Tiludronate Disodium *(USAN)*

Tiludronate Sodium *(BANM, rINNM)*; Disodium Tiludronate; Natrii Tiludronas; Sodium Tiludronate; SR-41319B; Tiludronate de Sodium; Tiludronato sódico. Disodium dihydrogen {[(*p*-chlorophenyl)thio]methylene}diphosphonate hemihydrate.

Натрий Тилудронат

$C_7H_7ClNa_2O_6P_2S, \cdot H_2O$ = 371.6.

CAS — 149845-07-8 (anhydrous disodium tiludronate); 155453-10-4 (tiludronate disodium hemihydrate).

ATC — M05BA05.

ATC Vet — QM05BA05.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Asthenia and dizziness have been reported rarely.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including tiludronate, see under Bisphosphonates, p.1091.

Effects on the skin. As with other bisphosphonates, tiludronate has been associated with rash and pruritus. For reference to a case of massive epidermal necrosis possibly associated with tiludronate, see Hypersensitivity, under Bisphosphonates, p.1091.

Interactions

As for the bisphosphonates in general, p.1091. Indometacin may increase the bioavailability of tiludronate two to fourfold; diclofenac does not appear to have this effect. Aspirin may decrease the bioavailability of tiludronate by 50%.

Pharmacokinetics

Like other bisphosphonates tiludronate is poorly absorbed after oral doses. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The oral bioavailability of tiludronate is about 6% in the fasting state, and is reduced by about 90% when given within 2 hours of food. Plasma protein binding is about 90%, mostly to albumin. Tiludronate is not metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

Uses and Administration

Tiludronate is a bisphosphonate with similar properties to those of the bisphosphonates in general (p.1091). It inhibits bone resorption and is used for Paget's disease of bone.

It is given orally as tiludronate disodium, but doses are expressed in terms of the equivalent amount of tiludronic acid; 117 mg of tiludronate disodium is equivalent to about 100 mg of tiludronic acid. To ensure adequate absorption doses should be taken with plenty of water (at least 200 mL), at least 2 hours before or after meals. In Paget's disease of bone the usual dose is 400 mg once daily for 3 months, and this may be repeated if necessary after an interval of at least 3 to 6 months.

Tiludronate has been tried in postmenopausal osteoporosis, but results were disappointing.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Skelid; ***Austria:*** Skelid; ***Belg.:*** Skelid; ***Fin.:*** Skelid†; ***Fr.:*** Skelid; ***Ger.:*** Skelid; ***Hung.:*** Skelid; ***Neth.:*** Skelid; ***Port.:*** Skelid; ***Spain:*** Skelid; ***Swed.:*** Skelid†; ***Switz.:*** Skelid; ***UK:*** Skelid; ***USA:*** Skelid.

Zoledronate

ATC — M05BA08.

ATC Vet — QM05BA08.

Zoledronic Acid *(BAN, USAN, rINN)*

Acide Zolédronique; Ácido zoledrónico; Acidum Zoledronicum; CGP-42446; Tsoledronihappo; Zoledronik Asit; Zoledronsyra. (1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid.

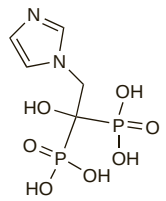
Золедроновая Кислота

$C_5H_{10}N_2O_7P_2$ = 272.1.

CAS — 118072-93-8 (anhydrous zoledronic acid); 165800-06-6 (zoledronic acid monohydrate).

ATC — M05BA08.

ATC Vet — QM05BA08.



Zoledronate Disodium *(BANM, USAN, rINNM)*

CGP-42446A; ZOL-446; Zoledronas Dinatricum; Zolédronate Disodique; Zoledronato disódico. Disodium dihydrogen (1-hydroxy-2-imidazol-1-ylethylidene)diphosphonate tetrahydrate.

Динатрий Золедронат

$C_5H_8N_2Na_2O_7P_2, 4H_2O$ = 388.1.

CAS — 165800-07-7.

ATC — M05BA08.

ATC Vet — QM05BA08.

Zoledronate Trisodium *(BANM, USAN, rINNM)*

CGP-42446B; Zoledronas Trinatricum; Zolédronate Trisodique; Zoledronato trisódico. Trisodium hydrogen (1-hydroxy-2-imidazol-1-ylethylidene)diphosphonate hydrate (5:2).

Тринатрий Золедронат

$C_5H_7N_2Na_3O_7P_2, 2 \cdot H_2O$ = 383.1.

CAS — 165800-08-8.

ATC — M05BA08.

ATC Vet — QM05BA08.

Adverse Effects and Precautions

As for Pamidronate, p.1101. It is important to ensure adequate hydration before and after doses of zoledronic acid as dehydration predisposes to deterioration in renal function.

Effect on electrolytes. Zoledronate has more potent effects on calcium than some of the other bisphosphonates, and has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in some patients.[1,2] In most cases, pre-existing conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1] Vitamin D deficiency should be treated before starting zoledronate.[1,2]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328:** 335–6.
2. Breen TL, Shane E. Prolonged hypocalcemia after treatment with zoledronic acid in a patient with prostate cancer and vitamin D deficiency. *J Clin Oncol* 2004; **22:** 1531–2.

Effects on the eyes. For reports of ocular effects with bisphosphonates, including zoledronate, see p.1090.

Effects on the heart. For a report of a possible association between zoledronate and serious atrial fibrillation, see Effects on the Heart, under Bisphosphonates, p.1090.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, see under Bisphosphonates, p.1091. Doses may need adjusting in some patients with renal impairment (see Administration in Renal Impairment, below).

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including zoledronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Plasma concentrations of zoledronate rise rapidly after the start of an intravenous infusion. Plasma protein binding is low; it has been variously reported as 22 or 56%. Zoledronate is not metabolised, and about 23 to 55% of the dose is excreted in the urine unchanged within 24 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment (see Administration in Renal Impairment, below).

◊ References.

1. Chen T, *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; **42:** 1228–36.

Uses and Administration

Zoledronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. Zoledronic acid is given as an intravenous infusion over not less than 15 minutes.

It is used for **hypercalcaemia of malignancy**, in a single dose of 4 mg, diluted with 100 mL of sodium chloride 0.9% or glucose 5%. The treatment may be repeated if necessary after at least 7 days, at a dose of 4 mg. Individual doses should not exceed 4 mg, as there is an increased risk of adverse renal effects, including renal failure.

Zoledronic acid is given for the prevention of skeletal events in patients with advanced **bone malignancies** (p.660) at a dose of 4 mg, diluted as above, every 3 to 4 weeks.

For the treatment of **Paget's disease** of bone, zoledronic acid is given as a single intravenous infusion of 5 mg.

Zoledronic acid is also used for the treatment of **osteoporosis** in postmenopausal women; the recommended dose is a single intravenous infusion of 5 mg given once a year.

◊ Reviews.

1. Cheer SM, Noble S. Zoledronic acid. *Drugs* 2001; **61:** 799–805.
2. Theriault RL. Zoledronic acid (Zometa) use in bone disease. *Expert Rev Anticancer Ther* 2003; **3:** 157–66.
3. Neville-Webbe H, Coleman RE. The use of zoledronic acid in the management of metastatic bone disease and hypercalcaemia. *Palliat Med* 2003; **17:** 539–53.
4. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther* 2003; **25:** 2669–2708.
5. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
6. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.
7. Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. *Cancer Treat Rev* 2008; **34:** 183–92.

Administration in renal impairment. Despite the fact that renal clearance of zoledronic acid correlates to renal function, a pharmacokinetic study[1] concluded that no dosage adjustment appeared necessary in patients with mild to moderate renal impairment (creatinine clearance 50 to 80 mL/minute, and 10 to 50 mL/minute, respectively).

Licensed product information also states that no adjustment is necessary in mild to moderate renal impairment for patients with *hypercalcaemia of malignancy*, but defines this degree of impairment in terms of serum creatinine less than 400 micromoles/litre or less than 4.5 mg per 100 mL.

However, for patients with *advanced bone malignancies*, the intravenous dose of zoledronic acid should be adjusted on the basis of creatinine clearance (CC) as follows:

- CC greater than 60 mL/minute: 4 mg (no adjustment necessary)
- CC 50 to 60 mL/minute: 3.5 mg
- CC 40 to 49 mL/minute: 3.3 mg
- CC 30 to 39 mL/minute: 3 mg
- CC below 30 mL/minute: treatment not recommended

Serum creatinine should be measured before each dose and treatment withheld if renal function has deteriorated. Renal deterioration is defined as an increase of 44 micromoles/litre or 0.5 mg per 100 mL for those patients with normal baseline creatinine, and an increase of 88 micromoles/litre or 1 mg per 100 mL for those with abnormal baseline creatinine. Treatment may be restarted at the dose used before treatment interruption once the creatinine returns to within 10% of the baseline value.

For patients with *Paget's disease* or *osteoporosis*, UK licensed product information states that no dose adjustment is considered necessary for those with CC of 40 mL/minute or more; due to a lack of clinical data, treatment is not recommended for those with CC of less than 40 mL/minute.

1. Skerjanec A, *et al.* The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003; **43:** 154–62.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. Zoledronate has been shown to have a faster onset, higher response rate, and longer duration of action than pamidronate.[1] It also has a shorter infusion time than pamidronate,[1] and some consider it the treatment of choice for hypercalcaemia of malignancy.[2-4] However, zoledronate has caused severe hypocalcaemia in some patients, see Effects on Electrolytes, above.

1. Major P, *et al.* Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; **19:** 558–67.
2. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. *Oncologist* 2002; **7:** 481–91.
3. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
4. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660) not

only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Zoledronate is licensed for such use in many countries.[1]

In the treatment of skeletal complications from bone metastases secondary to multiple myeloma or breast cancer, zoledronate was more effective than pamidronate in reducing the risk of complications from breast cancer; it was of similar efficacy in those with multiple myeloma.[2] In a placebo-controlled study in patients with prostate cancer,[3] zoledronate reduced the number of skeletal-related events, and increased the median time to events. In patients with bone metastases arising from lung cancer and other solid tumours (excluding breast or prostate cancer), zoledronate reduced skeletal morbidity; the primary end-point, which excluded hypercalcaemia as a skeletal-related event, did not reach statistical significance.[4] However, the authors noted that the patient groups had a shorter-than-expected survival-time. A longer term follow-up of this study[5] confirmed a sustained reduction in risk of developing skeletal events with zoledronate. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Dhillon S, Lyseng-Williamson KA. Zoledronic Acid: a review of its use in the management of bone metastases of malignancy. *Drugs* 2008; **68:** 507–34.
2. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003; **98:** 1735–44.
3. Saad F, *et al.* Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004; **96:** 879–82.
4. Rosen LS, *et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003; **21:** 3150–7.
5. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer* 2004; **100:** 2613–21.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Five different dosage regimens of zoledronate all increased bone mineral density (BMD) in **postmenopausal** women when given intermittently over the course of 1 year in a placebo-controlled study.[1] Compared with placebo, a once-yearly infusion of zoledronate over a 3-year period significantly reduced the risk of vertebral, hip, and other fractures in postmenopausal women with osteoporosis.[2] BMD was also significantly increased. Adverse events were similar in both groups, including renal function changes; however, serious atrial fibrillation occurred more frequently in the zoledronate group (see Effects on the Heart, under Bisphosphonates, p.1090). Once-yearly infusion of zoledronate beginning within 90 days after surgical repair of a low-trauma hip fracture was associated with a reduction in the rate of new vertebral and non-vertebral fractures, although the reduction in the risk of new hip fractures was non-significant.[3]

Preliminary results from a study evaluating zoledronate for the prevention of cancer **treatment-induced** bone loss, in postmenopausal women with early breast cancer treated with letrozole, suggest that adding zoledronate to the regimen from the start is more effective than delaying treatment until there is evidence of bone loss.[4] In a small study,[5] zoledronate also improved the calcium content of cancellous bone, maintained femoral neck BMD, and increased lumbar spine BMD after kidney transplantation. In a similar study of liver transplant recipients, zoledronate also had favourable effects on BMD. This effect tended to diminish at 12 months when compared with placebo; the authors considered this to be due to improved general health, mobility, muscle mass, and nutrition as a consequence of improved liver function.[6]

1. Reid IR, *et al.* Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002; **346:** 653–61.
2. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.
3. Lyles KW, *et al.* HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; **357:** 1799–1809.
4. Brufsky A, *et al.* Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007; **25:** 829–36.
5. Haas M, *et al.* Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 2003; **63:** 1130–6.
6. Crawford BAL, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; **144:** 239–48.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Zoledronate is highly effective in Paget's disease. Single infusions of up to 400 micrograms have been shown to inhibit bone resorption in patients with active Paget's disease.[1,2] In a patient[3] with disease refractory to other bisphosphonates, a single infusion of 4 mg improved symptoms and improved biochemical markers of disease activity. A placebo-controlled study compared a single infusion of 5 mg zoledronic acid with a 60-day course of oral risedronate 30 mg daily. Patients receiving zoledronic acid had significantly more rapid and marked reduction in serum alkaline phosphatase concentrations, higher response rates, and shorter median times to response than those on risedronate. During an open extension study, patients on risedronate had a significantly larger loss of therapeutic response than those given zoledronic acid.[4] A review[5] concluded that zoledronic acid was an important first-line treatment for Paget's disease.

1. Arden-Cordone M, *et al.* Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int* 1997; **60:** 415–18.
2. Buckler H, *et al.* Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone* 1999; **24** (suppl): 81S–85S.
3. Chung G, Keen RW. Zoledronate treatment in active Paget's disease. *Ann Rheum Dis* 2003; **62:** 275–6.
4. Reid IR, *et al.* Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005; **353:** 898–908.
5. Keating GM, Scott LJ. Zoledronic acid: a review of its use in the treatment of Paget's disease of bone. *Drugs* 2007; **67:** 793–804.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aclasta; Rionit; Zometa; ***Austral.:*** Zometa; ***Austria:*** Zometa; ***Belg.:*** Aclasta; Zometa; ***Braz.:*** Zometa; ***Canad.:*** Aclasta; Zometa; ***Chile:*** Zometa; ***Cz.:*** Aclasta; Zometa; ***Denm.:*** Aclasta; Zometa; ***Fin.:*** Aclasta; Zometa; ***Fr.:*** Aclasta; Zometa; ***Ger.:*** Aclasta; Zometa; ***Gr.:*** Aclasta; Zometa; ***Hong Kong:*** Zometa; ***Hung.:*** Aclasta; Zometa; ***India:*** Zoldria; Zometa; ***Indon.:*** Zometa; ***Irl.:*** Aclasta; Zometa; ***Israel:*** Zomera; ***Ital.:*** Zometa; ***Malaysia:*** Zometa; ***Mex.:*** Zometa; ***Neth.:*** Zometa; ***Norw.:*** Aclasta; Zometa; ***NZ:*** Zometa; ***Philipp.:*** Zometa; ***Pol.:*** Zometa; ***Port.:*** Zometa; ***Rus.:*** Zometa (Зомета); ***S.Afr.:*** Zometa; ***Singapore:*** Zometa; ***Spain:*** Aclasta; Zometa; ***Swed.:*** Aclasta; Zometa; ***Switz.:*** Zometa; ***Thai.:*** Zometa; ***Turk.:*** Zometa; ***UK:*** Aclasta; Zometa; ***USA:*** Reclast; Zometa; ***Venez.:*** Zoldria; Zometa.

40. Frost FJ, *et al.* Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest* 2007; **131:** 1006–12.
41. Mancini GBJ, *et al.* Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006; **47:** 2554–60.
42. Salpeter S, *et al.* Cardioselective beta-blockers for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 16/04/08).
43. Dransfield MT, *et al.* Use of β blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; **63:** 301–5.
44. Meyers BF, Patterson GA. Chronic obstructive pulmonary disease 10: bullectomy, lung volume reduction surgery, and transplantation for patients with chronic obstructive pulmonary disease. *Thorax* 2003; **58:** 634–8.
45. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; **348:** 2059–73.
46. Sabroe I, *et al.* Pathological networking: a new approach to understanding COPD. *Thorax* 2007; **62:** 733–8.
47. Barnes PJ. ABC of chronic obstructive pulmonary disease: future treatments. *BMJ* 2006; **333:** 246–8.
48. Barnes PJ, Hansel TT. Prospects for new drugs for chronic obstructive pulmonary disease. *Lancet* 2004; **364:** 985–96.
49. Mahler DA, *et al.* Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest* 2004; **126:** 926–34.
50. Lipworth BJ. Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease. *Lancet* 2005; **365:** 167–75.
51. Halpin DMG. Chronic obstructive pulmonary disease, inflammation and PDE4 inhibitors. *Br J Hosp Med* 2006; **67:** 370–4.
52. Roth MD, *et al.* FORTE Study Investigators. Feasibility of retinoids for the treatment of emphysema study. *Chest* 2006; **130:** 1334–45.
53. Broekhuizen R, *et al.* Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. *Thorax* 2005; **60:** 376–82.
54. Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; **370:** 786–96.
55. Rodríguez-Roisin R. COPD exacerbations 5: management. *Thorax* 2006; **61:** 535–44.
56. McCrory DC, Brown CD. Anticholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/04/08).
57. Barr RG, *et al.* Methylxanthines for exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/04/08).
58. Niewoehner DE, *et al.*. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999; **340:** 1941–7.
59. Davies L, *et al.* Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999; **354:** 456–60.
60. Wood-Baker RR, *et al.* Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 16/04/08).
61. Vondracek SF, Hemstreet BA. Retrospective evaluation of systemic corticosteroids for the management of acute exacerbations of chronic obstructive pulmonary disease. *Am J Health-Syst Pharm* 2006; **63:** 645–52.
62. Ram FSF, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 16/04/08).
63. El Moussaoui R, *et al.* Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax* 2008; **63:** 415–22.
64. Austin M, Wood-Baker R. Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 16/04/08).
65. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/04/08).

Acefylline Piperazine *(BAN, rINN)*

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

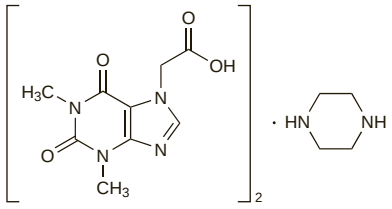
Ацефиллин Пиперазин

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

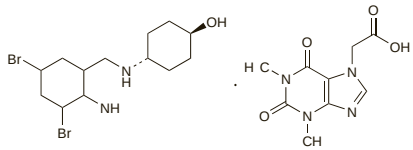
Ambroxol Acefyllinate *(BANM, rINNM)*

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.

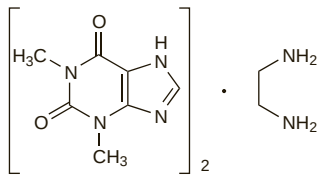
Аминофиллин

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