

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.

- Usui T, *et al.* Pharmacokinetics of incadronate, a new bisphosphonate, in healthy volunteers and patients with malignancy-associated hypercalcaemia. *Int J Clin Pharmacol Ther* 1997; **35**: 239–44.
- 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.

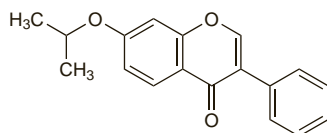
Иприфлавон

$C_{18}H_{16}O_3 = 280.3$.

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.

- 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.
- 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.: Ipristen†; **Braz.:** Osteoplus; Rebone; **Ital.:** Ipristen†; Osteofix; **Jpn:** Osten.

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

Medronate

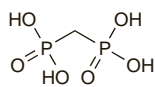
Medronic Acid (BAN, USAN, pINN)

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, pINN)

Disodium Medronate (BANM); Disodium Methylene Diphosphate; MDP; Medronas Dinatricum; Médronate Disodique; Medronato disódico. Disodium dihydrogen methylenediphosphate.

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

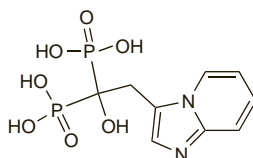
Minodronic Acid (rINN)

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

Минодроновая 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

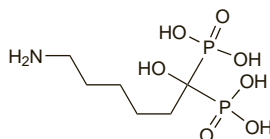
Neridronic Acid (rINN)

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

Неридроновая Кислота

$C_6H_{17}NO_7P_2 = 277.1$.

CAS — 79778-41-9.



Neridronate Sodium (rINN)

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.

- O'Rourke NP, *et al.* Treatment of malignant hypercalcaemia with aminohexane bisphosphonate (neridronate). *Br J Cancer* 1994; **69**: 914–17.
- 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.
- Adami S, *et al.* Short-term intravenous therapy with neridronate in Paget's disease. *Clin Exp Rheumatol* 2002; **20**: 55–8.
- Adami S, *et al.* Intravenous neridronate in adults with osteogenesis imperfecta. *J Bone Miner Res* 2003; **18**: 126–30.
- 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

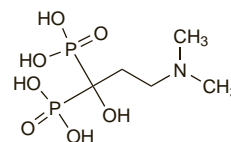
Olpadronic Acid (rINN)

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

Олпадроновая Кислота

$C_5H_{15}NO_7P_2 = 263.1$.

CAS — 63132-39-8.



Olpadronate Disodium

IG-880I; 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.

- 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.
- 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.
- 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.
- 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.
- 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

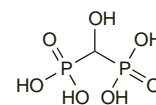
Oxidronic Acid (BAN, USAN, pINN)

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

Оксидроновая Кислота

$CH_6O_7P_2 = 192.0$.

CAS — 15468-10-7.



Oxidronate Disodium (pINN)

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.

Pamidronate

ATC — M05BA03.

ATC Vet — QM05BA03.

Pamidronic Acid (BAN, rINN)

Acide Pamidronique; Ácido pamidróico; Acidum Pamidronicum; Aminohydroxypropylenedibisphosphonate; APD; Pamidronihappo; Pamidronsyra. 3-Amino-1-hydroxypropylenedibis(phosphonic acid).

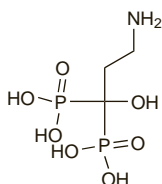
Памидроновая Кислота

$C_3H_{11}NO_7P_2 = 235.1$.

CAS — 40391-99-9.

ATC — M05BA03.

ATC Vet — QM05BA03.



Pamidronate Disodium (USAN, rINN)

Aminohydroxypropylenedibisphosphonate Disodium; CGP-23339A; CGP-23339AE; Dinatrii pamidronas pentahydricus; Dinatriumpamidronaatipentahydrat; Dinatrium-pamidronát pentahydrát; Disodium Aminohydroxypropylenedibisphosphonate; Disodium Pamidronate (BANM); Disodu pamidronian pięciowodny; Disodium Pamidronat; Pamidronaatdinatrium; Pamidronas Dinatrium; Pamidronatdinatrium; Pamidronatdinatriumpentahydrát; Pamidronate Disodique; Pamidronate disodique pentahydraté; Pamidronato disódico; Pamidronatum Dinatrium. Disodium 3-amino-1-hydroxypropylenedibisphosphonate pentahydrate.

Динатрий Памидронат

$C_3H_9NNa_2O_7P_2 \cdot 5H_2O = 369.1$.

CAS — 109552-15-0 (pamidronate disodium pentahydrate); 57248-88-1 (anhydrous pamidronate disodium).

ATC — M05BA03.

ATC Vet — QM05BA03.

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

Ph. Eur. 6.2 (Pamidronate Disodium Pentahydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in dichloromethane. It is sparingly soluble in dilute mineral acids and dissolves in dilute alkaline solutions. A 1.0% solution in water has a pH of 7.8 to 8.8.

USP 31 (Pamidronate Disodium). A white crystalline powder. Soluble in water and in 2N sodium hydroxide; sparingly soluble 0.1N acetic acid and in 0.1N hydrochloric acid; practically insoluble in organic solvents. pH of a 1% solution in water is between 7.8 and 8.8. Store in airtight containers at a temperature not exceeding 30°.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089.

Fever and flu-like symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes) are common during intravenous infusion of pamidronate but generally resolve spontaneously. Pamidronate should not be given by bolus injection, as severe local reactions and thrombophlebitis have occurred. CNS effects include agitation, confusion, dizziness, lethargy, insomnia, and somnolence. There have been isolated cases of seizures, and visual hallucinations. In addition to hypocalcaemia and hypophosphataemia, which are common, hypomagnesaemia or hypokalaemia may occur, and rarely, hypernatraemia, or hyperkalaemia. Both hypotension and hypertension have been reported. Anaemia, thrombocytopenia, and lymphocytopenia may occur. Bronchospasm and interstitial pneumonitis have occurred rarely.

Pamidronate should be used with caution in those with cardiac disease, because of the potential for fluid overload, and in those who have had thyroid surgery, because of the increased risk of hypocalcaemia due to relative hypoparathyroidism. Serum electrolytes, calcium and phosphate should be monitored during therapy,

along with renal function. Patients should be warned against driving or operating machinery after treatment if somnolence or dizziness occur.

Effects on the ears. Ototoxicity, manifest as tinnitus and sudden hearing loss, has been reported¹ in 2 patients given both intravenous and oral pamidronate for pre-existing otosclerosis.¹ A patient given 5 pamidronate infusions for Paget's disease developed tinnitus, vertigo, and hearing loss; the latter two symptoms resolved over 9 months, but tinnitus persisted.²

1. Boumans LJJM, Poulblon RML. The detrimental effect of aminohydroxypropylenedibisphosphonate (APD) in otospongiosis. *Eur Arch Otorhinolaryngol* 1991; **248**: 218–21.
2. Reid IR, *et al.* Ototoxicity associated with intravenous bisphosphonate administration. *Calcif Tissue Int* 1995; **56**: 584–5.

Effect on electrolytes. Pamidronate has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in 2 patients. In each case, other conditions interfered with the expected compensatory physiological response to the hypocalcaemia.¹

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328**: 335–6.

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

Effects on the gastrointestinal tract. The tolerability of pamidronate given orally may depend to some extent on the particular formulation. Gastrointestinal disturbances (in 21.8%) and haematological abnormalities (in 9.4%) were the main adverse effects associated with oral pamidronate in an open study of elderly patients.¹ Oesophagitis, noted earlier² in 4 of 49 patients given a different formulation, was not reported in this study.¹

1. Spivacow FR, *et al.* Tolerability of oral pamidronate in elderly patients with osteoporosis and other metabolic bone diseases. *Curr Ther Res* 1996; **57**: 123–30.
2. Lufkin EG, *et al.* Pamidronate: an unrecognised problem in gastrointestinal tolerability. *Osteoporosis Int* 1994; **4**: 320–2.

Effects on the kidneys. Like other bisphosphonates (see p.1091), pamidronate may cause adverse renal effects. UK licensed product information notes that there have been isolated cases of haematuria, acute renal failure, and deterioration of pre-existing renal disease. Renal function should be monitored during long-term pamidronate therapy, especially in patients with pre-existing renal disease or a predisposition to renal impairment. Longer infusion times may reduce the risk of renal toxicity, and various infusion rates have been recommended, see Uses and Administration, below.

Effects on mental state. Palpitations, followed by visual hallucinations, suicidal ideation, and clinical depression were reported in an elderly man after a single infusion of pamidronate for Paget's disease; he had no previous psychiatric history. Treatment with thioridazine reduced the frequency and effect of the hallucinations.¹

1. Foley-Nolan D, *et al.* Pamidronate associated hallucinations. *Ann Rheum Dis* 1992; **51**: 927–8.

Effects on the musculoskeletal system. Although pamidronate appears to be a less potent inhibitor of bone mineralisation than etidronate, mineralisation defects have been reported in patients with Paget's disease of bone receiving pamidronate.¹ The resultant osteomalacia was not associated with any adverse clinical effects. Pamidronate-induced osteopetrosis has also been reported.² Acute pseudogout arthritis in a woman treated with pamidronate for acute hypercalcaemia was possibly due to deposition of calcium in the joints.³ Severe bone pain occurred in more patients than expected when pamidronate was used for treatment of low bone density in cystic fibrosis;⁴ an increase in proinflammatory cytokines was postulated as a mechanism for this effect.⁵

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

1. Adamson BB, *et al.* Mineralisation defects with pamidronate therapy for Paget's disease. *Lancet* 1993; **342**: 1459–60.
2. Whyte MP, *et al.* Bisphosphonate-induced osteopetrosis. *N Engl J Med* 2003; **349**: 457–63.
3. Malnick SDH *et al.* Acute pseudogout as a complication of pamidronate. *Ann Pharmacother* 1997; **31**: 499–500.
4. Haworth CS, *et al.* Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. *Lancet* 1998; **352**: 1753–4.
5. Teramoto S, *et al.* Increased cytokines and pamidronate-induced bone pain in adults with cystic fibrosis. *Lancet* 1999; **353**: 750.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. Rash and pruritus occasionally follow pamidronate infusion. Mild skin rashes have also been reported in some patients taking oral pamidronate (see also under Bisphosphonates, p.1091).

Pregnancy. Bisphosphonates cross the placenta in animals and humans. These drugs also persist in mineralised bone for many years. Thus, in theory, even if use were to be avoided during pregnancy, the fetus might still be exposed to bisphosphonates from prior therapy released from the maternal skeleton. Furthermore, suppressed bone turnover caused by residual bisphosphonate might cause maternal complications during pregnancy.¹ However, no adverse effects were seen during pregnancy in 2

women with osteogenesis imperfecta given intravenous pamidronate before conception. One infant had transient asymptomatic hypocalcaemia, and one had bilateral talipes equinovarus (a congenital deformity in which the foot turns downwards and inwards). No other skeletal abnormalities were noted. The authors advised monitoring of neonatal calcium concentrations in infants born to mothers treated with pamidronate.¹ In another report of 3 women given long-term pamidronate before conception, 4 healthy infants were born with no evidence of biochemical or skeletal abnormalities.²

1. Munns CFJ, *et al.* Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. *J Bone Miner Res* 2004; **19**: 1742–5.
2. Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. *J Clin Endocrinol Metab* 2006; **91**: 2017–20.

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Plasma concentrations of pamidronate rise rapidly after the start of an intravenous infusion; the apparent plasma half-life is 0.8 hours. Plasma protein binding is about 54%. Pamidronate is not metabolised, and about 20 to 55% of the dose is excreted in the urine unchanged within 72 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment and infusion rates may need to be reduced (see below).

Like all bisphosphonates, oral pamidronate is poorly absorbed from the gastrointestinal tract; bioavailability is about 1 to 3%.

Uses and Administration

Pamidronate is an aminobisphosphonate 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.

Pamidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also used in the treatment of osteolytic lesions and bone pain in multiple myeloma or bone metastases associated with breast cancer. It may also be of benefit in bone disorders associated with excessive bone resorption, including Paget's disease of bone.

Pamidronate disodium is given by slow intravenous infusion. UK licensed product information recommends infusion at a rate not exceeding 60 mg/hour (or not exceeding 20 mg/hour in patients with established or suspected renal impairment) and at a concentration not exceeding 60 mg per 250 mL of infusion solution (sodium chloride 0.9% or glucose 5%). In the USA, the recommended concentration of infusion and rate vary depending on the indication.

In hypercalcaemia of malignancy pamidronate disodium is given by slow intravenous infusion in a total dose of 15 to 90 mg according to the initial plasma-calcium concentration. In the UK, the total dose is given as a single infusion or in divided doses over 2 to 4 days. In the USA, the total dose is given as a single infusion, doses of 60 mg to 90 mg being given over 2 to 24 hours. Plasma-calcium concentrations generally start declining 24 to 48 hours after a dose of pamidronate with normalisation within 3 to 7 days. Treatment may be repeated if normocalcaemia is not achieved within this time or if hypercalcaemia recurs.

In patients with **osteolytic lesions and bone pain** of multiple myeloma or bone metastases associated with breast cancer, pamidronate disodium may be given in doses of 90 mg by intravenous infusion every 3 to 4 weeks.

In the treatment of **Paget's disease** the dosage regimen in the UK is 30 mg by slow infusion once a week for 6 weeks (total dose 180 mg), or 30 mg in the first week then 60 mg every other week for 6 weeks (total dose 210 mg). These courses may be repeated every 6 months, and the total dose increased if necessary up to