — QR03DA09.



Profile

Acefylline piperazine is a derivative of theophylline (p.1140) that has been used for its bronchodilator effects. It is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Etophylate†; ***Indon.:*** Etaphylline.

Multi-ingredient: ***India:*** Cadiphylate.

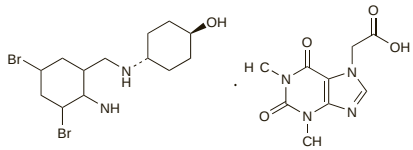
Ambroxol Acefyllinate *(BANM, rINNM)*

Acebrofylline; Acebrophylline; Acefilinato de ambroxol; Ambroxol Acéfylline; Ambroxoli Acefyllinas.

Амброксола Ацефиллинат

$C_{13}H_{18}Br_2N_2O,C_9H_{10}N_4O_4$ = 616.3.

CAS — 96989-76-3.



Profile

Ambroxol acefyllinate is a xanthine derivative that is used as a bronchodilator. It is given in an oral dose of 100 mg twice daily. For doses in children see below.

Administration in children. Ambroxol acefyllinate can be used as a bronchodilator in children. Children from 1 to 6 years of age may be given an oral dose of 25 mg twice daily, and children from 6 to 12 years, 50 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dogistin†; Mucomex†; ***Braz.:*** Brismucol; Brondilat; Bronfilil; Cebronfilina; Expecdilat; Filinar; Teomuc; ***Ital.:*** Ambromucil; Broncomnes; Surfolase; ***Mex.:*** Brismucol; ***Port.:*** Surfolase†; Tusolven†; ***Venez.:*** Brixilon; Bronilis.

Aminophylline *(BAN, pINN)*

Aminofilin; Aminofilina; Aminofylin; Aminofylliini; Aminofyllin; Aminophyllinum; Euphyllinum; Metaphyllin; Teofilinas-etilendiaminas; Teofillinetiléndiamin; Teofylliinetyleenidiamiini; Teofyllinetylendiamin; Theophyllaminum; Theophylline and Ethylenediamine; Theophylline Ethylenediamine Compound; Théophylline-éthylènediamine; Theophyllinum et ethylenediaminum. A mixture of theophylline and ethylenediamine (2:1), its composition approximately corresponding to the formula below.

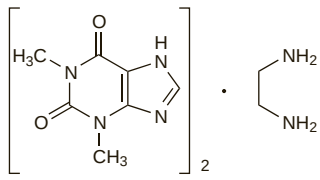
Аминофиллин

$(C_7H_8N_4O_2)_2,C_2H_4(NH_2)_2$ = 420.4.

CAS — 317-34-0 (anhydrous aminophylline).

ATC — R03DA05.

ATC Vet — QR03DA05.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 6.2 (Theophylline-ethylenediamine; Aminophylline BP 2008). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 31 (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Aminophylline Hydrate *(BANM, pINNM)*

Aminofilina dwuwodna; Aminofilina hidratada; Aminofylin hydratovaný; Aminophylline, Hydrate d'; Aminophyllini Hydratum; Aminophyllinum Dihydricum; Aminophyllinum Hydricum; Teofylliinietyleenidiamiinihydraatti; Teofyllinetylendiaminhydrat; Théophylline-éthylènediamine hydratée; Theophyllinum et ethylenediaminum hydricum.

Аминофиллина Гидрат

$(C_7H_8N_4O_2)_2,C_2H_4(NH_2)_2,2H_2O$ = 456.5.

CAS — 49746-06-7 (aminophylline dihydrate).

ATC — R03DA05.

ATC Vet — QR03DA05.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 6.2 (Theophylline-ethylenediamine Hydrate; Aminophylline Hydrate BP 2008). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in well-filled airtight containers. Protect from light.

USP 31 (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Incompatibility. Aminophylline solutions should not be allowed to come into contact with metals.

Solutions of aminophylline are alkaline and if the pH falls below 8, crystals of theophylline will deposit.[1] Drugs known to be unstable in alkaline solutions, or that would lower the pH below the critical value, should not be mixed with aminophylline.

1. Edward M. pH—an important factor in the compatibility of additives in intravenous therapy. *Am J Hosp Pharm* 1967; **24:** 440–9.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140. Hypersensitivity has been associated with the ethylenediamine content.

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

Interactions

As for Theophylline, p.1142.

Pharmacokinetics

Aminophylline, a complex of theophylline with ethylenediamine, readily liberates theophylline in the body. The pharmacokinetics of theophylline are discussed on p.1145.

◊ Studies in healthy subjects suggested that ethylenediamine does not affect the pharmacokinetics of theophylline after oral or intravenous dosage.[1,2]

1. Aslaksen A, *et al.* Comparative pharmacokinetics of theophylline and aminophylline in man. *Br J Clin Pharmacol* 1981; **11:** 269–73.
2. Caldwell J, *et al.* Theophylline pharmacokinetics after intravenous infusion with ethylenediamine or sodium glycinate. *Br J Clin Pharmacol* 1986; **22:** 351–5.

Uses and Administration

Aminophylline has the actions and uses of theophylline (see p.1146) and is used similarly as a bronchodilator in the management of asthma (p.1108) and chronic obstructive pulmonary disease (p.1112). Aminophylline is also used to relieve neonatal apnoea (p.1118). It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease. Aminophylline is usually preferred to theophylline when greater solubility in water is required, particularly in intravenous formulations.

Aminophylline may be given in the anhydrous form or as the hydrate, and doses may be expressed as either; aminophylline hydrate 1.09 mg is equivalent to about