1 mg of aminophylline. The USP 31 specifies that aminophylline preparations should be labelled with respect to their anhydrous *theophylline* content. As the pharmacokinetics of theophylline are affected by a number of factors including age, smoking, disease, diet, and drug interactions, the dose of aminophylline must be carefully individualised and serum-theophylline concentrations monitored (see Uses and Administration of Theophylline, p.1146).

In the management of **acute severe bronchospasm**, aminophylline may be given intravenously by slow injection or infusion. To reduce adverse effects, intravenous aminophylline should not be given at a rate greater than 25 mg/minute. In adults who have not been taking aminophylline, theophylline, or other xanthine-containing medication, a loading dose of 5 mg/kg ideal (lean) body-weight or 250 to 500 mg of aminophylline may be given intravenously over 20 to 30 minutes by slow injection or infusion, followed by a maintenance infusion dose of 500 micrograms/kg per hour. Older patients and those with cor pulmonale, heart failure, or liver disease may require lower maintenance doses; smokers often need higher maintenance doses. A loading dose may not be considered necessary unless the patient's condition is deteriorating.

Intravenous aminophylline is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, the serum-theophylline concentration should first be assessed and the initial loading dose should be calculated on the basis that each 600 micrograms/kg of aminophylline (equivalent to 500 micrograms/kg theophylline) will increase serum-theophylline concentration by 1 microgram/mL.

In the management of **chronic bronchospasm** aminophylline may be given orally as modified-release preparations; a usual dose is aminophylline hydrate 225 to 450 mg twice daily. Therapy should start with the lower dose and be increased as appropriate. Retitration of the dosage is required if the patient is changed from one modified-release preparation to another as the bioavailability of modified-release aminophylline preparations may vary.

For doses of aminophylline used in children, see Administration in Children, below.

Intramuscular injection of aminophylline causes intense local pain and is not recommended.

Aminophylline has also been used as the hydrochloride.

Administration. ***RECTAL ADMINISTRATION.*** Absorption from aminophylline suppositories is erratic and this dose form has been associated with toxicity, hence the warnings that suppositories should not be used, especially in children. In the UK suppositories are no longer readily available and one hospital wishing to use the rectal route for apnoea in premature infants (see Neonatal Apnoea, p.1118) achieved therapeutic plasma-theophylline concentrations with a specially formulated rectal gel.[1]

1. Cooney S, *et al*. Rectal aminophylline gel in treatment of apnoea in premature newborn babies. *Lancet* 1991; **337:** 1351.

Administration in children. Aminophylline may be given intravenously, by slow injection or infusion, to manage **acute severe bronchospasm** in children. Doses should be calculated using ideal or lean body-weight. In children who have not been taking aminophylline, theophylline or other xanthine-containing medicine, UK licensed product information recommends a loading dose of 5 mg/kg given by slow injection or infusion over 20 to 30 minutes. Initial maintenance dose ranges are:

- 6 months up to 10 years of age: 1 mg/kg per hour
- 10 to 16 years of age: 800 micrograms/kg per hour

Although unlicensed in the UK for use in children under 6 months, the *BNFC* allows a dose of 1 mg/kg per hour from 1 month of age. Children aged from 16 years and above may be given adult doses, see Uses and Administration, above. Serum-theophylline concentrations should be used to guide further dose adjustments.

Children who are already receiving theophylline, aminophylline or other xanthine-containing medicines, should not normally receive intravenous aminophylline unless serum-theophylline concentration is available to guide dosage. Loading doses are based on the expectation that each 500 micrograms/kg lean body-weight of theophylline will result in a 1-microgram/mL increase in serum-theophylline concentration.

Oral modified-release preparations are given to children with a body-weight over 40 kg in the long-term management of **chronic bronchospasm**. An initial dose of 225 mg twice daily may be given if the child has not previously received xanthine preparations, increased after 1 week to 450 mg twice daily according to serum-theophylline concentrations. Different modified-release preparations are not considered interchangeable.

Aminophylline may also be used in the management of **neonatal apnoea** (see p.1118). Although the injection is unlicensed in the UK in children under 6 months of age, the *BNFC* recommends an initial dose of 6 mg/kg by intravenous injection over 20 minutes. This is followed by 2.5 mg/kg every 12 hours, increased if necessary to 3.5 mg/kg every 12 hours. The plasma theophylline concentration for optimum response in neonatal apnoea is 8 to 12 mg/litre. For further information on the dosage of theophylline itself in neonates, see Administration in Infants, p.1147.

Erectile dysfunction. For reference to the use of a cream containing aminophylline, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p.1298.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p.747.

Motor neurone disease. A study[1] in 25 patients with amyotrophic lateral sclerosis (see p.2380) found that aminophylline improved the endurance of respiratory muscles and increased the handgrip strength of skeletal muscles; it may have some potential therapeutic benefit in such patients.

1. Berto MC, *et al*. Acute action of aminophylline in patients with amyotrophic lateral sclerosis. *Acta Neurol Scand* 2007; **115:** 301–5.

Reduction of body fat. Cosmetic aminophylline cream has been promoted for its supposed ability to remove fat ('cellulite') from the thighs.[1] Concern has been raised about the potential for topical sensitisation.[2]

1. Dickinson BI, Gora-Harper ML. Aminophylline for cellulite removal. *Ann Pharmacother* 1996; **30:** 292–3.
2. Simon PA. Comment: aminophylline-containing cream. *Ann Pharmacother* 1996; **30:** 1341.

Preparations

BP 2008: Aminophylline Injection; Aminophylline Tablets;
USP 31: Aminophylline Delayed-release Tablets; Aminophylline Injection; Aminophylline Oral Solution; Aminophylline Rectal Solution; Aminophylline Suppositories; Aminophylline Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cardirenal†; Fadafilina; Larjanfilina; ***Austria:*** Euphyllin; Mundiphyllin†; ***Braz.:*** Aminoima; Aminoliv; Asmafin; Asmapen; Asmodrin; Asmoquinol; Minoton; Unifilin; ***Canad.:*** Phyllocontin; ***Chile:*** Cardiomin†; ***Cz.:*** Pharophyllin†; Syntophyllin; ***Denm.:*** Teofylamin; ***Fin.:*** Aminocont; ***Ger.:*** Phyllotemp†; ***Hung.:*** Diaphyllin; ***Indon.:*** Phyllocontin; ***Irl.:*** Phyllocontin; ***Ital.:*** Aminomal; Tefamin; ***Jpn:*** Neophyllin; ***Mex.:*** Amofilin; Drafilyn-Z; ***Neth.:*** Euphyllin†; ***Port.:*** Filotempo; ***S.Afr.:*** Peterphyllin; Phyllocontin; ***Swed.:*** Teofyllamin; ***Switz.:*** Escophylline†; Phyllotemp†; ***Thai.:*** Asmalia; Fileen†; ***Turk.:*** Aminocardol; Asmafilin; Carena; ***UK:*** Amnivent†; Phyllocontin; ***USA:*** Truphylline†; ***Venez.:*** Broncophilina.

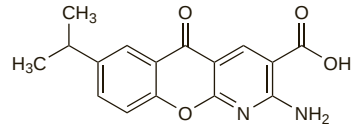
Multi-ingredient: ***Austria:*** Asthma-Hilfe; Limptar; Myocardon; ***Braz.:*** Alergo Filinal; Alergotox Expectorante†; Alergotox†; Dispneitrat; ***Ger.:*** Limptar†; ***Hong Kong:*** Asmeton; ***Mex.:*** Isobutil†; Paliatil; ***Port.:*** Anti-Asmatico; ***S.Afr.:*** Diphenamill†; Genasma; Lotussin Expectorant†; Natrophylline Compound; Repasma; ***Thai.:*** Asmeton†; ***USA:*** Emergent-Ez; ***Venez.:*** Fedratal†.

Amlexanox *(BAN, USAN, rINN)*

AA-673; Amlexanoxo; Amlexanoxum; Amoxanox; CHX-3673. 2-Amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acid.

Амлексанокс

$C_{16}H_{14}N_2O_4$ = 298.3.
CAS — 68302-57-8.
ATC — A01AD07; R03DX01.
ATC Vet — QA01AD07; QR03DX01.



Profile

Amlexanox has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1136) and also acts as a leukotriene inhibitor. It is given orally in the management of asthma (p.1108) and for allergic rhinitis (p.565); a dose of 25 or 50 mg three times daily has been suggested. Amlexanox is also given as a metered-dose nasal spray for allergic rhinitis.

Amlexanox is also applied as a 5% oral paste four times daily in the management of aphthous ulcers (see Mouth Ulceration, p.1700). A 2-mg biodegradable oral disc designed to deliver amlexanox locally is also available.

Preparations

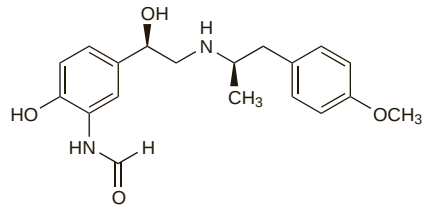
Proprietary Preparations (details are given in Part 3)
Jpn: Solfa; ***Neth.:*** Miraftil; ***USA:*** Aphthasol.

Arformoterol Tartrate *(USAN, rINNM)* ⊗

Arformotérol, Tartrate d'; Arformoteroli Tartras; *R,R*-Formoterol Tartrate; Tartrato de arformoterol. (-)-*N*-[2-Hydroxy-5-((1*R*)-1-hydroxy-2-{[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino}ethyl)phenyl]formamide hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Арформотерола Тартрат

$C_{19}H_{24}N_2O_4,C_4H_6O_6$ = 494.5.
CAS — 67346-49-0 (arformoterol); 200815-49-2 (arformoterol tartrate).



(arformoterol)

Profile

Arformoterol is the *R,R*-enantiomer of the beta$_2$-adrenoceptor agonist formoterol (p.1122) and has similar properties. Arformoterol is a long-acting selective beta$_2$ agonist which is used as a bronchodilator in the management of chronic obstructive pulmonary disease (p.1112). It is given as the tartrate, but doses are described in terms of the base; 22 micrograms of arformoterol tartrate is equivalent to about 15 micrograms of arformoterol. Given as a nebulised solution, a usual inhaled dose of arformoterol is 15 micrograms given every 12 hours.

◊ References.

1. Lötvall J, *et al*. The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
2. Anonymous. Arformoterol (Brovana) for COPD. *Med Lett Drugs Ther* 2007; **49:** 53–5.
3. Baumgartner RA, *et al*. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther* 2007; **29:** 261–78.
4. Matera MG, Cazzola M. Ultra-long-acting β -adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? *Drugs* 2007; **67:** 503–15.

Preparations

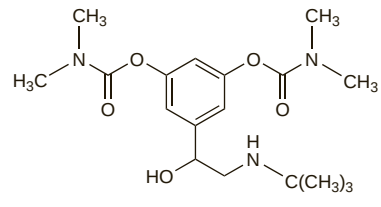
Proprietary Preparations (details are given in Part 3)
USA: Brovana.

Bambuterol Hydrochloride *(BANM, rINNM)* ⊗

Bambutérol, chlorhydrate de; Bambuterol-hidroklorid; Bambuterol-hydrochlorid; Bambuterolhydroklorid; Bambuteroli hydrochloridum; Bambuterolihydrokloridi; Bambuterolio hidrochloridas; Hidrocloruro de bambuterol; KWD-2183. (*RS*)-5-(2-*tert*-Butylamino-1-hydroxyethyl)-*m*-phenylene bis(dimethylcarbamate) hydrochloride.

Бамбутерола Гидрохлорид

$C_{18}H_{29}N_3O_5$,HCl = 403.9.
CAS — 81732-65-2 (bambuterol); 81732-46-9 (bambuterol monohydrochloride).
ATC — R03CC12.
ATC Vet — QR03CC12.



(bambuterol)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Bambuterol Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Bambuterol is not recommended for patients with severe hepatic impairment as its metabolism would be unpredictable. The dose of bambuterol should be reduced in

renal impairment (see below). It is unsuitable for the relief of acute bronchospasm or in patients with unstable respiratory disease.

Effects on the heart. A prescription event monitoring study found an excess risk of non-fatal heart failure in elderly patients receiving bambuterol, particularly in the first month of treatment.[1] See also under Salbutamol, p.1131.

1. Martin RM, *et al.* Risk of non-fatal cardiac failure and ischaemic heart disease with long acting β agonists. *Thorax* 1998; **53:** 558–62.

Interactions

As for Salbutamol, p.1132. Bambuterol inhibits plasma cholinesterases and can prolong the action of drugs such as suxamethonium (see Sympathomimetics, under Suxamethonium, p.1912) that are inactivated by these enzymes.

Pharmacokinetics

Nearly 20% of a dose of bambuterol is absorbed from the gastrointestinal tract after oral doses. It is slowly metabolised in the body to its active metabolite, terbutaline; peak terbutaline concentrations are reported to occur about 4 to 7 hours after a dose of bambuterol as tablets. The slow rate at which metabolism occurs determines the prolonged duration of action of bambuterol of at least 24 hours. Hydrolysis of bambuterol is catalysed by plasma cholinesterase; however, bambuterol also inhibits plasma cholinesterase and therefore partly inhibits its own metabolism. For the metabolism and excretion of terbutaline, see p.1139.

◊ References.

1. Sitar DS. Clinical pharmacokinetics of bambuterol. *Clin Pharmacokinet* 1996; **31:** 246–56.
2. Nyberg L, *et al.* Pharmacokinetics of bambuterol in healthy subjects. *Br J Clin Pharmacol* 1998; **45:** 471–8.
3. Bang U, *et al.* Pharmacokinetics of bambuterol in subjects homozygous for the atypical gene for plasma cholinesterase. *Br J Clin Pharmacol* 1998; **45:** 479–84.
4. Ahlström H, *et al.* Pharmacokinetics of bambuterol during oral administration to asthmatic children. *Br J Clin Pharmacol* 1999; **48:** 299–308.
5. Rosenborg J, *et al.* Pharmacokinetics of bambuterol during oral administration of plain tablets and solution to healthy adults. *Br J Clin Pharmacol* 2000; **49:** 199–206.

Uses and Administration

Bambuterol is an inactive prodrug of terbutaline (p.1138), a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has similar actions to those of salbutamol (p.1133) except that it has a more prolonged duration of action (at least 24 hours). Bambuterol hydrochloride is used as a long-acting bronchodilator for persistent reversible airways obstruction in conditions such as asthma (p.1108). The usual dose is 10 to 20 mg orally once daily at bedtime. Doses may need to be reduced in renal impairment (see below).

Administration in renal impairment. Licensed product information recommends that the initial dose of bambuterol hydrochloride should be halved in patients with renal impairment (glomerular filtration rate less than 50 mL/minute). Further doses should be adjusted according to response.

Asthma. References.

1. Fugleholm AM, *et al.* Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma. *Eur Respir J* 1993; **6:** 1474–8.
2. Gunn SD, *et al.* Comparison of the efficacy, tolerability and patient acceptability of once-daily bambuterol tablets against twice-daily controlled release salbutamol in nocturnal asthma. *Eur J Clin Pharmacol* 1995; **48:** 23–8.
3. Zarkovic JP, *et al.* The Bambuterol Multicentre Study Group. One-year safety study with bambuterol once daily and terbutaline three times daily in 2-12-year-old children with asthma. *Pediatr Pulmonol* 2000; **29:** 424–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Bambec; ***Braz.:*** Bambec; ***Cz.:*** Bambec†; ***Denm.:*** Bambec; ***Fr.:*** Oxeol; ***Ger.:*** Bambec; ***Hong Kong:*** Bambec†; ***Hung.:*** Bambec†; ***India:*** Bambudil; ***Ital.:*** Bambec†; ***Malaysia:*** Bambec†; ***Norw.:*** Bambec; ***NZ:*** Bambec; ***Philipp.:*** Bambec; ***Singapore:*** Bambec; ***Spain:*** Bambec; ***Swed.:*** Bambec; ***Thai.:*** Bambec; ***UK:*** Bambec.

Multi-ingredient: ***India:*** Montair Plus.

Bamifylline Hydrochloride *(BANM, USAN, rINNM)*

AC-3810; Bamifylline, Chlorhydrate de; Bamifyllini Hydrochloridum; BAX-2739Z; 8102-CB; CB-8102; Hidrocloruro de bamifilina. 8-Benzyl-7-[2-(*N*-ethyl-*N*-2-hydroxyethylamino)ethyl]theophylline hydrochloride.

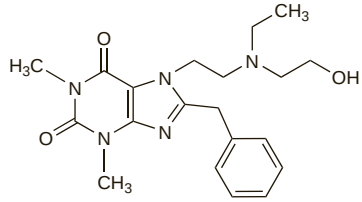
Бамифиллина Гидрохлорид

$C_{20}H_{27}N_5O_3,HCl$ = 421.9.

CAS — 2016-63-9 (bamifylline); 20684-06-4 (bamifylline hydrochloride).

ATC — R03DA08.

ATC Vet — QR03DA08.



(bamifylline)

Profile

Bamifylline hydrochloride is a theophylline derivative (p.1140) that is used for its bronchodilator properties in reversible airways obstruction. It is not converted to theophylline in the body. It is given in usual oral doses of 600 or 900 mg daily in 2 or 3 divided doses. It is also given rectally as suppositories, and by slow intravenous infusion.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Trentadil; ***Braz.:*** Bamifix; ***Fr.:*** Trentadil; ***Ital.:*** Airest†; Bamifix; Bamixol†; Briofil.

Bitolterol Mesilate *(BANM, rINNM)* ⊗

Bitoltérol, Mésilate de; Bitolterol Mesylate *(USAN)*; Bitolteroli Mesilas; Mesilato de bitolterol; Win-32784. 4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-*o*-phenylene di-*p*-toluate methanesulphonate.

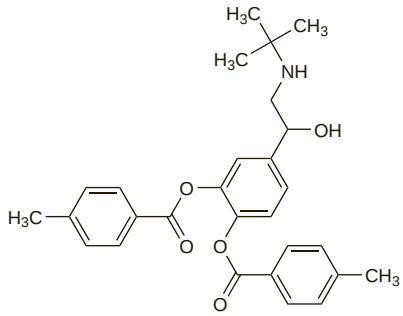
Битолтерола Мезилат

$C_{28}H_{31}NO_5,CH_4O_3S$ = 557.7.

CAS — 30392-40-6 (bitolterol); 30392-41-7 (bitolterol mesilate).

ATC — R03AC17.

ATC Vet — QR03AC17.



(bitolterol)

Profile

Bitolterol is an inactive prodrug that is hydrolysed in the body to colterol, a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has similar properties to those of salbutamol (p.1131).

It has been used as a bronchodilator in the management of diseases with reversible airways obstruction such as asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112); inhalation results in the rapid onset of bronchodilatation (2 to 4 minutes) with a duration of action of 5 or more hours.

Bitolterol has been given by inhalation via a metered-dose aerosol supplying 370 micrograms of bitolterol mesilate per inhalation. For the *relief* of bronchospasm the usual adult dose is 2 inhalations (740 micrograms) followed by a third inhalation (370 micrograms) if required. For the *prevention* of bronchospasm the usual adult dose is 2 inhalations (740 micrograms) every 8 hours. Maximum doses have been stated to be 3 inhalations (1110 micrograms) every 6 hours or 2 inhalations (740 micrograms) every 4 hours. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, bitolterol indicates deterioration of asthma control and the need for review of therapy.

Alternatively, a 0.2% inhalation solution of bitolterol mesilate has been given by nebulisation. Using *continuous flow* nebulisation, the usual adult dose is from 1.5 to 3.5 mg three or four times daily as required, to a maximum daily dose of 14 mg. Using *intermittent flow* nebulisation, the usual adult dose is 0.5 to 2 mg three or four times daily as required, up to a maximum daily dose of 8 mg. In all cases dosage intervals should be greater than or equal to 4 hours.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Tornalate.

Bufylline *(BAN)*

Ambuphylline *(USAN)*; Bufilina; Theophylline-aminoisobutanol. 2-Amino-2-methylpropan-1-ol theophyllinate.

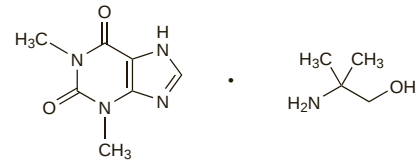
Буфиллин

$C_{11}H_{19}N_5O_3$ = 269.3.

CAS — 5634-34-4.

ATC — R03DA10.

ATC Vet — QR03DA10.



Profile

Bufylline is a theophylline derivative (p.1140) that has been used for its bronchodilator effects as an ingredient of preparations promoted for coughs and other respiratory-tract disorders. The ethiodide has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Broncolex†; EMS Expectorante; Revenil; Revenil Dospan; Revenil Expectorante; ***S.Afr.:*** Nethaprin Dospan; Nethaprin Expectorant.

Caffeine *(BAN)*

Anhydrous Caffeine; Cafeína; Caféine; Coffeinum; Guaranine; Kofeiini; Kofein; Kofeina; Kofeinas; Koffein; Methyltheobromine; Théine. 1,3,7-Trimethylpurine-2,6(3*H*,1*H*)-dione; 1,3,7-Trimethylxanthine; 7-Methyltheophylline.

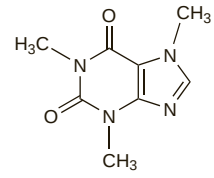
Кофеин

$C_8H_{10}N_4O_2$ = 194.2.

CAS — 58-08-2.

ATC — N06BC01.

ATC Vet — QN06BC01.



NOTE. Compounded preparations of caffeine may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 6.2 (Caffeine). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 31 (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Caffeine Citrate *(BANM)*

Cafeína, citrato de; Citrated Caffeine; Coffeinum Citricum.

Кофеина Цитрат

$C_8H_{10}N_4O_2,C_6H_8O_7$ = 386.3.

CAS — 69-22-7.

ATC — N06BC01.

ATC Vet — QN06BC01.