ports of swelling of neck and throat tissue, with resultant compression of the airway or vulnerable neurological structures. Complications were often life-threatening, and had required respiratory support and/or tracheotomy in some cases. The use of alternative treatments or enrollment in approved clinical studies was recommended when treating cervical spine problems.[1]

1. FDA. FDA Public Health Notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. Available at: http://www.fda.gov/cdrh/safety/070108-rhbmp.html (accessed 17/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: InductOs; ***Cz.:*** InductOs; Osigraft; ***Denm.:*** InductOs; Osigraft; ***Fin.:*** InductOs; ***Gr.:*** InductOs; Osigraft; ***Irl.:*** InductOs; ***Ital.:*** Osigraft; ***Neth.:*** Osigraft; ***Norw.:*** InductOs; ***Port.:*** Osigraft; ***Spain:*** InductOs; Osigraft; ***Swed.:*** InductOs; ***UK:*** InductOs; ***USA:*** Infuse Bone Graft.

Calcitonins

Calcitoninas.

ATC — H05BA01 (salmon synthetic); H05BA02 (pork natural); H05BA03 (human synthetic).

ATC Vet — QH05BA01 (salmon synthetic); QH05BA02 (pork natural); QH05BA03 (human synthetic).

Calcitonin (Human)

Calcitonina (humana); Calcitonin-human; Human Calcitonin.

$C_{151}H_{226}N_{40}O_{45}S_3$ = 3417.8.
CAS — 21215-62-3.
ATC — H05BA03 (human synthetic).
ATC Vet — QH05BA03 (human synthetic).

Description. Calcitonin (human) is a synthetic polypeptide comprising 32 amino acids in the same linear sequence as in naturally occurring human calcitonin.

Calcitonin (Pork) *(BANM)*

Calcitonina (cerdo).
CAS — 12321-44-7.
ATC — H05BA02 (pork natural).
ATC Vet — QH05BA02 (pork natural).

NOTE. The synonym thyrocalcitonin and the CAS number 9007-12-9 have been used for calcitonin that is often of pork origin.
Description. Calcitonin (pork) is a polypeptide hormone obtained from pork thyroid.

Calcitonin (Salmon) *(BAN)*

Calcitonina (salmón); Calcitonin-salmon; Calcitoninum salmonis; Kalcitonin lososí; Kalcytonina łososiowa; Kalsitoniini (lohi); Kalsitonin (Somon); Lašišų kalcitoninas; Laxkalcitonin; Lazac-kalcitonin; Salcatonin; Salkatonin; Salmon Calcitonin; SCT-1; SMC-20-051.

$C_{145}H_{240}N_{44}O_{48}S_2$ = 3431.9.
CAS — 47931-85-1.
ATC — H05BA01 (salmon synthetic).
ATC Vet — QH05BA01 (salmon synthetic).

NOTE. There may be some confusion between the terms Salcatonin and Calcitonin (Salmon) (Salmon Calcitonin; Calcitonin-salmon) although in practice these names appear to be used for the same substance.

- The Ph. Eur. 6.2 defines Calcitonin (Salmon) as a polypeptide having the structure determined for salmon calcitonin I. It is available as an acetate.
- Calcitonin (Salmon)/Salcatonin (*BAN*) is defined as a *component* of natural salmon calcitonin. The BP 2008 defines Calcitonin (Salmon)/Salcatonin as a synthetic polypeptide having the structure determined for salmon calcitonin I.
- In the USA, Calcitonin (*USAN*) includes calcitonin (human) and calcitonin (salmon) and there Salcatonin is understood to be a synthetic polypeptide structurally similar to natural salmon calcitonin (Calcitonin Salmon (Synthesis)). The US manufacturers use Calcitonin-salmon for a synthetic polypeptide with the same structure as calcitonin of salmon origin.

Pharmacopoeias. In *Chin*, *Eur.* (see p.vii), and *US.*.
Ph. Eur. 6.2 (Calcitonin (Salmon)). A white or almost white powder. It is obtained by chemical synthesis or by a method based on recombinant DNA (rDNA) technology. Freely soluble in water. Store at 2° to 8°. If the substance is sterile store in a sterile, airtight, tamper-proof container. Protect from light.
USP 31 (Calcitonin Salmon). It is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. One mg of acetic acid-free, anhydrous calcitonin salmon is equivalent to 6000 USP units. Store in airtight containers at a temperature of 2° to 8°, or maintain in a frozen state. Protect from light.

Elcatonin *(rINN)*

[Aminosuberic Acid 1,7]-eel Calcitonin; [Asu^{1,7}]-E-CT; Carbocalcitonin; Elcatonina; Elcatonine; Elcatoninum. 1-Butyric acid-7-(L-2-aminobutyric acid)-26-L-aspartic acid-27-L-valine-29-L-alanine-calcitonin (salmon).

Элькатонин

$C_{148}H_{244}N_{42}O_{47}$ = 3363.8.
CAS — 60731-46-6.
ATC — H05BA04.
ATC Vet — QH05BA04.

Description. Elcatonin is a synthetic analogue of eel calcitonin.

Pharmacopoeias. In *Jpn.*

Incompatibility. Like some other peptide drugs, calcitonin may be adsorbed onto the plastic of intravenous giving sets; it has been suggested that solutions for intravenous infusion should contain some protein to prevent the sorption and consequent loss of potency (see under Administration, below).

Units

0.8 units of calcitonin, porcine, are contained in one ampoule of the second International Standard Preparation (1991).

128 units of calcitonin, salmon, are contained in approximately 20 micrograms of freeze-dried purified synthetic salmon calcitonin, with mannitol 2 mg in one ampoule of the second International Standard Preparation (1989).

17.5 units of calcitonin, human, are contained in one ampoule of the second International Standard Preparation (1991).

88 units of calcitonin, eel, are contained in one ampoule of the first International Standard Preparation (1989).

Potency of calcitonins is estimated by comparing the hypocalcaemic effect, in *rats*, with that of the standard preparation, and is expressed in international or MRC units which are considered to be equivalent. One manufacturer states that 100 international units by this assay is equivalent to 1 mg of porcine or human calcitonin, and to 25 micrograms of salmon calcitonin although other, slightly different, equivalencies have been cited for other preparations. However, although 1 unit of pork calcitonin, 1 unit of salmon calcitonin, and 1 unit of human calcitonin should give the same response in humans this is not necessarily the case. Doses of calcitonin that have been considered approximately equivalent in practice are:

- 80 units of pork calcitonin
- 50 units of salmon calcitonin
- 500 micrograms of human calcitonin

Clinically, doses of pork and salmon calcitonin are expressed in units whereas those of human calcitonin can be expressed by weight, probably a reflection of its purity.

Adverse Effects, Treatment, and Precautions

Calcitonins may cause nausea, vomiting, diarrhoea, dizziness, flushing, and tingling of the hands. These reactions are dose dependent, usually transient, and occur more often with intravenous doses. Other adverse effects have included skin rash, an unpleasant taste, abdominal pain, urinary frequency, and tremor. A diabetogenic effect has been reported rarely. Inflammatory reactions at the injection site have been reported with some calcitonins, and rhinitis and other local reactions have been reported with nasal formulations. Transient hypocalcaemia may occur after injections of calcitonin, and use is contra-indicated in patients with hypocalcaemia.

Calcitonins should be given with care to patients with renal impairment (see below) or heart failure. If children receive calcitonin it should preferably be for short periods and bone growth should be monitored.

Circulating antibodies may develop after several months of use but resistance does not necessarily follow (see also below). In patients with suspected sensitivity, a skin test has been advised before use as hypersensitivity reactions, including anaphylaxis, have occurred.

Calcitonin has inhibited lactation in *animals*.

Nausea and vomiting may be reduced by giving doses at bedtime or by giving an antiemetic beforehand.

Calcitonin (pork) may contain trace amounts of thyroid hormones, but clinical effects are unlikely in most patients.

Antibody formation. Long-term treatment with heterologous calcitonins may lead to the formation of neutralising antibodies. This appears to be common in patients given calcitonin (pork) or, to a lesser extent, calcitonin (salmon). Calcitonin (human) is less immunogenic than pork or salmon, but a study[1] has also detected antibodies to human calcitonin in 1 of 33 women with postmenopausal osteoporosis after 6 months of therapy.

The degree to which such antibodies affect therapeutic activity is uncertain. Some studies have suggested a significant loss of therapeutic activity in patients who developed neutralising antibodies to calcitonin (salmon),[2] or a restoration in activity after a switch from salmon to human calcitonin in such patients;[3] equally, others have presented evidence that the activity of calcitonin (salmon) was not reduced by the development of antibodies to the drug.[4]

1. Grauer A, *et al.* Formation of neutralizing antibodies after treatment with human calcitonin. *Am J Med* 1993; **95:** 439–42.
2. Grauer A, *et al.* In vitro detection of neutralizing antibodies after treatment of Paget's disease of bone with nasal salmon calcitonin. *J Bone Miner Res* 1990; **5:** 387–91.
3. Muff R, *et al.* Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990; **89:** 181–4.
4. Reginster JY, *et al.* Influence of specific anti-salmon calcitonin antibodies on biological effectiveness of nasal salmon calcitonin in Paget's disease of bone. *Scand J Rheumatol* 1990; **19:** 83–6.

Effect on glucose metabolism. A single subcutaneous injection of calcitonin (salmon) has been reported to increase blood-glucose concentrations,[1] but long-term treatment with calcitonins was considered unlikely to cause diabetes.[2] Nevertheless, deterioration in diabetic control has been noted in a patient given calcitonin (pork)[3] and postprandial release of insulin was abolished by intravenous salmon calcitonin in 8 patients with duodenal ulcers.[4]

1. Gattereau A, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1977; **ii:** 1076–7.
2. Evans IMA, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1978; **i:** 280.
3. Thomas DW, *et al.* Deterioration in diabetic control during calcitonin therapy. *Med J Aust* 1979; **2:** 699–70.
4. Jonderko K. Effect of calcitonin on gastric emptying in patients with an active duodenal ulcer. *Gut* 1989; **30:** 430–5.

Gynaecomastia. A 62-year-old man developed painful gynaecomastia on two occasions after treatment with calcitonin (salmon) given by subcutaneous injection.[1]

1. Vankrunkelsven PJ, Thijs MM. Salcatonin and gynaecomastia. *Lancet* 1994; **344:** 482.

Interactions

There is a theoretical possibility that dosage adjustments of cardiac glycosides or calcium-channel blockers may be required in patients who are given injections of calcitonin, because of the effects of the latter on serum calcium.

Pharmacokinetics

Calcitonins are rapidly inactivated when given orally. After injection, calcitonins are quickly metabolised, primarily in the kidneys but also in blood and peripheral tissues. Bioavailability has been reported to be about 70%; plasma protein binding is about 30 to 40%. The inactive metabolites and a small proportion of unchanged drug are excreted in the urine. The elimination half-life after injection of calcitonin (human) is stated to be 60 minutes and that of calcitonin (salmon) about 70 to 90 minutes.

Calcitonins are also absorbed through the nasal and rectal mucosa. Although figures have varied widely, about 3% of an intranasal dose of calcitonin (salmon) is reported to be bioavailable compared with the same dose given by intramuscular injection, with peak plasma concentrations occurring after about 30 to 40 minutes compared with 15 to 25 minutes after the parenteral dose. Elimination half-life has been reported to be about 16 to 43 minutes.

◊ After the *subcutaneous injection* of 19.9 micrograms of synthetic calcitonin (salmon) in 16 healthy subjects,[1] absorption was rapid with an absorption half-life of 23.4 minutes. The maximum mean plasma concentration was 384 picograms/mL at 60 minutes after which excretion was fairly rapid with an elimination

half-life of 87 minutes. These results and those from previously reported investigations of salmon, human, and porcine calcitonin could not easily be compared, especially since different assay methods had been used. Nevertheless it was concluded that bioavailability from subcutaneous and intramuscular injection sites was good; that dosage may need to be adjusted in renal insufficiency because of low metabolic clearance rate; and that the higher potency of calcitonin (salmon) is due to higher intrinsic activity at the receptor site rather than to pharmacokinetic differences. The US manufacturers have cited a half-life of 1.02 hours after a single subcutaneous injection of calcitonin (human) 500 micrograms. The plasma elimination half-life of elcatonin was about 4.8 hours after *intramuscular injection* in healthy subjects.[2]

Calcitonins are absorbed on *intranasal* or *rectal* dosage. Peak plasma concentrations of calcitonin (salmon) were achieved after 20 to 60 minutes when given by nasal spray in doses ranging from 200 to 400 units.[3] In another study[4] calcitonin (salmon) 200 units, repeated once after 3 hours, was given by nasal spray or suppository to healthy subjects. Absorption was prompt and the total amount absorbed was similar with either route. However, whereas intranasal dosage produced low peaks with calcitonin (salmon) still detectable in the blood after 3 to 5 hours, rectal dosage produced peak plasma concentrations about 6 to 8 times higher but the drug was undetectable within 2 hours; plasma concentrations were lower than those found after injection. Another group[5] found calcitonin (human) to be poorly absorbed when given intranasally to healthy subjects. Absorption from nasal powder or spray solutions was improved by the presence of the surfactants dihydrofusinate or glycocholate.

Investigations carried out in 4 osteoporotic patients[6] suggested that the rectal calcitonin (salmon) could provide 65% of the bioavailability of intramuscular doses.

A study of an *oral* formulation of calcitonin (salmon) in healthy subjects evaluated different oral doses in comparison to intravenous dosing, and found 1.2 mg orally to be comparable to 10 micrograms intravenously, in terms of bioavailability and efficacy.[7]

1. Nüesch E, Schmidt R. Comparative pharmacokinetics of calcitonins. In: Pecile A, ed. *Calcitonin international congress series no. 540*. Amsterdam: Excerpta Medica, 1980: 352–64.
2. Segre G, *et al.* Pharmacokinetics of carbocalcitonin in humans. *Clin Trials J* 1986; **23** (suppl 1): 23–8.
3. Kurose H, *et al.* Intranasal absorption of salmon calcitonin. *Calcif Tissue Int* 1987; **41:** 249–51.
4. Buclin T, *et al.* The effect of rectal and nasal administration of salmon calcitonin in normal subjects. *Calcif Tissue Int* 1987; **41:** 252–8.
5. Pontiroli AE, *et al.* Nasal administration of glucagon and human calcitonin to healthy subjects: a comparison of powders and spray solutions and of different enhancing agents. *Eur J Clin Pharmacol* 1989; **37:** 427–30.
6. Gennari C, *et al.* Pharmacodynamic activity of synthetic salmon calcitonin in osteoporotic patients: comparison between rectal and intramuscular administration: pilot study. *Curr Ther Res* 1993; **53:** 301–8.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17:** 1478–85.

Uses and Administration

Calcitonin is a hormone produced by mammalian thyroid parafollicular cells or the ultimobranchial gland in non-mammalian vertebrates. In man its secretion and biosynthesis are regulated by the plasma-calcium concentration. It has a hypocalcaemic action that is due primarily to inhibition of osteoclastic bone resorption; of less importance is a direct effect on the kidneys resulting in increased urinary excretion of calcium and phosphorus. Calcitonin contains 32 amino acids; the sequence varies according to the species. Synthetic calcitonin (salmon) and synthetic calcitonin (human) are in clinical use; calcitonin (salmon) is the most potent. Naturally occurring calcitonin (pork) has been used and elcatonin, a synthetic derivative of eel calcitonin, is available in some countries.

Calcitonins are used in the treatment of diseases characterised by high bone turnover such as Paget's disease of bone. They are also given as an adjunct in the treatment of severe hypercalcaemia, especially that associated with malignancy. Some calcitonins are used in the management of osteoporosis.

Calcitonins are generally given by subcutaneous or intramuscular injection; some have been given intranasally, rectally, or by intravenous infusion or slow intravenous injection.

In **Paget's disease of bone** the usual dose range for calcitonin (salmon) is 50 units three times weekly to 100 units daily in single or divided doses by subcutaneous or intramuscular injection. Calcitonin (human) is usually given by subcutaneous or intramuscular injection; doses range from 500 micrograms two to three times weekly, to 250 or 500 micrograms daily; severe cases may require up to 1 mg daily in divided doses.

As an adjunct to the treatment of **hypercalcaemia**, calcitonins have a rapid effect which is greatest in patients with an increased bone turnover. Calcitonin (salmon) may be given by subcutaneous or intramuscular injection in a dose of 4 units/kg every 12 hours, increased if necessary after one or two days to 8 units/kg every 12 hours, up to a maximum of 8 units/kg every 6 hours after a further two days. Alternatively, 100 units every 6 to 8 hours may be given, increased after one or two days to a maximum of 400 units every 6 to 8 hours. Doses greater than 8 units/kg every 6 hours are considered to have no additional benefit. In the emergency treatment of hypercalcaemic crisis, calcitonin (salmon) has also been given intravenously: a suggested dose is up to 10 units/kg diluted in 500 mL of sodium chloride 0.9% and given by slow intravenous infusion over at least 6 hours (see also under Administration below for the problems of intravenous dosage). Calcitonin (human) 500 micrograms every 6 hours has also been given by slow intravenous injection for hypercalcaemia of malignancy.

Calcitonin (salmon) is used in the treatment of **postmenopausal osteoporosis** in a dose of 200 units daily intranasally by nasal spray, alternating nostrils each day. In some countries it has also been given in a dose of 100 units daily or every other day by subcutaneous or intramuscular injection. Supplementary calcium (equivalent to at least 600 mg of elemental calcium daily) and, if necessary, vitamin D (400 units daily) should also be given.

Calcitonin (salmon) is also used for the prevention of acute bone loss due to sudden **immobilisation** such as in patients with recent osteoporotic fractures. The recommended dose is 100 units daily (or 50 units twice daily) by subcutaneous or intramuscular injection, for 2 to 4 weeks. The dose may be reduced to 50 units daily at the start of remobilisation; treatment is maintained until patients are fully mobilised.

Calcitonin (salmon) has also been used for the control of **bone pain due to malignant neoplasms** although in the EU such use is no longer considered appropriate.

Oral formulations of calcitonin (salmon) are being studied.

Administration. Calcitonins have poor oral bioavailability and are usually given by subcutaneous or intramuscular injection. To improve patient acceptability, especially in diseases requiring long-term drug therapy, alternative routes have been investigated:[1]

- calcitonin (salmon) has proved effective when given **intranasally** in usual doses of 50 to 200 units daily (for references, see Osteoporosis below), and intranasal products for osteoporosis are available.
- suppositories containing 300 units of calcitonin (salmon) have been used **rectally** in the management of hypercalcaemia; one suppository being given three times daily (total daily dose of 900 units).[2,3] Daily doses of 100 units of calcitonin (salmon) by suppository have been tried in postmenopausal osteoporosis[4] and in patients with bone pain.[5]
- calcitonins have been given by **intravenous infusion**, but this is rarely necessary and may cause more adverse effects. If intravenous use is essential, it has been suggested[6] that some protein must be present in the solution to prevent adsorption onto the plastic of the giving set. However, in practice this does not seem to be the case; in the UK, manufacturer's recommendations are for dilution with normal saline, while acknowledging that such dilution results in a loss of potency, and dosage is adjusted accordingly. Presumably dilution with a protein-containing solution would allow lower doses to be used. The manufacturers do specify that solutions for infusion should be prepared immediately before use and that glass or hard plastic containers should not be used.

Novel formulations of an orally active calcitonin have been investigated; one such formulation using a low-molecular-weight carrier, was considered effective and well-tolerated in a Phase I study.[7]

1. Inzerillo AM, *et al.* Calcitonin: physiological actions and clinical applications. *J Pediatr Endocrinol Metab* 2004; **17:** 931–40.
2. Thiébaud D, *et al.* Effectiveness of salmon calcitonin administered as suppositories in tumor-induced hypercalcemia. *Am J Med* 1987; **82:** 745–50.
3. Thiébaud D, *et al.* Fast and effective treatment of malignant hypercalcemia: combination of suppositories of calcitonin and a single infusion of 3-amino 1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990; **150:** 2125–8.
4. Gonnelli S, *et al.* Effect of rectal salmon calcitonin treatment on bone mass and bone turnover in patients with established postmenopausal osteoporosis: a 1-year crossover study. *Curr Ther Res* 1993; **54:** 458–65.
5. Mannarini M, *et al.* Analgesic effect of salmon calcitonin suppositories in patients with bone pain. *Curr Ther Res* 1994; **55:** 1079–83.
6. Stevenson JC. Current management of malignant hypercalcaemia. *Drugs* 1988; **36:** 229–38.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17:** 1478–85.

Administration in renal impairment. Calcitonins are metabolised mainly in the kidneys and pharmacokinetic studies (see above) have indicated that the dosage of calcitonins may need to be reduced in patients with renal insufficiency, but there have been no specific guidelines.

Charcot neuroarthropathy. In a small study in patients with acute Charcot neuroarthropathy, intranasal calcitonin with calcium supplementation significantly reduced bone turnover compared with calcium supplementation alone.[1]

1. Bem R, *et al.* Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. *Diabetes Care* 2006; **29:** 1392–4.

Hypercalcaemia. Calcitonins can be used in addition to rehydration and diuresis in the management of moderate to severe symptomatic hypercalcaemia (p.1668), including that of malignancy (p.1083). Because of their rapid effect, they may be particularly useful in life-threatening hypercalcaemia. However, although they have a rapid effect it is usually short-lived; calcitonins are therefore generally given as an adjunct with other therapy such as a bisphosphonate.

Malignant neoplasms of the bone. Calcitonins may be useful adjuvants in the treatment of malignant disease involving the bone (p.660), not only to correct hypercalcaemia of malignancy (p.1083), but perhaps to relieve bone pain and osteolysis. A systematic review[1] concluded however that available evidence did not support the use of calcitonin for metastatic bone pain; the review was limited to only a few studies. Other therapeutic measures were recommended until further studies are done. In the EU, the use of injectable calcitonins for metastatic bone pain is no longer recommended.

1. Martinez-Zapata MJ, *et al.* Calcitonin for metastatic bone pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/04/08).

Osteogenesis imperfecta. There have been reports[1,2] of beneficial effects with calcitonins in the treatment of osteogenesis imperfecta (p.1083), but their use has declined in favour of bisphosphonates.

1. Castells S, *et al.* Therapy of osteogenesis imperfecta with synthetic salmon calcitonin. *J Pediatr* 1979; **95:** 807–11.
2. Nishi Y, *et al.* Effect of long-term calcitonin therapy by injection and nasal spray on the incidence of fractures in osteogenesis imperfecta. *J Pediatr* 1992; **121:** 477–80.

Osteoporosis. Calcitonins may be used in the prevention and treatment of osteoporosis (p.1084). In the treatment of **postmenopausal** osteoporosis they are usually second-line agents; however, because of their analgesic effect, they may be useful for the initial treatment of those with bone pain due to vertebral crush fractures.[1] Calcitonin (salmon) nasal spray has been shown to significantly reduce the risk of vertebral fractures in women with established osteoporosis,[2] although the study has been criticised[3] for a high drop-out rate. Any effect on hip fracture is unestablished.[1,2] In the management of **corticosteroid**-induced osteoporosis, calcitonin appears to maintain bone mineral density (BMD) at the lumbar spine, but not at the femoral neck. Effects on prevention of fractures have not been established.[1,4] Nasal calcitonin (salmon) has been found to increase lumbar spine BMD in **men** with idiopathic osteoporosis.[1]

1. Silverman SL. Calcitonin. *Endocrinol Metab Clin North Am* 2003; **32:** 273–84.
2. Chesnut CH, *et al.* A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med* 2000; **109:** 267–76.
3. Cummings SR, Chapurlat RD. What PROOF proves about calcitonin and clinical trials. *Am J Med* 2000; **109:** 330–1.
4. Cranney A, *et al.* Calcitonin for preventing and treating corticosteroid-induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 22/02/05).

Paget's disease of bone. Calcitonins 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. However, the bisphosphonates have largely superseded the calcitonins in this role.

Pain. In addition to bone pain associated with malignancy and with bone disorders such as Paget's disease, calcitonins may also have other analgesic properties. Beneficial results have been seen in various painful conditions, including complex regional pain syndrome (p.6), and particularly with intranasal salmon calcitonin.[1] Salmon calcitonin 100 or 200 units intravenously has also provided relief[2] from phantom limb pain (p.9) after amputation. A small double-blind crossover study of intravenous calci-

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.

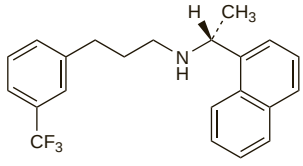
Proprietary Preparations (details are given in Part 3)
Arg.: Anguilcet†; Calsynar†; Citonina†; Osmil†; Salmocalcin†; ***Austral.:*** Miacalcic; ***Austria:*** Calcitonin; Calco; Casalm; Cibacalcin; Elcimen†; Miacalcic†; Ucecal; ***Belg.:*** Calsynar; Miacalcic; Steocalcin; ***Braz.:*** Acticalcin; Calsynar;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

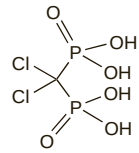
ATC — M05BA02.
ATC Vet — QM05BA02.

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