2 hours after food. About half of the absorbed portion is sequestered to bone; the remainder is excreted in urine. Plasma protein binding is about 87%. Bisphosphonates do not appear to be metabolised, and the unabsorbed fraction of ibandronate is excreted unchanged in the faeces.

◊ References.

1. Bergner R, *et al.* Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. *J Clin Pharmacol* 2007; **47:** 942–50.

Uses and Administration

Ibandronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. It is used as the sodium salt in hypercalcaemia of malignancy, for the prevention of fracture and bone complications in patients with breast cancer and bone metastases, and for the treatment and prevention of postmenopausal osteoporosis.

Ibandronate sodium is given by intravenous infusion or orally, the dose being expressed in terms of ibandronic acid; ibandronate sodium 1.13 mg is equivalent to about 1 mg of ibandronic acid. Specific instructions for oral use (see Precautions in Alendronate, p.1088) should be followed to minimise adverse effects and permit adequate absorption.

For **hypercalcaemia of malignancy**, a single intravenous dose of the equivalent of 2 to 4 mg ibandronic acid is given, up to a maximum of 6 mg; it is diluted in 500 mL of sodium chloride 0.9% or glucose 5%, and infused over 2 hours.

For the prevention of skeletal events in patients with breast cancer and **bone metastases**, the equivalent of 6 mg ibandronic acid is given intravenously, diluted in 100 mL of sodium chloride 0.9% or glucose 5%, and infused over at least 15 minutes. The dose is repeated every 3 to 4 weeks. Alternatively, ibandronic acid 50 mg daily may be given orally.

For the prevention and treatment of postmenopausal **osteoporosis**, ibandronate is given orally in a usual dose equivalent to 150 mg of ibandronic acid once monthly on the same date each month; alternatively, 2.5 mg daily by mouth may be given. If the once-monthly dose is missed, and the next scheduled dose is more than 7 days away, the dose should be taken the next morning, and the patient should then return to the original schedule. However, if the next dose is less than 7 days away, then the patient should wait until that next scheduled dose; 2 tablets must not be taken within the same week. Alternatively, treatment may be given intravenously, in a dose equivalent to 3 mg of ibandronic acid once every 3 months; the injection is given over 15 to 30 seconds. If the dose is missed, the injection should be given as soon as possible; the next injection should then be rescheduled 3 months from this injection, as it should not be given more frequently than once every 3 months.

◊ General references.

1. Dooley M, Balfour JA. Ibandronate. *Drugs* 1999; **57:** 101–108.
2. Barrett J, *et al.* Ibandronate: a clinical pharmacological and pharmacokinetic update. *J Clin Pharmacol* 2004; **44:** 951–65.
3. Anonymous. Ibandronate (Boniva): a new oral bisphosphonate. *Med Lett Drugs Ther* 2005; **47:** 35.
4. Guay DR. Ibandronate, an experimental intravenous bisphosphonate for osteoporosis, bone metastases, and hypercalcemia of malignancy. *Pharmacotherapy* 2006; **26:** 655–73.
5. Zaidi M, *et al.* Progression of efficacy with ibandronate: a paradigm for the development of new bisphosphonates. *Ann N Y Acad Sci* 2007; **1117:** 273–82.
6. Reginster JY, *et al.* Ibandronate in profile: drug characteristics and clinical efficacy. *Expert Opin Drug Metab Toxicol* 2008; **4:** 941–51.

Administration in renal impairment. UK and US licensed product information for ibandronate states that the dose should be adjusted on the basis of creatinine clearance (CC).

When used for the prevention of skeletal events in patients with breast cancer and **bone metastases**, the following *oral* doses are recommended:

- mild or moderate renal impairment (CC equal to or greater than 30 mL/minute): no adjustment necessary
- CC below 30 mL/minute: 50 mg once weekly

Since a 15-minute infusion time has not been studied in cancer patients with a CC less than 50 mL/minute, the following *intravenous* doses are recommended, to be given every 3 to 4 weeks in a solution of sodium chloride 0.9% or glucose 5%:

- CC equal to or greater than 50 mL/minute: no adjustment necessary
- CC less than 50 mL/minute, but equal to or greater than 30 mL/minute: 6 mg in 500 mL of infusion solution, infused over 1 hour
- CC less than 30 mL/minute: 2 mg in 500 mL of infusion solution, infused over 1 hour

In patients with **osteoporosis**, the following recommendations are given, for *oral* or *intravenous* use:

- mild or moderate renal impairment (CC equal to or greater than 30 mL/minute): no adjustment necessary
- CC below 30 mL/minute: not recommended

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. In a dose-response study,[1] 2 mg of ibandronate was found to be significantly less effective than 4 or 6 mg in correcting hypercalcaemia, and response was better in those patients with breast cancer or haematological tumours. In comparison to pamidronate,[2] ibandronate was reported to be more effective in those patients with higher initial baseline serum calcium; duration of response was also longer with ibandronate. In a series of case reports, intravenous ibandronate rapidly corrected hypercalcaemia and restored renal function in multiple myeloma patients. The authors suggested that, although unlicensed for this use, ibandronate should be considered in this patient population.[3]

1. Ralston SH, *et al.* Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. *Br J Cancer* 1997; **75:** 295–300.
2. Pecherstorfer M, *et al.* Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer* 2003; **11:** 539–47.
3. Henrich D, *et al.* Ibandronate for the treatment of hypercalcemia or nephrocalcinosis in patients with multiple myeloma and acute renal failure: case reports. *Acta Haematol (Basel)* 2006; **116:** 165–72.

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. Ibandronate is licensed for such use in many countries. In patients with bone metastases from breast cancer, both oral[1] and intravenous[2] ibandronate reduced the skeletal morbidity period rate (the number of 12-week periods with new bone complications). A pilot study[3] in 18 patients with skeletal metastases from various tumours, and with bone pain insufficiently controlled with opioid analgesics, found short-term intensive intravenous ibandronate (4 mg for 4 consecutive days) to significantly reduce bone pain scores; this analgesic effect was obtained within 7 days, and sustained for a further 5 weeks. A review[4] concluded that once-monthly intravenous dosing could aid compliance, since it can be given simultaneously with cancer therapy; the absence of any apparent renal toxicity associated with ibandronate was a further advantage in its use in cancer patients.

Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Tripathy D, *et al.* Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* 2004; **15:** 743–50.
2. Body J-J, *et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003; **14:** 1399–1405.
3. Mancini I, *et al.* Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. *J Clin Oncol* 2004; **22:** 3587–92.
4. McCormack PL, Plosker GL. Ibandronic acid: a review of its use in the treatment of bone metastases of breast cancer. *Drugs* 2006; **66:** 711–28.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). In the treatment of **postmenopausal** osteoporosis, *oral* ibandronate in intermittent regimens of 20 mg every alternate day,[1] or 20 mg weekly[2] has been found to have equivalent effects on bone mineral density (BMD) to 2.5 mg daily. Intermittent oral ibandronate (20 mg every alternate day for 12 doses every 3 months) was also as effective as the lower daily dose in reducing the incidence of osteoporotic fractures in postmenopausal women.[3] In the prevention of postmenopausal osteoporosis, both 2.5 mg daily[4] and 20 mg weekly[5] prevented bone loss at the spine and hip. A large study comparing three different monthly regimens with the 2.5 mg daily regimen found them to be of similar efficacy in terms of improvement in lumbar BMD after 1 year; 150 mg given once monthly was considered to be superior to the low-dose daily regimen.[6] A review[7] concluded that this unique once-monthly regime could benefit patients by improving compliance.

Intravenous ibandronate 2 mg given every 3 months has also proven effective in increasing BMD in the treatment[8] and prevention[9] of postmenopausal osteoporosis. A large, randomised, double-blind study compared 2 intravenous regimens (2 mg every 2 months and 3 mg every 3 months) with oral ibandronate 2.5 mg daily in postmenopausal women with osteoporosis. After 1 year, both intravenous regimens increased lumbar BMD scores significantly more than the oral regimen. Similar results were obtained for proximal femoral BMD scores, except that for femoral neck BMD, the 2-monthly regimen and daily oral regimen were not significantly different.[10] After 2 years, these results were reported to have been maintained.[11] In **corticosteroid-induced** osteoporosis, intravenous ibandronate 2 mg every 3 months was better than daily oral alfacalcidol at reducing vertebral fractures.[12,13] Intravenous ibandronate has also shown to be of benefit in reducing bone loss after kidney **transplantation**.[14] A pilot study[15] of intermittent ibandronate given intravenously to **men** with severe osteoporosis significantly increased BMD at the lumbar spine, trochanter, and femoral neck.

1. Riis BJ, *et al.* Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. *J Bone Miner Res* 2001; **16:** 1871–8.
2. Cooper C, *et al.* Efficacy and safety of oral weekly ibandronate in the treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88:** 4609–15.
3. Chesnut CH, *et al.* Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004; **19:** 1241–9.
4. McClung MR, *et al.* Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res* 2004; **19:** 11–18.
5. Tankó LB, *et al.* Oral weekly ibandronate prevents bone loss in postmenopausal women. *J Intern Med* 2003; **254:** 159–67.
6. Miller PD, *et al.* Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* 2005; **20:** 1315–22.
7. Chesnut CH. Treating osteoporosis with bisphosphonates and addressing adherence: a review of oral ibandronate. *Drugs* 2006; **66:** 1351–9.
8. Adami S, *et al.* Efficacy and safety of ibandronate given by intravenous injection once every 3 months. *Bone* 2004; **34:** 881–9.
9. Stakkestad JA, *et al.* Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. *Ann Rheum Dis* 2003; **62:** 969–75.
10. Delmas PD, *et al.* Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006; **54:** 1838–46.
11. Croom KF, Scott LJ. Intravenous ibandronate: in the treatment of osteoporosis. *Drugs* 2006; **66:** 1593–1601.
12. Ringe JD, *et al.* Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. *Osteoporosis Int* 2003; **14:** 801–7.
13. Ringe JD, *et al.* Three-month ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis. *Rheumatology (Oxford)* 2003; **42:** 743–9.
14. Grotz W, *et al.* Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001; **12:** 1530–7.
15. Lamy O, *et al.* Intravenous ibandronate in men with osteoporosis: an open pilot study over 2 years. *J Endocrinol Invest* 2003; **26:** 728–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Bandrobon; Bonviva; Elasterin; Femorel; Idena; Modifical; ***Austria:*** Bondronat; ***Belg.:*** Bondronat; ***Chile:*** Bondronat; Bonviva; ***Cz.:*** Bondenza; Bondronat; Bonviva; ***Denm.:*** Bondronat; ***Fin.:*** Bondronat; Bonviva; ***Fr.:*** Bondronat; Bonviva; ***Ger.:*** Bondronat; Bonviva; ***Gr.:*** Bondronat; Bonviva; ***Hong Kong:*** Bondronat; ***Hung.:*** Bondronat; Bonviva; ***Indon.:*** Bonviva; ***Irl.:*** Bondronat; Bonviva; ***Israel:*** Bonat; ***Ital.:*** Bondronat; Bonviva; ***Malaysia:*** Bonviva; ***Mex.:*** Bondronat; ***Neth.:*** Bondenza; Bondronat; Bonviva; Destara; ***Norw.:*** Bondronat; ***Philipp.:*** Bondronat; Bonviva; ***Pol.:*** Bondronat; Bonviva†; ***Port.:*** Bondenza; Bondronat; Bonviva; ***Rus.:*** Bondronat (Бондронат); ***S.Afr.:*** Bondronat; ***Singapore:*** Bondronat; Bonviva; ***Spain:*** Bondronat; ***Swed.:*** Bondronat; Bonviva; ***Switz.:*** Bondronat; ***Thai.:*** Bondronat; ***UK:*** Bondronat; Bonviva; ***USA:*** Boniva.

Multi-ingredient: ***Arg.:*** Femorel Max.

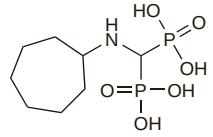
Incadronate

Incadronic Acid *(rINN)*

Acide Incadronique; Ácido incadrónico; Acidum Incadronicum; Cimadronic Acid; YM-175. [(Cycloheptylamino)methylene]diphosphonic acid.

Инкадроновая Кислота

$C_8H_{19}NO_6P_2$ = 287.2.
CAS — 124351-85-5.



Incadronate Disodium

Disodium Incadronate *(rINNM)*; Incadronas Dinatricum; Incadronate Disodique; Incadronato disódico. Disodium [(cycloheptylamino)methylene]diphosphonate.

Динатрий Инкадронат

$C_8H_{17}NNa_2O_6P_2$ = 331.2.
CAS — 138330-18-4.

Profile

Incadronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. It is given by intravenous infusion

as incadronate disodium for hypercalcaemia of malignancy in a dose of 10 mg over 2 to 4 hours; if necessary this dose may be repeated at intervals of no less than 1 week. Hypocalcaemia and hypotension may occur. Incadronate is under investigation for the treatment of bone metastases in patients with breast cancer.

◊ References.

1. Usui T, *et al.* Pharmacokinetics of incadronate, a new bisphosphonate, in healthy volunteers and patients with malignancy-associated hypercalcemia. *Int J Clin Pharmacol Ther* 1997; **35:** 239–44.
2. Matsumoto T, *et al.* Comparative study of incadronate and elcatonin in patients with malignancy-associated hypercalcaemia. *J Int Med Res* 2002; **30:** 230–43.

Preparations

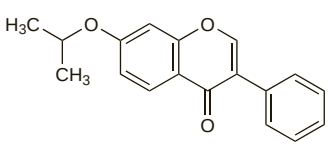
Proprietary Preparations (details are given in Part 3)
Jpn: Bisphonal; ***Philipp.:*** Bisphonal; ***Thai.:*** Bisphonal.

Ipriflavone *(rINN)*

FL-113; Ipriflavona; Ipriflavonum. 7-Isopropoxyisoflavone.

Иприфлавон

$C_{18}H_{16}O_3$ = 280.3.
CAS — 35212-22-7.
ATC — M05BX01.
ATC Vet — QM05BX01.



Profile
Ipriflavone is a synthetic isoflavonoid that inhibits resorption of bone and is available in some countries for the treatment of osteoporosis (p.1084). It is given orally in a dose of 200 mg three times daily.

Osteoporosis. Despite an earlier favourable report,[1] a prospective randomised controlled study in postmenopausal women with low bone mass failed to show prevention of bone loss or improvements in markers of bone metabolism with ipriflavone.[2] There was also a significant incidence of lymphopenia with the drug.

1. Agnusdei D, *et al.* Effects of ipriflavone on bone mass and bone remodeling in patients with established postmenopausal osteoporosis. *Curr Ther Res* 1992; **51:** 82–91.
2. Alexandersen P, *et al.* Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001; **285:** 1482–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Iprioston†; ***Braz.:*** Osteoplus; Rebone; ***Ital.:*** Iprosten†; Osteofix; ***Jpn:*** Osten.

Multi-ingredient: ***Indon.:*** Vosteon; ***UK:*** Osteopro.

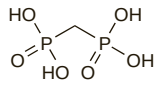
Medronate

Medronic Acid *(BAN, USAN, pINN)*

Acid medronique; Acide Médronique; Ácido medrónico; Acidum medronicum. Methylenebis(phosphonic acid).

Медроновая Кислота

$CH_6O_6P_2$ = 176.0.
CAS — 1984-15-2.



Medronate Disodium *(USAN, pINNM)*

Disodium Medronate *(BANM)*; Disodium Methylene Diphosphonate; MDP; Medronas Dinatricum; Médronate Disodique; Medronato disódico. Disodium dihydrogen methylenediphosphonate.

Динатрий Медронат

$CH_4Na_2O_6P_2$ = 220.0.
CAS — 25681-89-4.

Profile
Medronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1089). It has a strong affinity for bone. Complexes of medronate disodium and stannous chloride or fluoride, or medronic acid, stannous chloride dihydrate, and ascorbic acid, are labelled with radioactive technetium-99m (p.2055) and used diagnostically as bone scanning agents; they are given intravenously.

Hypersensitivity. For reference to a severe allergic reaction attributed to the medronate component of a radiopharmaceutical, see under Adverse Effects and Precautions of Bisphosphonates, p.1091.

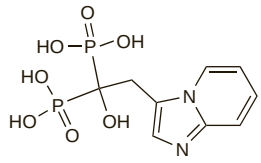
Minodronate

Minodronic Acid *(rINN)*

Acide Minodronique; Ácido minodrónico; Acidum minodronicum; YH-529; YM-529. (1-Hydroxy-2-imidazo[1,2-*a*]pyridin-3-ylethylidene)diphosphonic acid.

Миндроновая Кислота

$C_9H_{12}N_2O_7P_2$ = 322.1.
CAS — 127657-42-5.



Profile
Minodronate is a bisphosphonate under investigation for osteoporosis, multiple myeloma, and bone metastases.

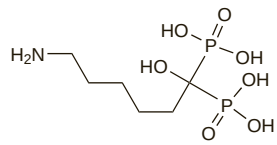
Neridronate

Neridronic Acid *(rINN)*

Acide Néridronique; Ácido neridrónico; Acidum neridronicum; AHDP; AHHexBP; Aminohexane Diphosphonate. (6-Amino-1-hydroxyhexylidene)diphosphonic acid.

Неридроновая Кислота

$C_6H_{17}NO_7P_2$ = 277.1.
CAS — 79778-41-9.



Neridronate Sodium *(rINNM)*

Natrii Neridronas; Néridronate de Sodium; Neridronato sódico.

Натрий Неридронат

Profile
Neridronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p.1089). It inhibits bone resorption and is given intravenously as the sodium salt in the management of osteogenesis imperfecta (p.1083); it has been used in the treatment of malignant hypercalcaemia (p.1083) and diseases associated with excessive bone turnover such as Paget's disease of bone (p.1086) and osteoporosis (p.1084).

◊ References.

1. O'Rourke NP, *et al.* Treatment of malignant hypercalcaemia with aminohexane bisphosphonate (neridronate). *Br J Cancer* 1994; **69:** 914–17.
2. Filipponi P, *et al.* Paget's disease of bone: benefits of neridronate as a first treatment and in cases of relapse after clodronate. *Bone* 1998; **23:** 543–8.
3. Adami S, *et al.* Short-term intravenous therapy with neridronate in Paget's disease. *Clin Exp Rheumatol* 2002; **20:** 55–8.
4. Adami S, *et al.* Intravenous neridronate in adults with osteogenesis imperfecta. *J Bone Miner Res* 2003; **18:** 126–30.
5. Braga V, *et al.* Intravenous intermittent neridronate in the treatment of postmenopausal osteoporosis. *Bone* 2003; **33:** 342–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Nerixia.

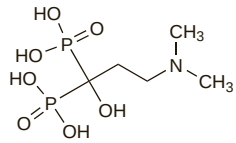
Olpadronate

Olpadronic Acid *(rINN)*

Acide Olpadronique; Ácido olpadrónico; Acidum olpadronicum; Alpudronic Acid. [3-(Dimethylamino)-1-hydroxypropylidene]diphosphonic acid.

Олпадроновая Кислота

$C_5H_{15}NO_7P_2$ = 263.1.
CAS — 63132-39-8.



Olpadronate Disodium

IG-8801; Sodium Olpadronate.

$C_5H_{13}NNa_2O_7P_2$ = 307.1.
CAS — 121368-58-9.

Profile
Olpadronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p.1089). It has been investigated for the treatment of Paget's disease of bone and osteogenesis imperfecta.

◊ References.

1. González DC, Mautalen CA. Short-term therapy with oral olpadronate in active Paget's disease of bone. *J Bone Miner Res* 1999; **14:** 2042–7.
2. Soerdjbalie-Maikoe V, *et al.* Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton. *Eur J Nucl Med Mol Imaging* 2002; **29:** 494–8.
3. Cremers SCLM, *et al.* Relationships between pharmacokinetics and rate of bone turnover after intravenous bisphosphonate (olpadronate) in patients with Paget's disease of bone. *J Bone Miner Res* 2003; **18:** 868–75.
4. Eekhoff MEMW, *et al.* Determinants of induction and duration of remission of Paget's disease of bone after bisphosphonate (olpadronate) therapy. *Bone* 2003; **33:** 831–8.
5. Sakkers R, *et al.* Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. *Lancet* 2004; **363:** 1427–31.

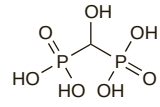
Oxidronate

Oxidronic Acid *(BAN, USAN, pINN)*

Acide Oxidronique; Ácido oxidrónico; Acidum Oxidronicum. (Hydroxymethylene)diphosphonic acid.

Оксидроновая Кислота

$CH_6O_7P_2$ = 192.0.
CAS — 15468-10-7.



Oxidronate Disodium *(pINNM)*

Disodium Oxidronate; HMDP; Oxidronas Dinatricum; Oxidronate Disodique; Oxidronate Sodium; Oxidronato disódico; Sodium Oxidronate *(BANM)*. Disodium (hydroxymethylene)diphosphonate.

Динатрий Оксидронат

$CH_4Na_2O_7P_2$ = 236.0.
CAS — 14255-61-9.

Profile
Oxidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1089). It has a strong affinity for bone. A chelate of oxidronate disodium with radioactive technetium-99m (p.2055) is used diagnostically as a bone scanning agent; it is given intravenously.