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.

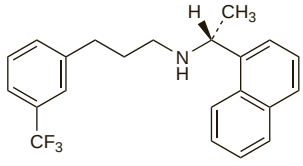
Proprietary Preparations (details are given in Part 3)
Arg.: Anguilcet†; Calsynar†; Citonina†; Osmil†; Salmocalcin†; ***Austral.:*** Miacalcic; ***Austria:*** Calcitonin; Calco; Casalm; Cibacalcin; Elcimen†; Miacalcic†; Ucecal; ***Belg.:*** Calsynar; Miacalcic; Steocalcin; ***Braz.:*** Acticalcin; Calsynar; 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

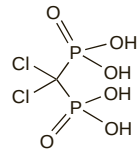
ATC — M05BA02.
ATC Vet — QM05BA02.

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