For the treatment and prevention of corticosteroid-induced osteoporosis a dose of 5 mg daily is given; postmenopausal women who do not take HRT should be given 10 mg daily.

In adults with **Paget's disease** of bone the usual dose is 40 mg daily for 6 months; treatment may be repeated if necessary after an interval of a further 6 months.

Alendronate has also been given by intravenous infusion.

Administration. Alendronate once-weekly was considered to be therapeutically equivalent to once-daily dosing in both the treatment[1,2] and prevention[3] of osteoporosis, although the treatment study[1] was considered[4,5] to lack information about other drugs being taken and reasons for withdrawal, and studied bone mineral density, not fracture. Tolerability of a once-weekly regimen was comparable to placebo in one study[6] and to once-daily dosing in another;[7] a review[5] concluded that weekly dosage carried a lower risk of upper gastrointestinal symptoms.

1. Schnitzer T, *et al.* Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)* 2000; **12:** 1–12.
2. The Alendronate Once-Weekly Study Group. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002; **17:** 1988–96.
3. Luckey MM, *et al.* Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. *Obstet Gynecol* 2003; **101:** 711–21.
4. Tsun EC, Heck AM. Intermittent dosing of alendronate. *Ann Pharmacother* 2001; **35:** 1471–5.
5. Sambrook P. Once weekly alendronate. *Drugs Today* 2003; **39:** 339–46.
6. Greenspan S, *et al.* Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2002; **77:** 1044–52.
7. Simon JA, *et al.* Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. *Clin Ther* 2002; **24:** 1871–86.

Administration in renal impairment. Elimination of alendronate is reduced in *rats* with kidney failure and is likely to be reduced in patients with renal impairment. Licensed product information makes the following recommendations for oral dosage based on creatinine clearance (CC):

- mild to moderate renal impairment (CC greater than 35 mL/minute): no dose adjustment needed
- severe renal impairment (CC less than 35 mL/minute): use is not recommended due to lack of experience with alendronate in this population

Charcot neuroarthropathy. Six months of treatment with once-weekly alendronate has been reported[1] to improve signs and symptoms of Charcot neuroarthropathy (a sometimes painful deformity in limbs that have lost sensory innervation).

1. Pitocco D, *et al.* Six-month treatment with alendronate in acute Charcot neuroarthropathy: a randomized controlled trial. *Diabetes Care* 2005; **28:** 1214–15.

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 a small study,[1] intravenous alendronate 7.5 mg daily for 3 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Adami S, *et al.* Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; **56:** 201–4.

Gaucher disease. In a placebo-controlled study of patients with Gaucher disease (p.2249), the addition of oral alendronate 40 mg daily to enzyme therapy increased lumbar bone mineral density, but had no effect on focal lesions;[1] the authors concluded that alendronate may be useful adjunctive therapy especially in those patients at risk of osteopenic fracture.

1. Wenstrup RJ, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004; **104:** 1253–7.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. A randomised dose-response study[1] found that single intravenous doses of alendronate 5 mg or more effectively lowered serum-calcium concentrations in patients with tumour-induced hypercalcaemia. Alendronate has also been used to treat hypercalcaemia associated with vitamin D intoxication in children.[2,3]

1. Nussbaum SR, *et al.* Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. *J Clin Oncol* 1993; **11:** 1618–23.
2. Orbak Z, *et al.* Vitamin D intoxication and therapy with alendronate (case report and review of literature). *Eur J Pediatr* 2006; **165:** 583–4.
3. Doneray H, *et al.* Intragastric alendronate therapy in two infants with vitamin D intoxication: a new method. *Clin Toxicol* 2008; **46:** 300–2.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p.1087), but seem to be of little benefit for long-term treatment. In patients with primary hyperparathyroidism, oral alendronate significantly increased bone mineral density, especially at the lumbar spine; virtually all of this gain appeared to occur within the first year of treatment. Alendronate is considered to be useful in those patients for whom parathyroidectomy is not possible.[1-4]

1. Rossini M, *et al.* Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 113–19.
2. Parker CR, *et al.* Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. *J Clin Endocrinol Metab* 2002; **87:** 4482–9.
3. Chow CC, *et al.* Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 581–7.
4. Khan AA, *et al.* Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3319–25.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Alendronate significantly increases bone mineral density (BMD) of the lumbar spine and femoral neck in **postmenopausal women** with osteoporosis;[1,2] it increases vertebral BMD in postmenopausal women without osteoporosis, but not quite to the same extent as HRT.[1]

Continuous long-term therapy appears to be more effective than short-term treatment in terms of skeletal benefits,[1-4] but a residual effect on BMD remains for several years after stopping treatment,[3-5] despite resumption of bone loss after withdrawal of alendronate.[4-6] Studies[7,8] in early postmenopausal women suggested that a *higher initial dosage* might be more effective in terms of BMD gain and residual effect.

The effect of alendronate on fracture risk may depend on *baseline bone mineral density*.[2] Treatment reduced the incidence of new vertebral and nonvertebral fractures in women with prior fractures; in women without prior fractures, alendronate reduced the incidence of clinical fractures in those with osteoporosis,[9] but not in those with higher BMD.[10] A systematic review[11] found that alendronate showed a clinically important benefit in the secondary prevention of all osteoporotic fractures; statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were seen. No significant reductions were found for primary prevention of osteoporotic fractures, but the reduction in vertebral fractures with alendronate was deemed to be clinically important.

Alendronate is also used in **men** with osteoporosis; in a 2-year randomised study, 10 mg daily by mouth was found to increase vertebral and nonvertebral BMD and help prevent vertebral fractures.[12] Alendronate at 70 mg weekly by mouth also increased BMD significantly in osteoporotic men after 1 year when compared to placebo; fracture incidence, not a primary end-point, was similar in both groups.[13]

Alendronate also increases bone mass density in men and women receiving oral **corticosteroids** at doses equivalent to at least 7.5 mg prednisone daily,[14,15] and may be of some benefit in reducing bone loss after heart[16] and liver[17] **transplantation**.

In men with prostate cancer given androgen deprivation therapy, BMD of the spine and hip significantly improved in those given once-weekly alendronate compared with those given calcium and vitamin D supplementation alone.[18]

Limited available data suggest that alendronate may be safe and effective for patients with HIV who have decreased BMD.[19]

1. Sharpe M, *et al.* Alendronate: an update of its use in osteoporosis. *Drugs* 2001; **61:** 999–1039.
2. Pérez-López FR. Postmenopausal osteoporosis and alendronate. *Maturitas* 2004; **48:** 179–92.
3. Tonino RP, *et al.* Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000; **85:** 3109–15.
4. Bone HG, *et al.* Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; **350:** 1189–99.
5. Black DM, *et al.* FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; **296:** 2927–38.
6. Ravn P, *et al.* Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. *J Clin Endocrinol Metab* 2000; **85:** 1492–7.
7. Sambrook PN, *et al.* Alendronate in the prevention of osteoporosis: 7-year follow-up. *Osteoporosis Int* 2004; **15:** 483–8.
8. McClung MR, *et al.* Early Postmenopausal Intervention Cohort (EPIC) Group Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab* 2004; **89:** 4879–85.
9. Black DM, *et al.* Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. *J Clin Endocrinol Metab* 2000; **85:** 4118–24.
10. Cummings SR, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:** 2077–82.
11. Wells GA, *et al.* Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
12. Orwoll E, *et al.* Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000; **343:** 604–10.
13. Miller PD, *et al.* Weekly oral alendronic acid in male osteoporosis. *Clin Drug Invest* 2004; **24:** 333–41.
14. Saag KG, *et al.* Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med* 1998; **339:** 292–9.
15. de Nijs RNJ, *et al.* STOP Investigators. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. *N Engl J Med* 2006; **355:** 675–84.
16. Shane E, *et al.* Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. *N Engl J Med* 2004; **350:** 767–76.
17. Atamaz F, *et al.* The prevention of bone fractures after liver transplantation: experience with alendronate treatment. *Transplant Proc* 2006; **38:** 1448–52.
18. Greenspan SL, *et al.* Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 2007; **146:** 416–24.
19. Lin D, Rieder MJ. Interventions for the treatment of decreased bone mineral density associated with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 15/04/08).

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. Alendronate, at oral doses of 40 mg daily for 6 months, has been shown to be more effective than both etidronate and placebo in the treatment of Paget's disease,[1] although an earlier study[2] found a more sustained reduction in biochemical markers with an oral dose of 80 mg daily.

1. Reid IR, Siris E. Alendronate in the treatment of Paget's disease of bone. *Int J Clin Pract* 1999; **101** (suppl): 62–6.
2. Khan SA, *et al.* Alendronate in the treatment of Paget's disease of bone. *Bone* 1997; **20:** 263–71.

Polymyositis and dermatomyositis. Alendronate has been reported to be effective in the treatment of calcinosis[1] associated with juvenile dermatomyositis (p.1510).

1. Mukamel M, *et al.* New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment. *J Pediatr* 2001; **138:** 763–6.

Preparations

USP 31: Alendronate Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Actimax; Alenato; Arendal; Berlex; Brek; Dronat; Elandur†; Filxine; Findeclin; Findeclin Combi; Fosamax; Lafedam†; Lendronal; Marvil; Maxtral†; Oseotenk; Osteobon; Osteofene; Osteonate; Phostarac†; Regenesis; Silidral; Tilios; ***Austral.:*** Adronat; Alendro; Fosamax; Ossmax; ***Austria:*** AlendronHexal; Fosamax; ***Belg.:*** Fosamax; ***Braz.:*** Alendil; Bonalen; Cleveron; Endronax; Fosamax; Minusorb†; Ossomax†; Ostenan; Osteofar; Osteoform; Osteoral; Osteotrat†; Recalfe†; Terost; ***Canad.:*** Fosamax; ***Chile:*** Aldrox; Arendal; Fosamax; Fosval; Holadren; Leodrin; Osdren; Oseotal; Osteofem†; Osteosan; Pasodron; ***Cz.:*** Alendrogen; Alenwin; Bonalen; Fosamax; Fosteofos; Gendron; Lindron; Ralenost; Siranin; ***Denm.:*** Fosamax; ***Fin.:*** Fosamax; ***Fr.:*** Fosamax; ***Ger.:*** Alendro-Q; Fosamax; Tevanate; ***Gr.:*** Aldromax; Alefos; Alendo; Alendral; Ampine; Aurodren; Bestalen; Bonedron; Caltera; Dargol; Debenal; Deparex; Difonate; Discozal; Dronalent; Fosalen; Fosamax; Fosazom; Jamax-S; Osaston; Ostalert; Ostomax; Promax; Ridon; Riledron; Tevanate; Tivarun; ***Hong Kong:*** Fosamax; Osteofos; ***Hung.:*** Alendromax; Alendron; Epolar; Fortimax; Fosamax; Massidron; Sedron; Trabecan; ***India:*** Bifosa; Osteofos; ***Indon.:*** Alexonal; Alovell; Fosamax; Nichospor; Osteofar; Voroste; ***Irl.:*** Fosamax; Osteomel; ***Israel:*** Fosalan; Maxibone; ***Ital.:*** Adronat; Alendros; Dronal; Fosamax; Genalen; ***Jpn:*** Bonalon; Onclast†; ***Malaysia:*** Fosamax; ***Mex.:*** Apodrolen; Blindafe; Dronadil; Drovitan; Fosamax; Fosfacid; Landrolen; Sinfract; Synostep; Zondra; ***Neth.:*** Fosamax; ***Norw.:*** Fosamax; ***NZ:*** Fosamax; ***Philipp.:*** Fosamax; ***Pol.:*** Alenato; Fosamax; Lindron; Osalen; Ostemax; Ostenil; Ostolek; Rekostin; ***Port.:*** Adronat; Fosamax; ***Rus.:*** Fosamax (Фосамакс); Tevanate (Теванат); ***S.Afr.:*** Fosagen; Fosamax; Osteobon; ***Singapore:*** Fosamax; ***Spain:*** Fosamax; ***Swed.:*** Alenat; Fosamax; ***Switz.:*** Fosamax; ***Thai.:*** Fosamax; ***Turk.:*** Andante; Bonemax; Fosamax; Osteomax; ***UK:*** Fosamax; ***USA:*** Fosamax; ***Venez.:*** Aldronac; Aliot; Defixal; Denfos†; Fixopan; Fosamax; Genalmen†; Osteodur; Osteomax; Porosal.

Multi-ingredient: ***Arg.:*** Fosamax Plus; Regenesis Max; Silidral Plus; ***Austral.:*** Fosamax Plus; ***Belg.:*** Fosavance; ***Braz.:*** Alendil Calcio D; ***Cz.:*** Adrovance; Fosavance; ***Fin.:*** Fosavance; ***Fr.:*** Adrovance; Fosavance; ***Ger.:*** Fosavance; ***Gr.:*** Adrovance; Fosavance; ***Hong Kong:*** Fosamax Plus; ***Hung.:*** Calcisedron-D; Fosavance; ***Indon.:*** Fosamax Plus; ***Irl.:*** Fosavance; ***Ital.:*** Fosavance; ***Malaysia:*** Fosamax Plus; ***Mex.:*** Fosamax Plus; ***NZ:*** Fosamax Plus; ***Philipp.:*** Fosavance; ***Port.:*** Fosavance; ***Singapore:*** Fosamax Plus; ***Spain:*** Fosavance; ***UK:*** Fosavance; ***USA:*** Fosamax Plus.

Bisphosphonates

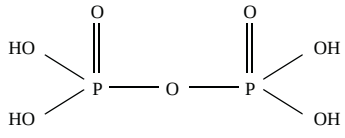
Bifosfonatos; Biphosphonates; Diphosphonates.

Bisphosphonates are analogues of pyrophosphate, in which the central oxygen atom is replaced by a carbon atom with two further substituents—see Figure 1, p.1090. Like pyrophosphate they have a strong affinity for bone. The bisphosphonates are used chiefly for their antiresorptive and hypocalcaemic properties (see Uses and Administration, below).

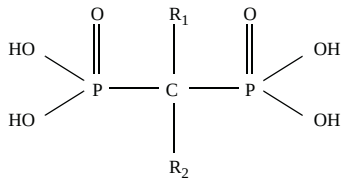
Adverse Effects, Treatment, and Precautions

Bisphosphonates may cause gastrointestinal disturbances including abdominal pain, nausea and vomiting, and diarrhoea or constipation. Peptic ulceration has been reported. Existing gastrointestinal problems may be exacerbated, and oral bisphosphonates should generally be given with care or avoided if acute upper gastrointestinal inflammation is present. Gastrointestinal disturbances may be more frequent with aminobisphosphonates such as alendronate, ibandronate, and risedronate; oesophagitis has also occurred. General

Figure 1. Comparative structures of the bisphosphonates.



Pyrophosphate



Generic structure of a bisphosphonate

R_1	R_2	Name
$C_3H_6.NH_2$	OH	Alendronic Acid
Cl	Cl	Clodronic Acid
CH_3	OH	Etidronic Acid
$C_2H_4.NCH_3.C_5H_{11}$	OH	Ibandronic Acid
$C_7H_{13}.NH$	H	Incadronic Acid
H	H	Medronic Acid
$CH_2.C_7H_5N_2$	OH	Minodronic Acid
$C_5H_{10}.NH_2$	OH	Neridronic Acid
$C_2H_4.N(CH_3)_2$	OH	Olpadronic Acid
H	OH	Oxidronic Acid
$C_2H_4.NH_2$	OH	Pamidronic Acid
$CH_2.C_5H_4N$	OH	Risedronic Acid
$S.C_6H_4Cl$	H	Tiludronic Acid
$CH_2.C_3H_3N_2$	OH	Zoledronic Acid

precautions to minimise the risk of oesophageal reactions, (see under Alendronate, p.1088) should be observed.

Disturbances in serum electrolytes may occur, most commonly hypocalcaemia and hypophosphataemia. Existing hypocalcaemia or other disturbances of bone and mineral metabolism should be effectively treated before starting bisphosphonate therapy. Adequate intake of calcium and vitamin D is important, and supplementation may be needed if dietary intake is insufficient. Bisphosphonates may cause musculoskeletal pain (which can be severe and incapacitating), osteonecrosis of the jaw (see also Dental Care, below), ocular disturbances, and headache. Hypersensitivity reactions have occurred rarely; angioedema, rashes, urticaria, and pruritus have been reported. Other rare adverse effects include blood disorders such as anaemia, thrombocytopenia, leucopenia and disturbances in liver enzyme values.

Transient fever and flu-like symptoms have been reported, usually at the start of treatment, and are common with infusions of ibandronate, pamidronate, and zoledronate. There may be local reactions, including thrombophlebitis, after parenteral doses. Dizziness, vertigo, asthenia, peripheral oedema, paraesthesia, taste disturbances, and joint disorders have also occurred.

Impairment of renal function has been reported with bisphosphonates, particularly when given parenterally. As a result their use should generally be avoided in patients with moderate to severe renal impairment and they should be used with care in those with lesser degrees of renal impairment.

Etidronate interferes with bone mineralisation, especially at higher doses, which can result in osteomalacia and an increased incidence of fracture. Etidronate should be stopped if a fracture occurs, until healing is complete. It has also been associated with a flare in bone pain in some patients with Paget's disease. Impaired mineralisation is much less marked at usual doses of other bisphosphonates.

Overdosage with bisphosphonates would be likely to result in symptoms of hypocalcaemia; if necessary, parenteral infusion of a calcium salt could be given. Giving milk or antacids, to bind the bisphosphonate and minimise absorption, has been suggested for oral overdosage.

There is little clinical experience with bisphosphonates in pregnancy and they are generally contra-indicated; bisphosphonates have been associated with skeletal abnormalities in the fetus when given to pregnant *animals.*

◊ Reviews.

1. Adami S, Zamberlan N. Adverse effects of bisphosphonates: a comparative review. *Drug Safety* 1996; **14:** 158–70.
2. Body J-J. Dosing regimens and main adverse events of bisphosphonates. *Semin Oncol* 2001; **28** (suppl): 49–53.
3. Kherani RB, *et al.* Long-term tolerability of the bisphosphonates in postmenopausal osteoporosis: a comparative review. *Drug Safety* 2002; **25:** 781–90.
4. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol* 2006; **17:** 897–907.
5. Bobba RS, *et al.* Tolerability of different dosing regimens of bisphosphonates for the treatment of osteoporosis and malignant bone disease. *Drug Safety* 2006; **29:** 1133–52.
6. Strampel W, *et al.* Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Safety* 2007; **30:** 755–63.

Dental care. Osteonecrosis of the jaw has been reported in patients given bisphosphonates (see Effects on the Musculoskeletal System, below). Of the published cases most were associated with intravenous therapy in cancer patients, although some have followed oral therapy in patients with osteoporosis. In many cases the effect followed dental surgery. The Adverse Drug Reactions Advisory Committee in Australia has recommended that all patients scheduled to receive intravenous bisphosphonates should have a dental review,[1] and that any dental procedures be completed before beginning the drug.[1,2] Furthermore, health professionals should be aware of the presenting clinical features of osteonecrosis.[2] In the UK, the Commission on Human Medicines has recommended that a dental review should be considered before bisphosphonate treatment in patients with risk factors such as cancer, chemotherapy, corticosteroid therapy, or poor oral hygiene.[3] Licensed information for some bisphosphonates has been amended in a number of countries to include similar warnings.[4]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and osteonecrosis of the jaw. *Aust Adverse Drug React Bull* 2005; **24:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.pdf (accessed 30/11/06)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Osteonecrosis of the jaw (ONJ) with bisphosphonates. *Aust Adverse Drug React Bull* 2006; **25:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 30/11/06)
3. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Osteonecrosis of the jaw with bisphosphonates. *Current Problems* 2006; **31:** 4–5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
4. Tarassoff P, Hei Y-J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; **353:** 101–102. Correction. *ibid.*; 2728.

Effects on the ears. For mention of ototoxicity associated with the use of etidronate in 2 patients with pre-existing otosclerosis, and a recommendation that such patients be monitored when given bisphosphonates, see p.1097. For similar effects with pamidronate, see p.1101.

Effects on the eyes. Ocular effects have been associated with bisphosphonates and although reactions to pamidronate appeared to be rare, the manufacturers were aware of 23 cases up to September 1993 that were possibly associated with the drug.[1] The reactions included anterior uveitis in 7 patients and unilateral episcleritis or scleritis in 3. In one previously reported case,[2] bilateral iritis was associated with risedronate and subsequently pamidronate in a patient who had earlier received etidronate without ill-effect. There have been subsequent reports of unilateral and bilateral scleritis with pamidronate, requiring the drug to be stopped.[3] Anterior[3,4] and posterior[5] uveitis have continued to be reported, and more recently, diplopia with conjunctival swelling and eyelid oedema.[6,7] Similarly, alendronate[8-11] and zoledronate[12] have been associated with scleritis and anterior uveitis. Scleritis,[13] episcleritis,[14] and uveitis[15] have also been reported with risedronate, and bilateral anterior uveitis with clodronate.[16] Non-specific conjunctivitis and abnormal or blurred vision have occurred with most of the bisphosphonates, including etidronate.[13] Dry eye, sore eye, and conjunctivitis were the most frequently reported ophthalmological events assessed as related to risedronate therapy in a prescription-event monitoring study in England.[17] The Australian Adverse Drug Reactions Advisory Committee was aware of 38 reports of serious ocular reactions to bisphosphonates as of April 2004; these were associated with pamidronate or alendronate in 18 cases each, and risedronate or zoledronate in 1 case each.[15] Most reports were of inflammatory reactions such as uveitis, iritis, scleritis, episcleritis, or optic neuritis, and occurred a median of 3 weeks after starting therapy. The risk might be higher with intravenous bisphosphonates, but the frequency of reports was thought to relate mostly to usage.[15] Acute retinal pigment epitheliitis has been reported after an intravenous infusion of zoledronate.[18] Patients who have ocular pain or vision loss while taking bisphosphonates should have the drug stopped and be referred to an ophthalmologist.[13]

1. Macarol V, Fraunfelder FT. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol* 1994; **118:** 220–4.
2. Siris ES. Bisphosphonates and iritis. *Lancet* 1993; **341:** 436–7.
3. Fraunfelder FW, *et al.* Scleritis and other ocular side effects associated with pamidronate disodium. *Am J Ophthalmol* 2003; **135:** 219–22.
4. Rey J, *et al.* Uveitis, an under-recognized adverse effect of pamidronate: case report and literature review. *Joint Bone Spine* 2000; **67:** 337–40.
5. Haverbeke G, *et al.* Posterior uveitis: an under-recognized adverse effect of pamidronate: 2 case reports. *Bull Soc Belge Ophtalmol* 2003; **290:** 71–6.
6. Meaney TPJ, *et al.* Diplopia following intravenous administration of pamidronate. *Eye* 2004; **18:** 103–4.
7. Ryan PJ, Sampath R. Idiopathic orbital inflammation following intravenous pamidronate. *Rheumatology (Oxford)* 2001; **40:** 956–7.
8. Mbekeani JN, *et al.* Ocular inflammation associated with alendronate therapy. *Arch Ophthalmol* 1999; **117:** 837–8.
9. Malik AR, *et al.* Bilateral acute anterior uveitis after alendronate. *Br J Ophthalmol* 2002; **86:** 1443.
10. Salmen S, *et al.* Nongranulomatous anterior uveitis associated with alendronate therapy. *Invest Clin* 2002; **43:** 49–52.
11. Asensio Sánchez VM, *et al.* Bifosfonatos e inflamación intraocular. *Arch Soc Esp Oftalmol* 2004; **79:** 85–8.
12. Moore MM, Beith JM. Acute unilateral anterior uveitis and scleritis following a single infusion of zoledronate for metastatic breast cancer. *Med J Aust* 2008; **188:** 370–1.
13. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. *N Engl J Med* 2003; **348:** 1187–8.
14. Viñas G, *et al.* Episcleritis secundaria a risedronato. *Med Clin (Barc)* 2002; **118:** 598–9.
15. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and ocular inflammation. *Aust Adverse Drug React Bull* 2004; **23:** 7–8. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0404.htm (accessed 22/02/05)
16. Fietta P, *et al.* Clodronate induced uveitis. *Ann Rheum Dis* 2003; **62:** 378.
17. Aurich-Barrera B, *et al.* Ophthalmological events in patients receiving risedronate: summary of information gained through follow-up in a prescription-event monitoring study in England. *Drug Safety* 2006; **29:** 151–60.
18. Gilhotra JS, *et al.* Acute retinal pigment epitheliitis associated with intravenous bisphosphonate. *Br J Ophthalmol* 2006; **90:** 798–9.

Effects on the heart. In a study of once-yearly zoledronate for the treatment of postmenopausal osteoporosis, the number of patients who had arrhythmia in the zoledronate group was significantly higher than that in the placebo group.[1] An increased incidence of serious atrial fibrillation was also seen in the zoledronate group. Fifty patients in the zoledronate group had serious atrial fibrillation, compared with 20 patients in the placebo group. Among the 50 patients, the events occurred more than 30 days after infusion in 47 patients, by which time zoledronate would be undetectable in the circulation. The mechanism by which bisphosphonates might cause arrhythmia or atrial fibrillation is unclear; little or no effect on serum calcium concentrations was seen when measured 9 to 11 days after zoledronate infusion.

In an analysis[2] of a randomised study of alendronate in postmenopausal women with osteoporosis, 47 serious atrial fibrillation adverse events were reported in the alendronate group, compared with 31 events among those receiving placebo. There was no increased risk of all atrial fibrillation adverse events.

Although the observed association might have been due to chance,[1] it was felt that the possibility of an increased risk of atrial fibrillation with bisphosphonates should be explored.[2] Two case-control studies examining the association[3,4] came to opposite conclusions as to whether bisphosphonate treatment increased the risk of atrial fibrillation. In the UK, the MHRA stated in July 2008 that any risk appeared low and the balance of risk and benefit for bisphosphonates remained favourable.[5] The FDA in the USA, which came to similar preliminary conclusions, was said to be seeking additional data for a more detailed analysis.

1. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.
2. Cummings SR, *et al.* Alendronate and atrial fibrillation. *N Engl J Med* 2007; **356:** 1895–6.
3. Heckbert SR, *et al.* Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med* 2008; **168:** 826–31.
4. Sørensen HT, *et al.* Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ* 2008; **336:** 813–16.
5. MHRA/CHM. Bisphosphonates: atrial fibrillation. *Drug Safety Update* 2008; **1** (12): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased (accessed 16/07/08)

Effects on the kidneys. Renal failure was associated with the intravenous use of etidronate in 2 patients with hypercalcaemia of malignancy.[1] One had been given a high dose (1 g) by short intravenous infusion on two successive days and the other had an elevated serum-creatinine concentration before treatment. A third patient given clodronate, who also developed renal failure, also had a slightly raised serum-creatinine concentration beforehand. Others[2] commented that with smaller doses of etidronate or clodronate (up to 300 mg daily) by intravenous infusion over 2 to 3 hours, renal impairment had not been seen in more than 40 patients treated. They noted a trend towards raised creatinine concentrations which was reversed when etidronate infusions were stopped. Another group[3] found increased serum-creatinine concentrations after the first infusion of etidronate when compared with placebo, but not after subsequent infusions. An overdose of parenteral etidronate led to acute renal failure in one patient.[4] Pamidronate has been associated with nephrotoxicity,[5] proteinuria,[6] acute tubular necrosis,[7,8] and collapsing focal segmental glomerulosclerosis.[9] Over a period of 2 years, 72 cases of renal failure associated with intravenous zoledronate were reported to the FDA.[10] Of 7 cases reported over the course of 3.5 years in France, 3 patients recovered completely, and 1 partially, after stopping zoledronate. Two fatalities were reported, but comorbidities prohibited a direct causal link to zoledronate; the outcome in the remaining case was unknown.[11] Six cases of acute tubular necrosis have been reported with zoledronate;[12] all patients had received pamidronate on previous occasions, and most had mildly raised baseline serum creatinine. While pamidronate may have potentiated the renal toxicity seen with zoledronate, the authors noted that the patterns of nephrotoxicity differ between the 2 drugs. Reports to the Australian Adverse Drug Reactions Advisory Committee have suggested that renal failure or renal impairment may occur more often with zoledronate than with other bisphosphonates. While the deterioration in renal function with zoledronate was acute, in many cases it appeared to be unrelated to the infusion rate; patients may also have been predisposed to renal impairment.[13] There has also been a report of acute renal failure with alendronate treatment in a patient with myeloma,[14] and with tiludronate in a patient treated for hypercalcaemia of malignancy.[15]

1. Bounameaux HM, *et al.* Renal failure associated with intravenous diphosphonates. *Lancet* 1983; **i:** 471.
2. Kanis JA, *et al.* Effects of intravenous diphosphonates on renal function. *Lancet* 1983; **i:** 1328.
3. Hasling C, *et al.* Etidronate disodium for treating hypercalcaemia of malignancy: a double blind placebo-controlled study. *Eur J Clin Invest* 1986; **16:** 433–7.
4. O'Sullivan TL, *et al.* Acute renal failure associated with the administration of parenteral etidronate. *Ren Fail* 1994; **16:** 767–73.
5. Lockridge L, *et al.* Pamidronate-associated nephrotoxicity in a patient with Langerhans' histiocytosis. *Am J Kidney Dis* 2002; **40:** E2.
6. Desikan R, *et al.* Nephrotic proteinuria associated with high-dose pamidronate in multiple myeloma. *Br J Haematol* 2002; **119:** 496–9.
7. Banerjee D, *et al.* Short-term, high-dose pamidronate-induced acute tubular necrosis: the postulated mechanisms of bisphosphonate nephrotoxicity. *Am J Kidney Dis* 2003; **41:** E18.
8. Smetana S, *et al.* Pamidronate-induced nephrotoxic tubular necrosis—a case report. *Clin Nephrol* 2004; **61:** 63–7.
9. Markowitz GS, *et al.* Nephrotic syndrome after treatment with pamidronate. *Am J Kidney Dis* 2002; **39:** 1118–22.
10. Chang JT, *et al.* Renal failure with the use of zoledronic acid. *N Engl J Med* 2003; **349:** 1676–8.
11. Munier A, *et al.* Zoledronic acid and renal toxicity: data from French Adverse Effect Reporting Database. *Ann Pharmacother* 2005; **39:** 1194–7.
12. Markowitz GS, *et al.* Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 2003; **64:** 281–9.
13. Adverse Drug Reactions Advisory Committee (ADRAC). Renal impairment with zoledronic acid. *Aust Adverse Drug React Bull* 2007; **26:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0710.htm (accessed 06/11/07)
14. Zazgornik J, *et al.* Acute renal failure and alendronate. *Nephrol Dial Transplant* 1997; **12:** 2797–8.
15. Dumon JC, *et al.* Efficacy and safety of the bisphosphonate tiludronate for the treatment of tumor-associated hypercalcemia. *Bone Miner* 1991; **15:** 257–66.

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported with the use of some bisphosphonates.[1-8] The majority of reports have been in cancer patients treated with intravenous bisphosphonates who were also receiving chemotherapy and corticosteroids. However, osteonecrosis has also been reported in patients receiving oral bisphosphonates for osteoporosis or Paget's disease. Most cases have been associated with dental procedures such as tooth extraction, and many patients had local infection including osteomyelitis.[6,7,9,10] Presenting features may include altered local sensation, maxillofacial pain, toothache, denture sore spots, loose teeth, exposed bone or impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour.[7] A history of underlying dental problems, such as infection, dental extraction, or maxillofacial surgery may exacerbate the problem.[1] Other predisposing factors include oral trauma, periodontitis, and poor dental hygiene.[11] For recommendations on dental care in patients prescribed intravenous bisphosphonates see above.

Length of exposure was found to correlate with development of osteonecrosis,[9,12,13] although some cases have occurred only a few months after bisphosphonate use.[9] There is also some evidence for a dose-response relationship.[8] Furthermore, the type of bisphosphonate used may affect the risk; intravenous use of bisphosphonates containing an aminoterminal group of a nitrogen-containing side-chain appear to present the highest risk,[9] and there is some suggestion that the risk may be higher with zoledronate than with pamidronate.[1,12] The incidence appears to be higher in patients with multiple myeloma,[1,9,12] and elderly myeloma patients may be at increased risk.[9,13]

The mechanism by which bisphosphonates induce osteonecrosis has not been fully elucidated. Avascular necrosis of the hip has been reported; it is possible that osteonecrosis may be a systemic bone disease with initial manifestation in the jaw.[13] A case of osteonecrosis of the auditory canal has been reported;[14] the patient had concurrent osteonecrosis of the jaw.

No effective treatment is known and there is no consensus on management. Stopping bisphosphonate therapy does not necessarily promote healing of the necrotic process;[8,9,13] recovery of normal osteoclast function and bone turnover may be too gradual for this measure to have clinical significance.[10] However, there have been anecdotal reports of healing and complete resolution of lesions several months after cessation of therapy.[10] Treatment is directed towards control of pain and infection and careful local debridement of necrotic bone, but not wide excision of lesions.[8,10]

1. Durie BGM, *et al.* Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; **353:** 99–100.
2. Migliorati CA. Bisphosphanates [sic] and oral cavity avascular bone necrosis. *J Clin Oncol* 2003; **21:** 4253–4.
3. Ruggiero SL, *et al.* Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; **62:** 527–34.
4. Carter G, *et al.* Bisphosphonates and avascular necrosis of the jaw: a possible association. *Med J Aust* 2005; **182:** 413–15.
5. Gibbs SDJ, *et al.* Bisphosphonate-induced osteonecrosis of the jaw requires early detection and intervention. *Med J Aust* 2005; **183:** 549–50.
6. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Osteonecrosis of the jaw with bisphosphonates. *Current Problems* 2006; **31:** 4–5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
7. Adverse Drug Reactions Advisory Committee (ADRAC). Osteonecrosis of the jaw (ONJ) with bisphosphonates. *Aust Adverse Drug React Bull* 2006; **25:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 28/11/06)
8. Krueger CD, *et al.* Bisphosphonate-induced osteonecrosis of the jaw. *Ann Pharmacother* 2007; **41:** 276–84.
9. Migliorati CA, *et al.* Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol* 2006; **7:** 508–14.
10. Woo S-B, *et al.* Narrative review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; **144:** 753–61. Correction. *ibid.*; **145:** 235. [title]
11. Bilezikian JP. Osteonecrosis of the jaw—do bisphosphonates pose a risk? *N Engl J Med* 2006; **355:** 2278–81.
12. Bamias A, *et al.* Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 2005; **23:** 8580–7.
13. Badros A, *et al.* Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* 2006; **24:** 945–52.
14. Polizzotto MN, *et al.* Bisphosphonate-associated osteonecrosis of the auditory canal. *Br J Haematol* 2006; **132:** 114.

Effects on the respiratory system. Bronchospasm induced by bisphosphonates has been reported in 2 patients who were aspirin-sensitive asthmatics. The first patient complained of shortness of breath and wheezing 10 minutes after the start of an infusion of clodronate while the second developed similar symptoms 2 days after the start of cyclical therapy with etidronate by mouth. Oral rechallenge in both patients resulted in a fall in the forced expiratory values at 1 second.[1] The reaction in these 2 patients was not considered to be immune-mediated. Risedronate reportedly induced bronchiolitis obliterans organising pneumonia in a patient with sarcoidosis.[2]

For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, under Etidronate, p.1097.

1. Rolla G, *et al.* Bisphosphonate-induced bronchoconstriction in aspirin-sensitive asthma. *Lancet* 1994; **343:** 426–7.
2. Arai T, *et al.* Risedronate induced BOOP complicated with sarcoidosis. *Thorax* 2005; **60:** 613–14.

Hypersensitivity. Bisphosphonates may rarely cause hypersensitivity reactions such as angioedema, urticaria, and pruritus. Reports include a severe allergic reaction to medronate disodium when given as a radiopharmaceutical,[1] and mild skin rashes in 2 patients given oral pamidronate.[2] There has also been a report of erythroderma with lesions of the mucous membranes associated with use of clodronate in one patient,[3] and severe epidermal necrosis may have been associated with tiludronate in another.[4] A possibly drug-related rash has also been reported in a patient receiving alendronate.[5] Other cutaneous reactions reported with alendronate include urticaria,[6] erythematous papules and petechiae,[7] gyrate erythema,[8] and drug-induced lichen planus;[9] licensed product information states that Stevens-Johnson syndrome has been reported. Two patients with cutaneous reactions to pamidronate or clodronate were able to continue oral clodronate after desensitisation.[10] Licensed product information states that zoledronate has been associated with rare reports of hypersensitivity, including angioedema and bronchoconstriction, and very rarely, with anaphylaxis.

1. Elliott AT, *et al.* Severe reaction to diphosphonate: implications for treatment of Paget's disease. *BMJ* 1988; **297:** 592–3.
2. Mautalen CA, *et al.* Side effects of disodium aminohydroxypropylidenediphosphonate (APD) during treatment of bone diseases. *BMJ* 1984; **288:** 828–9.
3. Pajus I, *et al.* Erythroderma after clodronate treatment. *BMJ* 1993; **307:** 484.
4. Roux C, *et al.* Long-lasting dermatological lesions after tiludronate therapy. *Calcif Tissue Int* 1992; **50:** 378–80.
5. Chesnut CH, *et al.* Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995; **99:** 144–52.
6. Kontoleon P, *et al.* Urticaria after administration of alendronate. *Acta Derm Venereol* 2000; **80:** 398.
7. Kimura M, *et al.* Drug eruption due to alendronate sodium hydrate. *Contact Dermatitis* 2003; **48:** 116.
8. High WA, *et al.* Superficial gyrate erythema as a cutaneous reaction to alendronate for osteoporosis. *J Am Acad Dermatol* 2003; **48:** 945–6.
9. Lazarov A, *et al.* Alendronate-induced lichen planus. *Isr Med Assoc J* 2002; **4:** 389–90.
10. Phillips EJ, *et al.* Allergic reactions to bisphosphonates: a report of three cases and an approach to management. *J Clin Pharmacol* 1998; **38:** 842–86.

Interactions

The bisphosphonates are not well absorbed from the gastrointestinal tract, and dosage with food further impairs their absorption.

Compounds containing aluminium, calcium, iron, or magnesium, including antacids and mineral supplements and some osmotic laxatives, can also impair the absorption of bisphosphonates given by mouth.

It has been suggested that the use of certain bisphosphonates with NSAIDs may result in an increased incidence of gastrointestinal or renal adverse effects.

There may be additive hypocalcaemic effects with aminoglycosides.

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

The bisphosphonates are poorly absorbed after oral doses, with bioavailabilities in the fasting state ranging from about 0.7% (alendronate; risedronate) to up to 6% (etidronate; tiludronate). Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. They have a high affinity for bone, with about 50% of an absorbed dose sequestered to ossified tissues and retained in the body for prolonged periods. Excretion is in the urine, as unchanged drug; they do not appear to be metabolised.

◊ References.

1. Cremers SCLM, *et al.* Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet* 2005; **44:** 551–70.

Uses and Administration

The bisphosphonates inhibit bone resorption and thus have a hypocalcaemic effect. They are pyrophosphate analogues that have a high affinity for the hydroxyapatite of bone, and that inhibit bone resorption by osteoclasts; because of the coupling of resorption and formation this results in an overall reduction in remodelling and bone turnover (see Bone and Bone Disease, p.1083). Their antiresorptive potency varies widely. The bisphosphonates also inhibit the formation and dissolution of hydroxyapatite crystals and thus have the potential to interfere with bone mineralisation. The degree to which the bisphosphonates inhibit mineralisation in clinical practice varies; etidronate is the most potent inhibitor of those now in general clinical use.

Because bone resorption increases plasma-calcium concentrations, the bisphosphonates are used as adjuncts to the treatment of severe hypercalcaemia, especially when associated with malignancy. They are also used in disorders associated with excessive bone re-

sorption and turnover, such as Paget's disease of bone and osteoporosis, as well as in the management of bone metastases. Etidronate has been used in the prevention and treatment of ectopic ossification.

The affinity of bisphosphonates for bone allows complexes labelled with radioactive technetium-99m (see p.2055) to be used diagnostically as bone scanning agents.

Bisphosphonates have been given by intravenous infusion or orally. In the latter case food should be avoided for a suitable period before and after a dose, especially foods with a high calcium content such as milk.

◊ References.

1. Brown DL, Robbins R. Developments in the therapeutic applications of bisphosphonates. *J Clin Pharmacol* 1999; **39:** 651–60.
2. Shoemaker LR. Expanding role of bisphosphonate therapy in children. *J Pediatr* 1999; **134:** 264–7.
3. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* 2003; **9:** 2643–58.
4. Cohen SB. An update on bisphosphonates. *Curr Rheumatol Rep* 2004; **6:** 59–65.
5. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005; **39:** 668–77.
6. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics* 2007; **119** (suppl 2): S150–S162.
7. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. *J Dent Res* 2007; **86:** 1022–33.
8. Russell RG, *et al.* Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci* 2007; **1117:** 209–57.

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.

Ectopic ossification. Bisphosphonates that are potent inhibitors of mineralisation such as etidronate have been advocated for prevention of ectopic ossification (p.100), but they do not prevent the formation of the osteoid matrix, and delayed mineralisation may occur once they are withdrawn.

Hypercalcaemia. In patients with severe symptomatic hypercalcaemia restoration and maintenance of adequate hydration and urine flow is essential, and helps to reduce plasma-calcium concentrations by promoting calcium diuresis. In hypercalcaemia of malignancy (p.1083) therapy with inhibitors of bone resorption such as the bisphosphonates is used. Although sustained, the action of bisphosphonates is not particularly rapid; they may be used with a calcitonin where both rapid and prolonged diminution of plasma-calcium concentration is desired.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p.1087), but seem to be of little benefit for long-term treatment.

Juvenile idiopathic arthritis. Bisphosphonates may have a role[1] in preventing low bone mineral density and fragility fractures in children with juvenile idiopathic arthritis (p.10).

1. Thornton J, *et al.* Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child* 2006; **91:** 753–61.

Malignant neoplasms of the bone. There is good evidence that some bisphosphonates are of benefit in **treatment** of patients with metastatic bone disease (p.660) not only to control bone pain[1,2] and to manage the attendant hypercalcaemia, but also to reduce skeletal complications such as fractures.[2-8] Maximum benefit in terms of skeletal events occurs only after 6 months of treatment.[9] It has been suggested that given the strength of the evidence, treatment with bisphosphonates should be begun at first diagnosis of bone metastases, and continued until no longer clinically relevant.[2,10] While some continue treatment despite disease progression, others advocate changing to a more potent bisphosphonate, or stopping treatment altogether.[9] Starting bisphosphonates in women with breast cancer without evidence of bone metastases is not recommended.[11]

There are concerns over the development of osteonecrosis of the jaw with bisphosphonate treatment (see Effects on the Musculoskeletal System, under Adverse Effects, above), and a possibly increased incidence in patients with multiple myeloma. Some have recommended[12,13] that monthly intravenous bisphosphonate therapy continue for 2 years in myeloma patients. After 2 years, therapy can be stopped in those who have achieved a complete response or who are in a stable plateau phase. If disease is still active, frequency of infusion can be decreased to once every 3 months. However, others recommend stopping therapy after 1 year in those with a complete response or very good partial response. For those with a poorer response and ongoing active bone disease, bisphosphonates may be continued for up to 2 years.[14] In newly diagnosed patients, pamidronate is favoured over zoledronate as data suggest the risk of osteonecrosis may be higher with the latter.[12-14] However, routinely switching patients from zoledronate to pamidronate is not recommended, as no data suggest that this will prevent osteonecrosis. Multiple myeloma patients without evidence of skeletal involvement should not routinely be given bisphosphonates.[12]

There is also much interest in the use of bisphosphonates to **prevent** the development of bone metastases;[2,4,5,8] however, preliminary evidence of their efficacy is conflicting. Specific references may be found under the individual drugs.

1. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 30/11/06).
2. Aapro M, *et al.* Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008; **19:** 420–32.
3. Rule S. Managing cancer-related skeletal events with bisphosphonates. *Hosp Med* 2004; **65:** 355–60.
4. Brown JE, *et al.* The role of bisphosphonates in breast and prostate cancers. *Endocr Relat Cancer* 2004; **11:** 207–24.
5. Pavlakis N, *et al.* Bisphosphonates for breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 30/11/06).
6. Saad F, Schulman CC. Role of bisphosphonates in prostate cancer. *Eur Urol* 2004; **45:** 26–34.
7. Djulbegovic B, *et al.* Bisphosphonates in multiple myeloma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/11/06).
8. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* 2005; **23:** 8219–24.
9. Gainford MC, *et al.* Recent developments in bisphosphonates for patients with metastatic breast cancer. *BMJ* 2005; **330:** 769–73.
10. Ross JR, *et al.* Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003; **327:** 469–72. Correction. *ibid.* 2004; **328:** 384.
11. Hillner BE, *et al.* American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003; **21:** 4042–57. Correction. *ibid.* 2004; **22:** 1351.
12. Lacy MQ, *et al.* Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. *Mayo Clin Proc* 2006; **81:** 1047–53.
13. Kyle RA, *et al.* American Society of Clinical Oncology. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; **25:** 2464–72.
14. Durie BGM, *et al.*. International Myeloma Working Group. Use of bisphosphonates in multiple myeloma: IMWG response to Mayo Clinic consensus statement. *Mayo Clin Proc* 2007; **82:** 516–7; author reply 517–18.

Osteogenesis imperfecta. Bisphosphonates have been tried in osteogenesis imperfecta (p.1083), but orthopaedic treatment and physical activity programmes form the basis of therapy.

Osteoporosis. Bisphosphonates are used first-line in the prevention and treatment of osteoporosis (p.1084). Alendronate, risedronate and cyclical etidronate are used orally; clodronate and ibandronate have been used both orally and parenterally, and ibandronate, pamidronate, and zoledronate by intermittent intravenous infusion. Generally, in the management of **postmenopausal** osteoporosis, bisphosphonates increase bone mineral density (BMD) at both the spine and hip and reduce vertebral fractures; effect on non-vertebral fractures varies.[1,2] Treatment in women at highest risk, with prevalent fractures or low BMD, is considered most effective.[2] In the UK, NICE[3] recommends the use of bisphosphonates for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Alendronate, etidronate, or risedronate may be given to all women aged 75 years and older, to women aged between 65 and 74 years with confirmed osteoporosis, and to postmenopausal women younger than 65 with very low BMD or with confirmed osteoporosis and one or more additional age-independent risk factors. Data also suggest that the more severe the osteoporosis, the greater the benefit, and since bone density continues to decline with age, and vertebral fracture incidence rises after age 75, some consider it more beneficial in older women.[4] However, others have expressed concern about a possible increase in brittleness of bones with long-term bisphosphonate treatment.[5]

Although there is less evidence for the efficacy of bisphosphonates for the treatment of idiopathic osteoporosis in **men**, some consider them the treatment of choice. A systematic review[6] stated that, while further evaluation of bisphosphonate therapy in **children** with secondary osteoporosis is warranted, evidence does not support their use as standard therapy.

Bisphosphonates are also considered effective at prevention and treatment of **corticosteroid-induced** osteoporosis.[7] Fracture risk (see p.1491) may also be reduced although a systematic review was inconclusive in this respect.[7]

A meta-analysis of bisphosphonate use in the early **post-transplant** period found that they were effective in reducing BMD decline at the lumbar spine; however, prolonged and more intensive treatment may increase the risk of adynamic or low bone turnover disease.[8]

1. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med* 2003; **19:** 395–414.
2. Masud T, Giannini S. Preventing osteoporotic fractures with bisphosphonates: a review of the efficacy and tolerability. *Aging Clin Exp Res* 2003; **15:** 89–98.
3. NICE. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 87 (issued January 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/TA087guidance.pdf (accessed 23/07/08)
4. Dhesi JK, *et al.* The implications of a growing evidence base for drug use in elderly patients. Part 4: vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; **61:** 521–8.
5. Ott S. New treatments for brittle bones. *Ann Intern Med* 2004; **141:** 406–7.
6. Ward L, *et al.* Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/04/08).
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8. Mitterbauer C, *et al.* Effects of bisphosphonates on bone loss in the first year after renal transplantation—a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21:** 2275–81.

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.

Bone Morphogenetic Proteins

BMP; Proteínas morfogenéticamente óseas.

Костные Морфогенетические Белки

ATC — M05BC01 (BMP-2); M05BC02 (BMP-7).

Dibotermin Alfa *(BAN, USAN, rINN)*

Dibotermina alfa; Dibotermine Alfa; Diboterminum Alfa; hrBMP-2; rhBMP-2. Human recombinant bone morphogenetic protein 2.

Диботермин Альфа

CAS — 246539-15-1.

ATC Vet — QM05BC01.

Eptotermin Alfa *(rINN)*

Eptotermina alfa; Eptotermine Alfa; Eptoterminum Alfa; hrBMP-7; OP-1; Osteogenic Protein-1. Human recombinant bone morphogenetic protein 7.

Эптотермин Альфа

CAS — 129805-33-0.

ATC Vet — QM05BC02.

Profile

Bone morphogenetic proteins (BMPs) are growth factors that promote ectopic bone formation and can be extracted from demineralised bone matrix. Several have been identified and developed for use in orthopaedic and reconstructive surgery; some have been produced by recombinant technology.

Eptotermin alfa is a recombinant form used in adults for the treatment of non-union of tibia of at least 9 months duration in cases where autograft has failed or is unfeasible. Dibotermin alfa, another recombinant form, is used as an adjunct to standard care for the treatment of acute tibia fractures in adults, as an implant containing 12 mg. The implant is also indicated for anterior lumbar spine fusion, as a substitute for bone grafting, in adults with degenerative disc disease who have had at least 6 months of non-operative treatment. Dibotermin alfa is also used as an alternative to bone grafting for sinus augmentation, and for localised alveolar ridge augmentations for defects associated with extraction sockets. Osteogenin (BMP-3) is under investigation.

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Adverse effects. The FDA issued a warning in July 2008 that use of recombinant human bone morphogenetic protein products in cervical spine fusion had been associated with at least 38 re-