Pamidronate

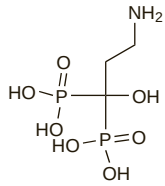
ATC — M05BA03.
ATC Vet — QM05BA03.

Pamidronic Acid *(BAN, rINN)*

Acide Pamidronique; Ácido pamidrónico; Acidum Pamidronicum; Aminohydroxypropylidenebisphosphonate; APD; Pamidronihappo; Pamidronsyra. 3-Amino-1-hydroxypropylidenebis(phosphonic acid).

Памидроновая Кислота

$C_3H_{11}NO_7P_2$ = 235.1.
CAS — 40391-99-9.
ATC — M05BA03.
ATC Vet — QM05BA03.



Pamidronate Disodium *(USAN, rINNM)*

Aminohydroxypropylidenebisphosphonate Disodium; CGP-23339A; CGP-23339AE; Dinatrii pamidronas pentahydricus; Dinatriumpamidronaattipentahydraatti; Dinatrium-pamidronát pentahydrát; Disodium Aminohydroxypropylidenediphosphonate; Disodium Pamidronate *(BANM)*; Disodu pamidronian pięciowodny; Disodyum Pamidronat; Pamidronaattidinatrium; Pamidronas Dinatricum; Pamidronatdinatrium; Pamidronatdinatriumpentahydrat; Pamidronate Disodique; Pamidronate disodique pentahydraté; Pamidronato disódico; Pamidronatum Dinatricum. Disodium 3-amino-1-hydroxypropylidenebisphosphonate pentahydrate.

Динатрий Памидронат

$C_3H_9NNa_2O_7P_2,5H_2O$ = 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 reported[1] 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, Poublon RML. The detrimental effect of aminohydroxypropylidene bisphosphonate (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 earlier[2] 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

a maximum of 360 mg. Alternatively, the dose used in the USA is 30 mg by infusion over 4 hours, repeated on consecutive days to a total dose of 90 mg. This course is repeated when clinically indicated.

Pamidronate has also been given orally.

◊ General references.

1. Coukell AJ, Markham A. Pamidronate: a review of its use in the management of osteolytic bone metastases, tumour-induced hypercalcaemia and Paget's disease of bone. *Drugs Aging* 1998; **12:** 149–68.

Administration in renal impairment. Pharmacokinetic studies suggest that no dosage reduction of pamidronate disodium is required in patients with any degree of renal impairment.[1] However, UK product information currently recommends that the rate of infusion be reduced to a maximum of 20 mg/hour for patients with established or suspected renal impairment; use in those with severe renal impairment (creatinine clearance less than 30 mL/minute) is not advised as clinical experience is limited.

1. Berenson JR, *et al.* Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol* 1997; **37:** 285–90.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients. In small studies, intravenous pamidronate 30 mg daily for 3 days, or at 1 mg/kg daily for 1 or 3 days,[1] or 60 mg daily for 3 days,[2] significantly improved pain and range of movement in cases refractory to previous treatment.

1. Maillefert JF, *et al.* Pooled results from 2 trials evaluating bisphosphonates in reflex sympathetic dystrophy. *J Rheumatol* 1999; **26:** 1856–7.
2. Kubalek I, *et al.* Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases. *Rheumatology (Oxford)* 2001; **40:** 1394–7.

Gaucher disease. Treatment with oral pamidronate disodium in doses of 600 mg daily in adults,[1] and 150 to 300 mg daily in children,[2] or intravenous pamidronate disodium in doses of 45 mg every 3 weeks,[3] has been reported to improve bone lesions of Gaucher disease (p.2249) in a few patients.

1. Harinck HIJ, *et al.* Regression of bone lesions in Gaucher's disease during treatment with aminohydroxypropylidene bisphosphonate. *Lancet* 1984; **ii:** 513.
2. Samuel R, *et al.* Aminohydroxy propylidine bisphosphonate (APD) treatment improves the clinical skeletal manifestations of Gaucher's disease. *Pediatrics* 1994; **94:** 385–9.
3. Ciana G, *et al.* Short-term effects of pamidronate in patients with Gaucher's disease and severe skeletal involvement. *N Engl J Med* 1997; **337:** 712.

Hypercalcaemia. Bisphosphonates, of which pamidronate is one of the most effective, are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated.

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. Pamidronate is licensed for such use in many countries. A literature review[1] of phase II and III studies concluded that pamidronate was effective in the treatment of pain and skeletal complications from metastatic disease, particularly in patients with breast cancer or multiple myeloma, but that its efficacy in those with other neoplasms needed confirmation. A long-term follow-up[2] of 2 randomised trials of pamidronate in women with breast cancer confirmed its efficacy over placebo. However, a pooled analysis[3] of its use for palliation of bone pain in men with metastatic prostate cancer found no treatment benefit with pamidronate over placebo. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Ripamonti C, *et al.* Role of pamidronate disodium in the treatment of metastatic bone disease. *Tumori* 1998; **84:** 442–55.
2. Lipton A, *et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; **88:** 1082–90.
3. Small EJ, *et al.* Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003; **21:** 4277–84.

Osteogenesis imperfecta. Pamidronate has produced benefit in patients with osteogenesis imperfecta (p.1083). Although the dosage and timing varied between centres and age groups, all patients were given cyclical intravenous pamidronate;[1-5] bone mineral density increased, fracture incidence decreased, and patients reported improvements in mobility, pain and chronic fatigue. Treated infants achieved motor milestones earlier than untreated controls; vertebral height was also improved.[5] While bone size and density also increased in patients given pamidronate, especially in those with larger baseline deficits in bone mass,[6] serum calcium decreased markedly, and bone turnover was suppressed;[7] clinical problems were not evident if calcium intake was sufficient, but consequences of a chronically low bone turnover are unknown. A study in young patients found that bone metabolism is still suppressed, and that bone mass gains continue, for 2 years after stopping therapy.[8]

1. Glorieux FH, *et al.* Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998; **339:** 947–52.
2. Plotkin H, *et al.* Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab* 2000; **85:** 1846–50.
3. Åström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002; **86:** 356–64.
4. Falk MJ, *et al.* Intravenous bisphosphonate therapy in children with osteogenesis imperfecta. *Pediatrics* 2003; **111:** 573–8.
5. Åström E, *et al.* Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. *Arch Dis Child* 2007; **92:** 332–8.
6. Rauch F, *et al.* Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. *J Bone Miner Res* 2003; **18:** 610–14.
7. Rauch F, *et al.* Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. *J Clin Endocrinol Metab* 2003; **88:** 986–92.
8. Rauch F, *et al.* Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J Clin Endocrinol Metab* 2006; **91:** 1268–74.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p.1084). A placebo-controlled trial of oral pamidronate 150 mg daily found it to be effective in increasing bone mineral density (BMD) of the lumbar spine and femoral neck in both **men** and **women**.[1] Intravenous pamidronate at 30 mg every 3 months, or 60 mg every 6 months, also increased BMD in the lumbar spine, femoral neck, and trochanter in an observational, retrospective study.[2] Single intravenous infusions of pamidronate given every 3 months have also been reported to increase BMD and reduce fracture rates in **children** with osteoporosis;[3,4] annual doses were in the region of 4 mg/kg.

An open study[5] in men with prostate cancer (but no bone metastases) and receiving leuprolide, found that addition of pamidronate 60 mg intravenously every 12 weeks prevented **therapy-induced** bone loss in the hip and lumbar spine. Acute bone loss from the femur and pelvis after hip arthroplasty was also reduced by a single infusion of 90 mg pamidronate in a small prospective study.[6] Similarly, in premenopausal women with chemotherapy-induced bone loss, pamidronate 60 mg intravenously every 3 months prevented bone loss at the spine and hip compared with placebo.[7]

In a small study[8] of patients receiving **corticosteroids**, pamidronate given intravenously either as a single infusion of 90 mg, or as 90 mg followed by 30 mg every 3 months for 1 year, significantly increased BMD at the lumbar spine, femoral neck, and total hip. In lymphoma patients receiving corticosteroids as part of chemotherapy regimens, pamidronate 30 mg intravenously every 3 months reduced bone loss when compared with placebo.[9] Pamidronate has shown beneficial increases in or preservation of BMD in patients after heart,[10,11] liver,[11] lung,[12] or stem cell[13] transplantation.

1. Brumsen C, *et al.* Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. *J Bone Miner Res* 2002; **17:** 1057–64.
2. Chan SSY, *et al.* Intravenous pamidronate in the treatment and prevention of osteoporosis. *Intern Med J* 2004; **34:** 162–6.
3. Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. *J Pediatr* 2003; **142:** 417–23.
4. Gandrud LM, *et al.* Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. *J Pediatr Endocrinol Metab* 2003; **16:** 887–92.
5. Smith MR, *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; **345:** 948–55.
6. Wilkinson JM, *et al.* Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial. *J Bone Miner Res* 2001; **16:** 556–64.
7. Fuleihan GE-H, *et al.* Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90:** 3209–14.
8. Boutsen Y, *et al.* Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001; **16:** 104–12.
9. Kim SH, *et al.* Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. *Am J Med* 2004; **116:** 524–8.
10. Krieg MA, *et al.* Intravenous pamidronate as treatment for osteoporosis after heart transplantation: a prospective study. *Osteoporosis Int* 2001; **12:** 112–16.
11. Dodidou P, *et al.* Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. *Osteoporosis Int* 2003; **14:** 82–9.
12. Cahill BC, *et al.* Prevention of bone loss and fracture after lung transplantation: a pilot study. *Transplantation* 2001; **72:** 1251–5.
13. Grigg AP, *et al.* Pamidronate reduces bone loss after allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2006; **91:** 3835–43.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Pamidronate was initially used orally for Paget's disease, but intravenous therapy has been preferred because of a lower incidence of adverse effects.[1,2] With the usual total dose of 180 mg, remission is considered likely in most patients with mild to moderate disease, but unlikely if disease is severe.[2] However, higher doses (about 340 mg) were found to be effective in those with very active disease, and also associated with a longer remission.[1] In a 2-year study[3] of 3 different doses, pamidronate increased bone mineral density in pagetic bone of the lumbar spine, femoral neck, and total hip, but lacked this effect on non-pagetic bone in the same areas; loss of density was apparent in non-pagetic forearm bone in the group given the highest dose (240 mg). Patients with co-existent osteoarthritis or arthropathy responded less well to pamidronate in terms of pain perception, than those patients without joint disease.[4] While hearing loss may or may not improve with pamidronate,[5,6] there has been a report of successful treatment of optic neuropathy due to Paget's disease with pamidronate and dexamethasone.[7] Bisphosphonates have also been given in other bone diseases with a similar pathology, particularly increased osteoclastic resorption. For example, pamidronate has had beneficial effects in patients with fibrous dysplasia of bone, a rare congenital disease leading to osteolytic lesions.[8-10]

1. Selby PL. Pamidronate in the treatment of Paget's disease. *Bone* 1999; **24:** 57S–58S.
2. Tucci JR, Bontha S. Intravenously administered pamidronate in the treatment of Paget's disease of bone. *Endocr Pract* 2001; **7:** 423–9. Correction. *ibid.* 2002; **8:** 78.
3. Gutteridge DH, *et al.* Bone density changes in Paget's disease 2 years after iv pamidronate: profound, sustained increases in pagetic bone with severity-related loss in forearm nonpagetic cortical bone. *Bone* 2003; **32:** 56–61.
4. Vasireddy S, *et al.* Patterns of pain in Paget's disease of bone and their outcomes on treatment with pamidronate. *Clin Rheumatol* 2003; **22:** 376–80.
5. Donáth J, *et al.* Effect of bisphosphonate treatment in patients with Paget's disease of the skull. *Rheumatology (Oxford)* 2004; **43:** 89–94.
6. Murdin L, Yeoh LH. Hearing loss treated with pamidronate. *J R Soc Med* 2005; **98:** 272–4.
7. Isasi C, *et al.* Successful treatment of optic neuropathy in osteitis deformans. *Rheumatology (Oxford)* 2002; **41:** 948–50.
8. Liens D, *et al.* Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet* 1994; **343:** 953–4.
9. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. *J Pediatr* 2000; **137:** 403–9.
10. Plotkin H, *et al.* Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *J Clin Endocrinol Metab* 2003; **88:** 4569–75.

Rheumatoid arthritis and spondyloarthropathies. Intravenous[1] and oral[2] use of pamidronate has reportedly produced some modification of disease in a few patients with rheumatoid arthritis (p.11). Continuous oral pamidronate therapy was shown to be effective in preserving and increasing bone mass in a 3-year randomised controlled trial involving 105 patients with rheumatoid arthritis.[3] In contrast, a small controlled study[4] in 26 patients found no significant effect on rheumatoid arthritis disease activity with intravenous pamidronate. There are reports of an analgesic response to pamidronate in patients with acute rheumatic pain of various aetiologies, including arthritis and ankylosing spondylitis, and a trial[5] in patients with ankylosing spondylitis found a dose-dependent therapeutic effect with pamidronate.[6] Use of intravenous pamidronate and methylprednisolone has also been investigated as part of the management of patients with NSAID-unresponsive ankylosing spondylitis.[7]

1. Eggelmeijer F, *et al.* Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. *J Rheumatol* 1994: **21:** 2016–20.
2. Maccagno A, *et al.* Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand J Rheumatol* 1994; **23:** 211–14.
3. Eggelmeijer F, *et al.* Increased bone mass with pamidronate treatment in rheumatoid arthritis: results of a three-year randomized, double-blind trial. *Arthritis Rheum* 1996; **39:** 396–402.
4. Lodder MC, *et al.* Effects of high dose intravenous pamidronate on disease activity and bone metabolism in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2003; **30:** 2080–1.
5. El-Shafei A, *et al.* Is pamidronate effective for acute rheumatic pain? *Ann Rheum Dis* 2002; **61:** 183.
6. Maksymowych WP, *et al.* A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; **46:** 766–73.
7. Malaviya AN, *et al.* A new strategy of drug treatment in NSAID-unresponsive ankylosing spondylitis: combination of pamidronate and methylprednisolone monthly intravenous infusions on the background of a combination of disease modifying drugs sulfasalazine and methotrexate. *J Assoc Physicians India* 2007; **55:** 193–7.

Preparations

BP 2008: Pamidronate Disodium Intravenous Infusion;
USP 31: Pamidronate Disodium for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Aminomux; Pamdosa; Pandrat; ***Austral.:*** Aredia; Pamisol; ***Austria:*** Aredia; Pamitor; ***Belg.:*** Aredia; Pamidrin; ***Braz.:*** Aredia; Pamidrom; ***Canad.:*** Aredia; ***Chile:*** Aminomux; Aredia†; ***Cz.:*** Aredia; Pamitor; ***Denm.:*** Aredia; Pamifos; ***Fin.:*** Aredia; Pamifos; ***Fr.:*** Aredia; Ostepam; ***Ger.:*** Aredia; Pamidro-cell; Pamidron; Pamifos; Ribodronat; ***Gr.:*** Aredia; Pamerit; ***Hong Kong:*** Aredia; Pamisol; ***Hung.:*** Aredia; Pamifos; Pamitor; ***India:*** Aredronet†; Pamidria; Pamifos; ***Indon.:*** Aredia; ***Irl.:*** Aredia; ***Israel:*** Aredia; ***Ital.:*** Amidrox; Aredia; ***Malaysia:*** Aredia; Pamired; Pamisol; ***Mex.:*** Aredia; Pamisol; ***Neth.:*** Aredia; Pamipro; ***Norw.:*** Aredia†; ***NZ:*** Aredia†; Pamisol;

Philipp.: Aredia; ***Pol.:*** Aredia; Pamifos; Pamitor; ***Port.:*** Aredia†; Pamidran; ***Rus.:*** Aredia (Аредиа); ***S.Afr.:*** Aredia; ***Singapore:*** Aredia†; Pamisol; ***Spain:*** Aredia; Linoten; Pamifos; Xinsidona; ***Swed.:*** Aredia; Pamifos; ***Switz.:*** Aredia; ***Thai.:*** Aredia; Pamisol; ***Turk.:*** Aredia; ***UK:*** Aredia; ***USA:*** Aredia; ***Venez.:*** Aminomux; Aredia†.

Parathyroid Hormone *(BAN, USAN, rINN)*

1-84 Parathormone; ALX1-11 (human recombinant parathyroid hormone); Hormona paratiroidea; Hormone Parathyroïde; Hormonum Parathyroidum; Parathormone; Parathyrin; Parathyroid hormone (1-84); PTH; PTH (1-84).

Паратироид Гормон

CAS — 9002-64-6; 68893-82-3 (human parathyroid hormone); 345663-45-8 (human recombinant parathyroid hormone).
ATC — H05AA03.
ATC Vet — QH05AA03.

Adverse Effects, Treatment, and Precautions

Transient hypercalcaemia and hypercalciuria are very common with parathyroid hormone treatment; persistent hypercalcaemia may necessitate dose reduction or withdrawal of therapy (see Uses and Administration, below). Patients should be monitored at months 1, 3, and 6 for elevated concentrations of serum or urinary calcium; monitoring beyond 6 months is not considered necessary for those whose serum calcium is within normal limits at 6 months. On injection, serum calcium concentrations reach a maximum after 6 to 8 hours, returning to baseline after 20 to 24 hours; blood samples for monitoring should thus be taken at least 20 hours after the most recent dose. Gastrointestinal disturbances, especially nausea, also occur commonly, as do headache, dizziness, fatigue, palpitations, muscle cramps, extremity or back pain, and injection site erythema. Hyperuricaemia has also been reported.

Pharmacokinetics

Subcutaneous parathyroid hormone produces peak plasma concentrations 1 to 2 hours after injection. The average half-life is about 1.5 hours and the absolute bioavailability is about 55%. Parathyroid hormone is removed from the blood by a receptor-mediated process in the liver and broken down into smaller peptide fragments, which either undergo further degradation within the cell or are released back into the blood and renally cleared.

Uses and Administration

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first (N-terminal) 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Endogenous parathyroid hormone is involved in the maintenance of plasma-calcium concentrations through its actions on bone, kidney, and indirectly on the gastrointestinal tract (see also under Parathyroid Disorders, p.1087).

Exogenous parathyroid hormone was formerly used in acute hypoparathyroidism with tetany. It has also been used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism. A human recombinant form is under investigation for the treatment of hypoparathyroidism.

The human recombinant form is used for the treatment of osteoporosis in postmenopausal women at high risk of fractures. The recommended dose is 100 micrograms once daily, given by subcutaneous injection into the abdomen; treatment may be continued for up to 24 months. Supplemental calcium and vitamin D may be needed if dietary intake is inadequate. However, if serum calcium becomes persistently raised, and there is no underlying disease, calcium and vitamin D should be withdrawn, and parathyroid hormone dosing changed to 100 micrograms on every other day. If elevated concentrations persist, parathyroid hormone therapy should be stopped until values return to normal.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones are now used for diagnostic purposes, and for the treatment of osteoporosis (see Teriparatide, p.1105).

◊ References.

1. Rittmaster RS, *et al.* Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 2000; **85:** 2129–34.
2. Hodsman AB, *et al.* Efficacy and safety of human parathyroid hormone-(1–84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88:** 5212–20.
3. Anonymous. ALX 111: ALX1-11, parathyroid hormone (1-84)–NPS Allelix, PREOS, PTH, recombinant human parathyroid hormone, rhPTH (1-84). *Drugs R D* 2003; **4:** 231–5.
4. White H, Ahmad A. PREOS NPS (Allelix/Nycomed). *Curr Opin Investig Drugs* 2005; **6:** 1057–66.
5. Shrader SP, Ragucci KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother* 2005; **39:** 1511–16.
6. Moen MD, Scott LJ. Recombinant full-length parathyroid hormone (1-84). *Drugs* 2006; **66:** 2371–81; discussion 2382–5.
7. Greenspan SL, *et al.* Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med* 2007; **146:** 326–39.

Administration in renal or hepatic impairment. UK licensed product information states that no dose adjustment is necessary for parathyroid hormone when it is used in patients with mild to moderate renal or hepatic impairment, defined as those with a creatinine clearance of 30 to 80 mL/minute, and a total score of 7 to 9 on the Child-Pugh scale, respectively. Use in severe renal or hepatic impairment is not recommended due to lack of data.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Preotact; ***Gr.:*** Preotact; ***UK:*** Preotact.

Plicamycin *(BAN, USAN, rINN)*

A-2371; Aureolic Acid; Mithramycin; Mithramycinum; Mitramycin; Mitramysiini; NSC-24559; PA-144; Plicamicina; Plicamycine; Plicamycinum.

Пликамицин

$C_{52}H_{76}O_{24}$ = 1085.1.
CAS — 18378-89-7.
ATC — L01DC02.
ATC Vet — QL01DC02.

Description. Plicamycin is an antineoplastic antibiotic produced by the growth of *Streptomyces argillaceus, S. plicatus* and *S. tanashiensis.*

Pharmacopoeias. In *US.*
USP 31 (Plicamycin). A yellow, odourless, hygroscopic, crystalline powder, with a potency of not less than 900 micrograms/mg, calculated on the dry basis. It loses not more than 8% of its weight when dried. Slightly soluble in water and in methyl alcohol; very slightly soluble in alcohol; freely soluble in ethyl acetate. A 0.05% solution in water has a pH of 4.5 to 5.5. Store at 2° to 8° in airtight containers. Protect from light.

Profile

Plicamycin is a highly toxic antibiotic with antineoplastic and hypocalcaemic properties. It may act by complexing with DNA in the presence of divalent cations and inhibiting synthesis of ribonucleic acid. Lowering of serum calcium concentrations has been suggested to result from antagonism of the effects of vitamin D and parathyroid hormone on osteoclasts.

Plicamycin has been used in the symptomatic management of hypercalcaemia and hypercalciuria associated with malignancy if it cannot be managed by other means (see below). It has also been used in the treatment of malignant neoplasms of the testis not susceptible to surgery or radiotherapy; however, other agents are preferred (p.673).

The major adverse effect of plicamycin is a dose-related bleeding syndrome, manifest initially as epistaxis, which may progress to haematemesis and potentially fatal haemorrhage. Severe thrombocytopenia may also occur due to bone-marrow depression. Gastrointestinal effects are common and other adverse effects include fever, malaise, drowsiness, lethargy and weakness, headache, depression, skin rashes, facial flushing, and reduced serum concentrations of calcium, phosphorus, and potassium. There may also be reversible impairment of renal and hepatic function.

Extravasation of plicamycin solutions may cause local irritation, cellulitis, and phlebitis.

Hypercalcaemia. Where treatment is required for hypercalcaemia it is aimed at increasing urinary excretion of calcium and maintaining adequate hydration. Drugs that inhibit bone resorption may also be used if hypercalcaemia is severe, particularly when it is associated with malignancy (see p.1083). Plicamycin is highly toxic, and the bisphosphonates and calcitonins are generally preferred; however, it has been given in a dose of 25 micrograms/kg intravenously over 4 to 6 hours.[1,2] Although a single dose might be sufficient to normalise the serum calcium concentration, the dose can be repeated several times at intervals of 24 to 72 hours.

1. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326:** 1196–1203.
2. Hall TG, Schaiff RAB. Update on the medical treatment of hypercalcemia of malignancy. *Clin Pharm* 1993; **12:** 117–25.

Paget's disease of bone. Plicamycin has been used as a second- or third-line drug in the therapy of Paget's disease of bone (p.1086), reserved for patients refractory to other treatment. Nonetheless, occasional successes are reported: one patient with refractory Paget's disease had apparent cure of her symptoms after treatment with plicamycin 25 micrograms/kg daily for 15 doses, followed by 1500 micrograms weekly for about 2 months and every 2 weeks for 6 weeks.[1] She had remained asymptomatic for 18 years after treatment. However, similar regimens have been used in other patients without this degree of success.[1] Another patient, who was refractory to calcitonin and pamidronate therapy, showed a considerable improvement in pain relief and biochemical parameters when treated with 30 micrograms/kg plicamycin daily for 3 days.[2]

1. Ryan WG, *et al.* Apparent cure of Paget's disease of bone. *Am J Med* 1990; **89:** 825–6.
2. Wimalawansa SJ. Dramatic response to plicamycin in a patient with severe Paget's disease refractory to calcitonin and pamidronate. *Semin Arthritis Rheum* 1994; **23:** 267.

Preparations

USP 31: Plicamycin for Injection.

Proprietary Preparations (details are given in Part 3)
Gr.: Mithracin†.

Risedronate

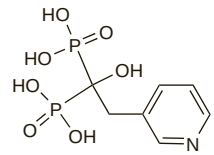
Risedronaatti; Risedronat; Risedronatum.
ATC — M05BA07.
ATC Vet — QM05BA07.

Risedronic Acid *(BAN, rINN)*

Acide Risédronique; Ácido risedrónico; Acidum Risedronicum.
[1-Hydroxy-2-(3-pyridinyl)ethylidene]diphosphonic acid.

Ризедроновая Кислота

$C_7H_{11}NO_7P_2$ = 283.1.
CAS — 105462-24-6.
ATC — M05BA07.
ATC Vet — QM05BA07.



Risedronate Sodium *(BANM, USAN, rINNM)*

Monosodium Risedronate; Natrii Risedronas; NE-58095; Risedronat Sodyum; Risédronate de Sodium; Risedronato sódico; Sodium Risedronate. Sodium trihydrogen [1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate.

Натрий Ризедронат

$C_7H_{10}NNaO_7P_2$ = 305.1.
CAS — 115436-72-1.
ATC — M05BA07.
ATC Vet — QM05BA07.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. The most frequent adverse effects during risedronate therapy are arthralgia and gastrointestinal disturbances. To minimise the risk of gastrointestinal effects precautions similar to those for alendronate should be observed (see p.1088), although UK licensed product information allows for the tablets to be taken other than on rising (but not at bedtime or within 2 hours of food or drink). Hypocalcaemia should be corrected before beginning risedronate therapy.

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

Effects on the gastrointestinal tract. Although, like other oral bisphosphonates, it is recommended that risedronate be taken with care (see above) to avoid gastrointestinal effects, pooled analysis of 9 studies involving 10 068 patients receiving risedronate 5 mg daily indicated that the drug was not associated with an increased frequency of upper gastrointestinal effects, even among patients at increased risk due to active gastrointestinal disease or treatment with aspirin or NSAIDs as well.[1] However, it was noted that comprehensive postmarketing data would be required to see how these results would be reflected in clinical practice. Studies in women previously intolerant to alendronate found that risedronate 5 mg daily[2] and 30 mg once weekly[3] were well tolerated.

In 2 large trials, male and female patients with mild to moderate osteoarthritis of the knee were given risedronate 5 mg once daily, 15 mg once daily, 35 mg once weekly, 50 mg once weekly, or placebo. Patients were allowed continued use of aspirin or NSAIDs. Again, pooled analysis found no increased frequency of upper gastrointestinal adverse events in those given risedronate, even in those patients considered at increased risk for such events.[4]

1. Taggart H, *et al.* Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* 2002; **77:** 262–70. Correction. *ibid.*; 601.
2. Adachi JD, *et al.* Tolerability of risedronate in postmenopausal women intolerant of alendronate. *Aging (Milano)* 2001; **13:** 347–54.
3. Delaney MF, *et al.* Bone density changes with once weekly risedronate in postmenopausal women. *J Clin Densitom* 2003; **6:** 45–50.
4. Adami S, *et al.* Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 1278–85.