tonin in amputee patients with phantom limb pain found it was ineffective, however, in contrast to ketamine.[3] Intranasal calcitonin at a dose of 200 units also provided only transient relief of phantom limb sensation after spinal cord injury in a patient refractory to clomipramine;[4] the authors speculated that optimal dosage may not have been used and noted that all previous studies were in amputees.

For a discussion on pain and its management, see p.2.

1. Appelboom T. Calcitonin in reflex sympathetic dystrophy syndrome and other painful conditions. *Bone* 2002; **30** (suppl): 84S–86S.
2. Wall GC, Heyneman CA. Calcitonin in phantom limb pain. *Ann Pharmacother* 1999; **33:** 499–501.
3. Eichenberger U, *et al.* Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* 2008; **106:** 1265–73.
4. Shapiro S, *et al.* Calcitonin treatment for phantom limb pain. *Can J Psychiatry* 2004; **49:** 499.

Preparations

BP 2008: Calcitonin (Salmon) Injection;
USP 31: Calcitonin Salmon Injection; Calcitonin Salmon Nasal Solution.

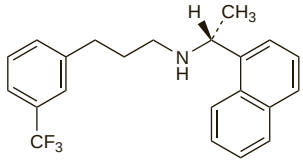
Proprietary Preparations (details are given in Part 3)
Arg.: Anguilcet†; Calsynar†; Citonina†; Osmil†; Salmocalcin†; ***Austral.:*** Miacalcic; ***Austria:*** Calcitonin; Calco; Casalm; Cibacalcin; Elcimen†; Miacalcic†; Ucecal; ***Belg.:*** Calsynar; Miacalcic; Steocalcin; ***Braz.:*** Acticalcin; Calsynar; Cibacalcina†; Miacalcic; Seacalcit; Serocalcin; ***Canad.:*** Calcimar; Caltine; Miacalcin; ***Chile:*** Calfosina†; Calnisan; Miacalcic; ***Cz.:*** Calsynar†; Caltine†; Fixocal†; Miacalcic; Osteodon; Ostostabil†; Tonocalcin; Ucecal†; ***Denm.:*** Miacalcic; ***Fin.:*** Miacalcic; ***Fr.:*** Cadens; Calsyn; Cibacalcine; Miacalcic; ***Ger.:*** Azucalcit†; Calci; Calsynar†; Casalm†; Cibacalcin†; Karil; Osteos; Ostostabil; ***Gr.:*** Alciton; Arsipor; Assocals; Aurocalcin; Brosidon; Calci-10; Calcicontrol; Calcideron; Calciphar; Calciplus; Calcispren; Calcitherapy; Calciton; Calco; Calsal; Calsynar; Caltec; Crocalcin; Doctadryle; Farmicalcine; Galcin; Genecalcin; Iamacalcin; Iricalcin; Latonina; Lixocam; Miacalcic; Miadenil; Mioser; Neostesin; Nopremin; Norcalcin; Nylex; Osanit; Osivan; Osteonorm; Osticalcin†; Ostifix; Ostoplus; Ostosalm; Pluston; Rafacalcin; Redicalcin; Rothrin; Sal-Cal; Salmocalcin; Salmofar†; Salmoten; Sanopor; Steocin; Tendolon; Tonocalcin; Tosicalcin; Transcalcium; Velkacalcin; ***Hong Kong:*** Miacalcic; Osteocalcin†; ***Hung.:*** Biostin; Calco; Miacalcic; ***India:*** Miacalcic; Zycalcit; ***Indon.:*** Miacalcic; Tonocalcin; ***Israel:*** Cibacalcin; Miacalcic; Salco; ***Ital.:*** Biocalcin; Calciben†; Calciosint†; Calcioton†; Calcitonina; Calco†; Carbicalcin†; Catonin†; Ipocalcin†; Miacalcic†; Miadenil†; Osteocalcin†; Osteotonina†; Osteovis; Rulicalcin†; Salmofar; Steocin†; Tonocalcin†; Turbocalcin†; ***Jpn:*** Calcitoran; Elcitonin; ***Malaysia:*** Menocal†; Miacalcic; Osteocalcin†; ***Mex.:*** Endocal†; Miacalcic; Oseum; Tonocalcin†; ***Norw.:*** Miacalcic; ***NZ:*** Miacalcic; ***Philipp.:*** Miacalcic; ***Pol.:*** Calcihexal; Calcitonin; Miacalcic; Tonocalcin; ***Port.:*** Calcimon†; Calcitar; Calogen†; Calsyn; Cibacalcina†; Forcaltonin; Miacalcic; Osseocalcina; Osteodon; Ostinate; Ostosalm†; Salcat; Tonocaltin; ***Rus.:*** Miacalcic (Миакальцик); ***S.Afr.:*** Miacalcic; ***Singapore:*** Calco†; Menocal†; Miacalcic; ***Spain:*** Calogen; Calsynar; Carbicalcin; Diatin; Miacalcic; Oseototal; Ospor; Osteobion; Ostetan; Sical†; Tonocaltin; Ucecal†; ***Swed.:*** Miacalcic; ***Switz.:*** Miacalcic; ***Thai.:*** Calco; Miacalcic; Osteocalcin†; Tonocalcin; ***Turk.:*** Calcitonina; Miacalcic; Salmocalcin; Tonocalcin; Ucecal; ***UK:*** Calsynar†; Miacalcic; ***USA:*** Calcimar; Fortical; Miacalcin; Osteocalcin; ***Venez.:*** Calnisan†; Caltanid†; Miacalcic†; Serocalcin†.

Cinacalcet Hydrochloride *(BANM, USAN, rINNM)*

AMG-073 (cinacalcet); Cinacalcet, Chlorhydrate de; Cinacalceti Hydrochloridum; Hidrocloruro de cinacalcet; KRN-1493. *N*-[(1*R*)-1-(Naphthalen-1-yl)ethyl]-3-[3-(trifluoromethyl)phenyl]-propan-1-amine hydrochloride.

Цинакальцета Гидрохлорид

$C_{22}H_{22}F_3N,HCl$ = 393.9.
CAS — 364782-34-3.
ATC — H05BX01.
ATC Vet — QH05BX01.



(cinacalcet)

Adverse Effects and Precautions

Hypocalcaemia and adynamic bone disease can occur; serum calcium and intact parathyroid hormone concentrations should be monitored regularly, especially in patients with a history of seizure disorders or hepatic impairment. Other adverse effects of cinacalcet include gastrointestinal disturbances, myalgia, dizziness, paraesthesia, hypertension, asthenia, anorexia, rashes, and non-cardiac chest pain. There have been isolated reports of hypotension, worsening heart failure, or both, in patients with impaired cardiac function. Hypersensitivity reactions have been reported rarely.

Interactions

Cinacalcet is partly metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Concentrations of cinacalcet have almost doubled when given with the CYP3A4 inhibitor ketoconazole. Dose adjustments of cinacalcet may be required if therapy with strong inhibitors or inducers of CYP3A4 is started, or stopped. Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism, and dose adjustments may be necessary if patients start or stop smoking. Cinacalcet is a strong inhibitor of cytochrome P450 isoenzyme CYP2D6; exposure to amitriptyline, desipramine, and nortriptyline has been increased when given with cinacalcet.

Pharmacokinetics

Peak plasma concentrations are obtained 2 to 6 hours after an oral dose of cinacalcet, and are substantially increased if given with food. Clearance from plasma is biphasic, with a terminal half-life of about 30 to 40 hours. Cinacalcet is approximately 93 to 97% bound to plasma proteins. It is rapidly and extensively metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Metabolites are renally excreted, with 80% of the dose recovered in the urine, and 15% in the faeces.

◊ References.

1. Kumar GN, *et al.* Metabolism and disposition of calcimimetic agent cinacalcet HCl in humans and animal models. *Drug Metab Dispos* 2004; **32:** 1491–1500.
2. Padhi D, *et al.* No effect of renal function or dialysis on pharmacokinetics of cinacalcet (Sensipar /Mimpara). *Clin Pharmacokinet* 2005; **44:** 509–16.

Uses and Administration

Cinacalcet is a calcimimetic agent that increases the sensitivity to extracellular calcium of the calcium-sensing receptors of the parathyroid gland, which regulate parathyroid hormone secretion; this results in a reduction in parathyroid hormone secretion as well as a decrease in serum calcium. Cinacalcet hydrochloride is given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, as well as for the reduction of hypercalcaemia in patients with parathyroid carcinoma or primary hyperparathyroidism (where parathyroidectomy is not an option). Doses are expressed in terms of the base; cinacalcet hydrochloride 33 mg is equivalent to about 30 mg of cinacalcet.

In the treatment of **secondary hyperparathyroidism**, the initial dose is 30 mg once daily, increased at intervals of 2 to 4 weeks by 30 mg to a maximum of 180 mg daily.

For the treatment of **hypercalcaemia** in patients with parathyroid carcinoma or primary hyperparathyroidism, cinacalcet is given in an initial dose of 30 mg twice daily, increased sequentially at intervals of 2 to 4 weeks to a maximum of 90 mg three or four times daily.

◊ References.

1. Franceschini N, *et al.* Cinacalcet HCl: a calcimimetic agent for the management of primary and secondary hyperparathyroidism. *Expert Opin Invest Drugs* 2003; **12:** 1413–21.
2. Shoback DM, *et al.* The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 5644–9.
3. Block GA, *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; **350:** 1516–25.
4. Joy MS, *et al.* Calcimimetics and the treatment of primary and secondary hyperparathyroidism. *Ann Pharmacother* 2004; **38:** 1871–80.
5. Peacock M, *et al.* Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90:** 135–41.
6. Barman Balfour JA, Scott LJ. Cinacalcet hydrochloride. *Drugs* 2005; **65:** 271–81.
7. Cunningham J, *et al.* Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68:** 1793–1800.
8. Dong BJ. Cinacalcet: an oral calcimimetic agent for the management of hyperparathyroidism. *Clin Ther* 2005; **27:** 1725–51.
9. NICE. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy: Technology Appraisal Guidance 117 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA117guidance.pdf (accessed 18/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Sensipar; ***Canad.:*** Sensipar; ***Cz.:*** Mimpara; Parareg; ***Denm.:*** Mimpara; ***Fin.:*** Mimpara; ***Fr.:*** Mimpara; ***Ger.:*** Mimpara; ***Gr.:*** Mimpara; ***Hung.:*** Mimpara; ***Irl.:*** Mimpara; ***Ital.:*** Mimpara; Parareg; ***Neth.:*** Mimpara; Parareg; ***Norw.:*** Mimpara; ***NZ:*** Sensipar; ***Pol.:*** Mimpara; ***Port.:*** Mimpara; Parareg; ***Spain:*** Mimpara; ***Swed.:*** Mimpara; ***Switz.:*** Mimpara; ***UK:*** Mimpara; ***USA:*** Sensipar.

Clodronate

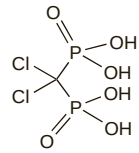
ATC — M05BA02.
ATC Vet — QM05BA02.

Clodronic Acid *(BAN, USAN, rINN)*

Acide clodronique; Ácido clodrónico; Acidum clodronicum; Cl_2MBP; Cl_2MDP; DkhMDF; Klodronihappo; Klodronsyra. (Dichloromethylene)diphosphonic acid.

Клодроновая Кислота

$CH_4Cl_2O_6P_2$ = 244.9.
CAS — 10596-23-3.
ATC — M05BA02.
ATC Vet — QM05BA02.



Clodronate Disodium *(USAN, rINNM)*

177501; BM-06.011; Clodronas Dinatricum; Clodronate disodique; Clodronate Sodium; Clodronato disódico; Dichloromethane Diphosphonate Disodium; Dichloromethylene Diphosphonate Disodium; Dinatrii clodronas; Dinatriumklodronaatti; Dinatriumklodronat; Disodium Clodronate; Sodium Clodronate *(BANM)*; Sodyum Klodronat; ZK-00091106. Disodium (dichloromethylene)diphosphonate tetrahydrate.

Динатрий Клодронат

$CH_2Cl_2Na_2O_6P_2,4H_2O$ = 360.9.
CAS — 22560-50-5.
ATC — M05BA02.
ATC Vet — QM05BA02.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Clodronate Disodium Tetrahydrate). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. A 5% solution in water has a pH of 3.0 to 4.5.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Gastrointestinal symptoms with oral clodronate may be reduced by giving it in divided doses rather than as a single daily dose. Reversible increases in liver enzyme values and serum parathyroid hormone have occurred; transient moderate leucopenia has been reported. Monitoring of hepatic and renal function, white cell counts, and serum calcium and phosphate is advised. Clodronate has precipitated bronchospasm, even in patients with no history of asthma. Transient proteinuria has been reported immediately after intravenous infusion.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including clodronate, see under Bisphosphonates, p.1090.

Effects on the kidneys. For mention of renal failure developing in a patient with slightly raised serum-creatinine concentrations who subsequently received an intravenous infusion of clodronate, see under Bisphosphonates, p.1091.

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

Effects on the respiratory system. For a report of bronchospasm in an aspirin-sensitive asthmatic, induced by an infusion of clodronate, see p.1091.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. For published reports of cutaneous reactions associated with clodronate, see p.1091.

Interactions

As for the bisphosphonates in general, p.1091.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*[1], or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

1. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* 1993; **4:** 432–3.
2. Pedersen-Bjergaard U, Myhre J. Severe hypocalcaemia after treatment with diphosphonate and aminoglycoside. *BMJ* 1991; **302:** 295. Correction. *ibid.*; 791.

Pharmacokinetics

Like other bisphosphonates, clodronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is only 1 to 4%, and may differ appreciably between different oral formulations. On absorption or intravenous dosage it is cleared rapidly from the blood with a reported plasma

half-life of only about 2 hours, but has a high affinity for bone. Binding to serum plasma proteins is low. Clodronate is not metabolised. Over 70% of an intravenous dose is excreted unchanged in the urine within 24 hours, the remainder being sequestered to bone tissue.

◊ References.

1. Conrad KA, Lee SM. Clodronate kinetics and dynamics. *Clin Pharmacol Ther* 1981; **30:** 114–20.
2. Yakatan GJ, *et al.* Clodronate kinetics and bioavailability. *Clin Pharmacol Ther* 1982; **31:** 402–10.
3. Ylitalo P, *et al.* Comparison of pharmacokinetics of clodronate after single and repeated doses. *Int J Clin Pharmacol Ther* 1999; **37:** 294–300.

Bioavailability. Enhanced bioavailability tablets of clodronate disodium are available in some countries, the licensed dose of which is less than the dose of the standard formulations (see below). However, an open, randomised, crossover study in 88 subjects found that a 1040-mg dose of the enhanced tablet formulation provided only 52% of the bioavailable dose of 1600 mg of the standard capsule formulation.[1]

1. Lapham G, *et al.* Bioavailability of two clodronate formulations. *Br J Hosp Med* 1996; **56:** 231–3.

Uses and Administration

Clodronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses. Clodronate is used, generally as the disodium salt, as an adjunct in the treatment of severe hypercalcaemia associated with malignancy. In addition, it is used in the management of osteolytic lesions and bone pain associated with skeletal metastases. Doses are expressed in terms of anhydrous clodronate disodium; 125 mg of clodronate disodium tetrahydrate is equivalent to about 100 mg of anhydrous substance.

Clodronate is given by slow intravenous infusion, diluted in sodium chloride 0.9% or glucose 5%, or orally, as a single daily dose or in 2 divided doses; food should be avoided for at least 1 hour before or 1 hour after an oral dose. Clodronate disodium is available in capsules of 400 mg and standard tablets of 800 mg. Tablets of clodronate disodium 520 mg are also available in some countries, and have a greater bioavailability than the capsules or standard tablets; one such tablet of clodronate disodium 520 mg is equivalent to about two capsules each containing clodronate disodium 400 mg or one 800-mg standard tablet (but see Bioavailability, above).

In the management of osteolytic lesions, hypercalcaemia, and bone pain associated with **skeletal metastases** in patients with breast cancer or multiple myeloma, clodronate disodium 1.6 g daily (4 capsules or 2 standard tablets) is given orally, and may be increased if necessary to a maximum of 3.2 g daily. Alternatively a dose of 1.04 g (2 tablets) daily, increased if necessary up to 2.08 g daily, may be given as enhanced bioavailability tablets.

In **hypercalcaemia of malignancy** clodronate disodium is given by intravenous infusion over not less than 2 hours in a dose of 300 mg in 500 mL of infusion solution daily on successive days until normocalcaemia is achieved (usually within 5 days); duration of treatment should not exceed 10 days. Alternatively, it may be given as a single intravenous infusion of 1.5 g in 500 mL of infusion solution over a period of 4 hours. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy may be given orally in similar doses to those used for initial oral treatment of metastases. If hypercalcaemia recurs, the intravenous dose may be repeated.

◊ General references.

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; **47:** 945–82.
2. Kanis JA, McCloskey EV. Clodronate. *Cancer* 1997; **80** (suppl): 1691–5.
3. Brandi ML. Impiego del clodronato nei disordini del metabolismo minerale: stato dell'arte nell'anno 2000. *Minerva Med* 2001; **92:** 251–68.
4. Dando TM, Wiseman LR. Clodronate: a review of its use in the prevention of bone metastases and the management of skeletal complications associated with bone metastases in patients with breast cancer. *Drugs Aging* 2004; **21:** 949–62.

Administration. In Italy, clodronate is also used *intramuscularly*.[1,2] The usual dose for maintenance therapy of hypercalcaemia is 100 mg daily for 2 to 3 weeks; in the prevention and treatment of postmenopausal osteoporosis, 100 mg is given every 7 to 14 days. However, injection into the gluteal muscle caused local hardening; severe pain at the injection site may limit prolonged use of this route.[1] In Canada, clodronate has been given *subcutaneously* in doses of 1500 mg in 50 to 250 mL of infusion solution over 2 to 3 hours, to treat hypercalcaemia associated with malignancy. The chest and abdomen were the sites most frequently used; pain was the most common adverse effect.[3]

1. Rossini M, *et al.* Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; **24:** 125–9.
2. Filipponi P, *et al.* Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; **26:** 269–74.
3. Roemer-Bécuwe C, *et al.* Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; **26:** 843–8.

Administration in renal impairment. A pharmacokinetic study[1] found that renal clearance of intravenous clodronate was highly dependent on renal function. While recommending caution in interpreting these results for patients with malignancy or severe bone disease, the authors recommended the following dose adjustments based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: up to 25% reduction in dose
- CC 12 to 49 mL/minute: 25 to 50% dose reduction
- CC less than 12 mL/minute: 50% dose reduction

However, some manufacturers recommend that *intravenous* infusion of clodronate should be avoided in patients with moderate to severe renal impairment (serum creatinine greater than 440 micromoles/litre). Others recommend, where multiple infusions are given, adjustment according to creatinine clearance (CC) as follows:

- mild renal impairment (CC 50 to 80 mL/minute): 25% reduction in dose
- moderate renal impairment (CC 10 to 50 mL/minute): 25 to 50% dose reduction
- severe impairment (CC below 10 mL/minute): contra-indicated

For the *oral* route the following adjustments may be made:

- CC between 10 and 30 mL/minute: 50% dose reduction
- CC below 10 mL/minute (or serum creatinine greater than 440 micromoles/litre): contra-indicated

1. Saha H, *et al.* Pharmacokinetics of clodronate in renal failure. *J Bone Miner Res* 1994; **9:** 1953–8.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous clodronate 300 mg daily for 10 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Varenna M, *et al.* Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome: a randomized, double blind, placebo controlled study. *J Rheumatol* 2000; **27:** 1477–83.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. Clodronate has been shown to be effective[1-4] in the treatment of malignant hypercalcaemia. A small dose-response study[3] found low-dose clodronate for mild cases to be as effective as high-dose clodronate for moderate to severe cases of tumour-induced hypercalcaemia.

1. O'Rourke NP, *et al.* Effective treatment of malignant hypercalcaemia with a single intravenous infusion of clodronate. *Br J Cancer* 1993; **67:** 560–3.
2. Elomaa I, Blomqvist C. Clodronate and other bisphosphonates as supportive therapy in osteolysis due to malignancy. *Acta Oncol* 1995; **34:** 629–36.
3. Shah S, *et al.* Is there a dose response relationship for clodronate in the treatment of tumour induced hypercalcaemia? *Br J Cancer* 2002; **86:** 1235–7.
4. Roemer-Bécuwe C, *et al.* Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; **26:** 843–8.

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. Clodronate is licensed for such use in many countries. Studies in breast cancer patients with bone metastases found that clodronate reduced the incidence of fractures,[1,2] and delayed the time to onset of new bone events.[2,3] Whether bisphosphonates can prevent the development of new skeletal metastases is unclear. Results of studies using clodronate to reduce skeletal metastases in women with breast cancer have been conflicting,[1,4-6] and one study in women with node-positive disease actually suggested an increase in concomitant visceral metastases.[5] Overall, the studies appeared limited by duration, and further data are needed.[7] In a trial of patients with multiple myeloma,[8] oral clodronate was found to slow the progression of skeletal disease, especially in those patients with less overt disease at diagnosis; the authors suggested starting clodronate early in the course of the disease.

1. Kanis JA, *et al.* Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* 1996; **19:** 663–7.
2. Kristensen B, *et al.* Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999; **246:** 67–74.
3. Tubiana-Hulin M, *et al.* Essai comparatif randomisé en double aveugle clodronate oral 1600 mg/j versus placebo chez des patientes avec métastases osseuses de cancer du sein: double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. *Bull Cancer* 2001; **88:** 701–7.
4. Diel IJ, *et al.* Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; **339:** 357–63.
5. Saarto T, *et al.* Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001; **19:** 10–17.
6. Powles T, *et al.* Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002; **20:** 3219–24.
7. Hurst M, Noble S. Clodronate: a review of its use in breast cancer. *Drugs Aging* 1999; **15:** 143–67.
8. McCloskey EV, *et al.* A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. *Br J Haematol* 1998; **100:** 317–25.

Osteogenesis imperfecta. Clodronate has been reported to be of benefit in a boy with osteogenesis imperfecta (p.1083) type I. Starting at 13⁄ years old he was given oral clodronate 400 mg daily for 5 years, and sustained no new low-trauma fractures during this time. Treatment was stopped for 8 months, but bone mineral density remained below normal limits. Clodronate was restarted at 800 mg daily and given with no untoward effects, until the patient was 22 years old, 8 years after initial referral.[1]

1. Ashford RU, *et al.* Oral clodronate as treatment of osteogenesis imperfecta. *Arch Dis Child* 2003; **88:** 945.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Clodronate is licensed for this use in some countries. Studies of its use in daily oral doses, or intermittent intravenous infusions,[1] or intramuscular injections (at 7-, 10- or 14-day intervals)[1,2] found increases in bone mineral density at various sites in postmenopausal women with osteoporosis or low bone mass. A large study[3] in postmenopausal women with vertebral osteopenia found that oral clodronate 800 mg daily prevented bone loss in the lumbar spine and femoral trochanter, but not the femoral neck; this dose has been shown to reduce vertebral fracture risk in women with postmenopausal or secondary osteoporosis.[4] The risk of vertebral fractures was also reduced in patients with arthritis receiving corticosteroids, who were given intramuscular clodronate once weekly.[5] Oral clodronate may be of benefit in reducing bone loss after heart transplantation,[6] but the benefits of intravenous clodronate in a small prospective study in patients receiving parenteral nutrition (who are at high risk of osteoporosis) were uncertain.[7]

1. Filipponi P, *et al.* Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; **26:** 269–74.
2. Rossini M, *et al.* Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; **24:** 125–9.
3. Välimäki MJ, *et al.* Prevention of bone loss by clodronate in early postmenopausal women with vertebral osteopenia: a dose-finding study. *Osteoporosis Int* 2002; **13:** 937–47.
4. McCloskey E, *et al.* Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004; **19:** 728–36.
5. Frediani B, *et al.* Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. *Bone* 2003; **33:** 575–81.
6. Ippoliti G, *et al.* Clodronate treatment of established bone loss in cardiac recipients: a randomized study. *Transplantation* 2003; **75:** 330–4.
7. Haderslev KV, *et al.* Effect of cyclical intravenous clodronate therapy on bone mineral density and markers of bone turnover in patients receiving home parenteral nutrition. *Am J Clin Nutr* 2002; **76:** 482–8.

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. A review[1] of clodronate stated that oral doses of 800 to 1600 mg daily were effective in reducing bone turnover in patients with Paget's disease, and that remission after stopping was longer with the higher dose. Duration of therapy also appears to affect response;[1] longer treatment was associated with a longer time to relapse.[2] Short-term intravenous clodronate (300 mg daily for 5 to 10 days) has also been found to reduce biochemical markers of bone turnover, and sustain remission for up to 1 year.[1,3]

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; **47:** 945–82.
2. Khan SA, *et al.* Duration of response with oral clodronate in Paget's disease of bone. *Bone* 1996; **18:** 185–90.
3. Broggini M, *et al.* Short courses of intravenous clodronate in the treatment of Paget's disease of bone: a long-term follow-up trial. *Int J Clin Pharmacol Res* 1993; **13:** 301–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Bonefos; ***Austria:*** Ascredar; Bonefos; Lodronat; ***Belg.:*** Bonefos; Ostac†; ***Braz.:*** Bonefos; Ostac; ***Canad.:*** Bonefos; Ostac; ***Chile:*** Lodronat†; ***Cz.:*** Bonefos; Lodronat; ***Denm.:*** Bonefos; ***Fin.:*** Bonefos; ***Fr.:*** Clastoban; Lytos; ***Ger.:*** Bonefos; Clodron; Clodron beta; Ostac; ***Gr.:*** Bonefos; Ostac; ***Hong Kong:*** Bonefos; Ostac; ***Hung.:*** Bonefos; Lodronat†; ***Indon.:*** Bonefos; ***Irl.:*** Bonefos; Loron; ***Israel:*** Bonefos; Ostac; ***Ital.:*** Clasteon; Climaclod; Clodeosten; Clodron; Clody; Difosfonal; Dolkin†; Moticlod; Niklod; Ossiten;

Osteonorm; Osteostab; ***Malaysia:*** Bonefos; ***Mex.:*** Bonefos; ***Neth.:*** Bonefos; Ostac; ***Norw.:*** Bonefos; ***Philipp.:*** Bonefos; ***Pol.:*** Bonefos; Sindronat; ***Port.:*** Bonefos; Ostac; ***Rus.:*** Bonefos (Бонефос); ***S.Afr.:*** Bonephos; Ostac†; ***Singapore:*** Bonefos; ***Spain:*** Bonefos; Hemocalcin†; Mebonat†; ***Swed.:*** Bonefos; Ostac; ***Switz.:*** Bonefos; Ostac; ***Thai.:*** Bonefos; ***Turk.:*** Bonefos; ***UK:*** Bonefos; Clasteon; Loron.

Denosumab *(USAN, rINN)*

AMG-162; Dénosumab; Denosumabum.

Денозумаб

CAS — 615258-40-7.

Profile

Denosumab is a human monoclonal antibody that specifically targets the receptor activator of nuclear factor-kappa B ligand (RANKL), a mediator of the resorptive phase of bone remodelling. Denosumab is under investigation for various conditions, including osteoporosis, treatment-induced bone loss, rheumatoid arthritis, bone metastases, and multiple myeloma.

◊ References.

1. Lewiecki EM. RANK ligand inhibition with denosumab for the management of osteoporosis. *Expert Opin Biol Ther* 2006; **6:** 1041–50.
2. Body J-J, *et al.* A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 2006; **12:** 1221–8.
3. McClung MR, *et al.* Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006; **354:** 821–31.
4. Hamdy NA. Targeting the RANK/RANKL/OPG signaling pathway: a novel approach in the management of osteoporosis. *Curr Opin Investig Drugs* 2007; **8:** 299–303.
5. Lewiecki EM, *et al.* AMG 162 Bone Loss Study Group. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res* 2007; **22:** 1832–41.
6. Lipton A, *et al.* Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 2007; **25:** 4431–7.
7. Bone HG, *et al.* Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab* 2008; **93:** 2149–57.
8. Cohen SB, *et al.* Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum* 2008; **58:** 1299–1309.
9. Miller PD, *et al.* Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008; **43:** 222–9.

Etidronate

ATC — M05BA01.

ATC Vet — QM05BA01.

Etidronic Acid *(BAN, USAN, rINN)*

Acide Étidronique; Ácido etidrónico; Acidum Etidronicum; Etidronihappo; Etidronsyra. 1-Hydroxyethylidenedi(phosphonic acid).

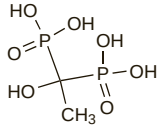
Этидроновая Кислота

$C_2H_8O_7P_2$ = 206.0.

CAS — 2809-21-4.

ATC — M05BA01.

ATC Vet — QM05BA01.



Etidronate Disodium *(USAN, rINNM)*

Dinatrii etidronas; Dinatriumetidronaatti; Dinatriumetidronat; Dinatrium-etidronát; Disodium Etidronate *(BANM)*; Disodu etydronian; Disodyum Etidronat; EHDP; Etidronas Dinatricum; Étidronate disodique; Etidronate Disodique; Etidronato disódico. Disodium dihydrogen (1-hydroxyethylidene)diphosphonate.

Динатрий Этидронат

$C_2H_6Na_2O_7P_2$ = 250.0.

CAS — 7414-83-7.

ATC — M05BA01.

ATC Vet — QM05BA01.

NOTE. Other etidronic acid sodium salts are designated as etidronate monosodium, etidronate trisodium, and etidronate tetrasodium. The name etidronate sodium is used only in *Martindale* where the salt cannot be identified more precisely.

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

Ph. Eur. 6.2 (Etidronate Disodium). A white or yellowish, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.2 to 5.2. Store in airtight containers.

USP 31 (Etidronate Disodium). A white powder that may contain lumps. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. pH of a 1% solution in water is between 4.2 and 5.2.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Unlike the newer bisphosphonates etidronate produces marked impairment of bone mineralisation at high therapeutic doses. An increase in bone pain may occur in patients with Paget's disease. Impairment of bone mineralisation may result in osteomalacia, and fractures have been reported. If a fracture occurs etidronate should be stopped until healing is complete. Hyperphosphataemia may occur, usually at high doses, but generally resolves 2 to 4 weeks after the end of therapy. There have been reports of paraesthesias, peripheral neuropathy, and confusion. Burning of the tongue, alopecia, erythema multiforme, and exacerbation of asthma have occurred rarely. Transient loss or alteration of taste has been reported mainly during and after intravenous infusion.

Effects on the blood. For a report of pancytopenia caused by etidronate therapy, see Effects on the Skin, below.

Effects on the ears. Ototoxicity, manifest as tinnitus and hearing loss, has been reported[1] in 2 patients given etidronate for osteoporosis; both patients had pre-existing otosclerosis and the authors recommended that those with ear pathology be monitored audiometrically when given bisphosphonates.

1. Yeşil S, *et al.* Further hearing loss during osteoporosis treatment with etidronate. *Postgrad Med J* 1998; **74:** 363–4.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including etidronate, see under Bisphosphonates, p.1090.

Effects on the gastrointestinal tract. Oral etidronate was not associated with an increased incidence of upper gastrointestinal problems in a retrospective cohort study.[1] There was also no evidence of an increased incidence of gastrointestinal effects when given with NSAIDs or corticosteroids. Similarly, another large cohort study found no increased risk of peptic ulcer disease associated with the use of cyclical etidronate.[2] However, oesophageal ulceration has been reported with daily etidronate;[3,4] in one case possibly associated with incorrect use,[3] and in another, complicated by prior use of diclofenac, and a history of gastro-oesophageal reflux disease.[4]

1. van Staa T, *et al.* Upper gastrointestinal adverse events and cyclical etidronate. *Am J Med* 1997; **103:** 462–7.
2. Burger H, *et al.* Cyclical etidronate use is not associated with symptoms of peptic ulcer disease. *Eur J Clin Pharmacol* 2000; **56:** 319–22.
3. Macedo G, *et al.* Ulcerative esophagitis caused by etidronate. *Gastrointest Endosc* 2001; **53:** 250–1.
4. Maroy B. Ulcère géant de l'œsophage probablement dû à la prise d'étidronate. *Gastroenterol Clin Biol* 2001; **25:** 917–18.

Effects on the kidneys. Bisphosphonates are excreted by the kidneys, thus caution is advised in patients with renal impairment. When given by intravenous infusion for the treatment of hypercalcaemia of malignancy they have been reported to affect renal function adversely; hypercalcaemia or malignancy may also have contributed. For reports of renal failure associated with etidronate see under Bisphosphonates, p.1091.

Effects on mental state. Sensory hallucinations and confusion were reported in an elderly woman given daily etidronate for a week. Symptoms resolved on stopping the drug and recurred on rechallenge.[1] Mood disturbances, lack of concentration, and memory impairment were also reported in 3 patients receiving longer-term cyclical treatment; symptoms again diminished on stopping etidronate and reappeared after rechallenge.[2]

1. Burnet SP, Petrie JP. 'Wake up and smell the roses'—a drug reaction to etidronate. *Aust N Z J Med* 1999; **29:** 93.
2. Wolffenbuttel BHR, van der Klauw MM. Psychische bijwerkingen van behandeling met bisfosfonaten. *Ned Tijdschr Geneeskd* 2003; **147:** 35–7.

Effects on the respiratory system. For a report of bronchospasm induced by etidronate in an aspirin-sensitive asthmatic, see p.1091. For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, below.

Effects on the skin. A 47-year old woman with a history of auto-immune rheumatic disease developed toxic epidermal necrolysis, pancytopenia, and acute respiratory distress syndrome 7 days after starting etidronate for osteoporosis; she died of cardiorespiratory failure, secondary to the acute respiratory distress syndrome, despite aggressive supportive measures.[1]

1. Coakley G, Isenberg DA. Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. *Br J Rheumatol* 1995; **34:** 798.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare (see p.1091).

Interactions

As for the bisphosphonates in general, p.1091.

Anti-inflammatory drugs. For a lack of apparent interaction between cyclical etidronate and corticosteroids or NSAIDs see under Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

After oral doses of etidronate, absorption is variable and appears to be dose dependent. At usual doses about 1 to 6% of a dose is absorbed. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. Etidronate is rapidly cleared from the blood and has been reported to have a plasma half-life of 1 to 6 hours. It is not metabolised. About 50% is excreted in the urine within 24 hours, the remainder being sequestered to bone and slowly eliminated. The half-life of etidronate in bone exceeds 90 days. Unabsorbed etidronate appears in the faeces.

Uses and Administration

Etidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It inhibits the growth and dissolution of hydroxyapatite crystals in bone and may also directly impair osteoclast activity. It diminishes bone resorption and thus reduces bone turnover.

Etidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also given in bone disorders in which excessive bone resorption is a problem, such as Paget's disease of bone and osteoporosis. In addition, it may be used for the prevention and treatment of ectopic (heterotopic) ossification. A chelate of etidronate with radioactive technetium-99m (p.2055) is used diagnostically as a bone scanning agent and a similar compound with rhenium-186 for the palliation of bone metastases in prostate cancer (see below).

Etidronate is given as the disodium salt, by intravenous infusion over at least 2 hours, or orally, usually as a single daily dose. Food should be avoided for 2 hours before and after oral doses.

In the treatment of **Paget's disease**, etidronate disodium is given orally in a usual initial dose of 5 mg/kg daily for not more than 6 months. Doses above 10 mg/kg daily should be reserved for severe disease and should not be given for more than 3 months at a time. The maximum dose is 20 mg/kg daily. The response to etidronate may be slow in onset and may continue for several months after stopping therapy. Therefore, further treatment should only be given after a drug-free interval of at least 3 months and after evidence of relapse; it should not be given for longer than the initial treatment.

In the treatment of **hypercalcaemia of malignancy** the recommended dose of etidronate disodium by slow intravenous infusion is 7.5 mg/kg daily for 3 successive days, although infusions may be continued for up to 7 days if necessary. This daily dose should be diluted in at least 250 mL of sodium chloride 0.9% and infused over at least 2 hours. There should be at least a 7-day interval between courses of treatment. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy with oral etidronate disodium 20 mg/kg daily for 30 days may be started on the day after the last intravenous dose; treatment may be extended to a maximum of 90 days.

For the prevention and treatment of **ectopic ossification** complicating hip replacement etidronate disodium has been given orally in a dose of 20 mg/kg daily for 1 month before and 3 months after the operation. For ectopic ossification due to spinal cord injury it has been