Osteoporosis. Strontium ranelate, given orally with calcium and vitamin D supplements, has been found to reduce the risk of vertebral[1] and non-vertebral[2] fractures in postmenopausal women with osteoporosis. A pooled analysis of data from these 2 studies concluded that strontium ranelate reduced both vertebral and non-vertebral fractures in patients aged 80 years or older.[3] Protection against fractures was detected within 12 months, and sustained throughout 3 years of treatment. Hip fractures were also reduced over 3 years, but this did not reach statistical significance; the authors concluded that the analysis may not have been sufficiently powered in this respect. A systematic review[4] concluded that while strontium ranelate reduces vertebral fractures, there is less of a reduction with non-vertebral fractures, and the effect on hip fracture remains unclear. Some have cautioned about the interpretation of bone mineral density (BMD) changes with strontium ranelate, since stronger X-ray attenuation by strontium compared with calcium must be corrected for to avoid overestimating the effect. However, increases in BMD could be useful clinically in gauging long-term compliance.[5]

A review[6] of the place of strontium ranelate in therapy considered that although it might be an alternative in patients who could not tolerate a bisphosphonate there was no convincing published evidence to support claims that it stimulated bone formation as well as reducing resorption. Further reviews[4,7] concluded that additional research to confirm its mechanism of action is required and that long-term fracture data are needed, along with comparative trials evaluating the efficacy of strontium ranelate relative to other therapies such as bisphosphonates.

1. Meunier PJ, *et al.* The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004; **350:** 459–68.
2. Reginster JY, *et al.* Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005; **90:** 2816–22.
3. Seeman E, *et al.* Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006; **21:** 1113–20.
4. O'Donnell S, *et al.* Strontium ranelate for preventing and treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Fogelman I, Blake GM. Strontium ranelate for the treatment of osteoporosis: is useful, but changes in bone mineral density need careful interpretation. *BMJ* 2005; **330:** 1400–1.
6. Anonymous. Strontium ranelate for osteoporosis? *Drug Ther Bull* 2006; **44:** 29–32.
7. Stevenson M, *et al.* The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007; **11:** 1–134.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Osteovital; Protos; ***Austral.:*** Protos; ***Belg.:*** Protelos; ***Braz.:*** Protos; ***Cz.:*** Osseor; Protelos; ***Denm.:*** Protelos; ***Fr.:*** Protelos; ***Ger.:*** Protelos; ***Gr.:*** Protelos; ***Hong Kong:*** Protos; ***Hung.:*** Protelos; ***Indon.:*** Protos; ***Irl.:*** Protelos; ***Ital.:*** Osseor; Protelos; ***Malaysia:*** Protaxos; ***Neth.:*** Osseor; Protelos; ***NZ:*** Protos; ***Philipp.:*** Protos; ***Pol.:*** Protelos; ***Port.:*** Osseor; Protelos; ***Rus.:*** Bivalos (Бивалос); ***S.Afr.:*** Protos; ***Singapore:*** Protos; ***Spain:*** Osseor; Protelos; ***Swed.:*** Protelos; ***UK:*** Protelos.

Teriparatide *(USAN, rINN)*

(1-34) Human parathormone; (1-34) Human parathyroid hormone; 1-34 Parathormone (human); hPTH 1-34; Human parathormone (1-34); Human parathyroid hormone (1-34); Human PTH (1-34); LY-333334; Parathyroid hormone peptide (1-34); Teriparatid; Teriparatida; Tériparatide; Teriparatidum.

Терипаратид

$C_{181}H_{291}N_{55}O_{51}S_2$.
CAS — 52232-67-4.
ATC — H05AA02.
ATC Vet — QH05AA02.

Teriparatide Acetate *(USAN, rINNM)*

Acetato de teriparatida; Tériparatide, Acétate de; Teriparatidi Acetas.

Терипаратида Ацетат

$C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.yC_2H_4O_2$.
CAS — 99294-94-7 (teriparatide acetate).
ATC — H05AA02.
ATC Vet — QH05AA02.

Adverse Effects and Precautions

Gastrointestinal disturbances, pain in the limb of injection, headache, and dizziness are the most common adverse effects in patients treated with subcutaneous teriparatide. Dizziness, vertigo, and syncope may be associated with transient orthostatic hypotension in some patients, particularly when beginning treatment. Those so affected should not drive or operate potentially hazardous machinery. Asthenia, arthralgia, and rhinitis may occur. Angina pectoris, depression, dyspnoea, leg cramps, pneumonia, urinary disorders, and sciatica have also been reported. A metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate. It is a peptide and the possibility of systemic hypersensitivity reactions should be borne in mind. Hypercalcaemia may develop with teriparatide or the acetate and it is therefore contra-indicated in patients with pre-existing hypercalcaemia.

Teriparatide is contra-indicated in patients with severe renal impairment and should be used with caution with those with moderate impairment.

There have been reports of osteosarcoma in *rats* given teriparatide and patients who may be at increased risk, including those with a history of skeletal metastases or previous radiotherapy to the skeleton, should not receive it. It is also contra-indicated in those with metabolic bone disease including Paget's disease and hyperparathyroidism, or unexplained elevations of serum alkaline phosphatase. Use in children or those with open epiphyses is also contra-indicated. In the UK treatment is also limited to a maximum of 18 months.

Pharmacokinetics

Teriparatide is extensively absorbed after subcutaneous injection; peak plasma concentrations are reached after about 30 minutes. Absolute bioavailability is reported to be about 95%. The serum half-life is 5 minutes after intravenous use, and approximately 1 hour after subcutaneous injection (reflecting time needed for absorption from the injection site). No studies have been done on the metabolism or excretion of teriparatide; parathyroid hormone is believed to be enzymatically metabolised in the liver and excreted by the kidneys.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid biologically active N-terminal region of human parathyroid hormone (p.1103). It is used in the treatment of established postmenopausal osteoporosis, especially in those with a high fracture risk, and in men with primary or hypogonadal osteoporosis who are at increased risk of fracture. The usual dose is 20 micrograms subcutaneously daily into the thigh or abdominal wall. Treatment is limited to a maximum of 18 months in the UK, although it has been used for up to 2 years in the USA. Teriparatide acetate has been given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism. Hypoparathyroidism is characterised by a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism is characterised by resistance to the effects of parathyroid hormone (see p.1087). Teriparatide acetate is used *diagnostically* to distinguish between these 2 conditions.[1] A synthetic 1-38 fragment of human parathyroid hormone (hPTH 1-38) has been used similarly.[2] Teriparatide has also been used to *treat* hypoparathyroidism.[3-5]

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; **109:** 800–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; **146:** 373–7.
3. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* 1996; **276:** 631–6.
4. Winer KK, *et al.* A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998; **83:** 3480–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.

Osteoporosis. Parathyroid hormone is capable of stimulating both formation and resorption of bone. Continuous infusion of teriparatide leads to a persistent elevation of parathyroid hormone and greater bone resorption by stimulating osteoclasts, with a net decrease in bone volume, and resultant hypercalcaemia; in contrast, daily (intermittent) injections increase bone volume by increasing osteoblastic proliferation.[1-3] Teriparatide appears to have less effect on cortical than trabecular bone,[3] suggesting that, although it may be helpful in preventing vertebral fractures, its impact on fractures of the proximal femur may be more limited. However, while treatment with teriparatide substantially increases lumbar spine bone mineral density (BMD), beneficial increases are also seen at the hip,[1] and in a pivotal study (the Fracture Prevention Trial)[4] in **postmenopausal** women with osteoporosis (p.1084), it decreased the risk of both vertebral and non-vertebral fracture. In a follow-up study, the reduction in vertebral fracture risk in patients treated with teriparatide for a mean of 19 months persisted for at least an additional 18 months after daily treatment was stopped.[5] Teriparatide appears to improve bone geometry, with no detrimental effect on cortical bone.[6] In the UK, NICE recommends teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women aged 65 years and older who have had an unsatisfactory response to bisphosphonates or who are intolerant to bisphosphonates, and who have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3 standard deviations or more) plus one or more additional risk factors.[7] It has been pointed out that evidence of reduction in teriparatide's effect with current or recent alendronate therapy (see below) might make its use as a second-line agent problematic.[8]

Data on combination therapy are limited, but some studies suggest that teriparatide with HRT is more effective than HRT alone.[9] The effect of teriparatide with the antiresorptive bisphosphonates has yet to be determined.[2,6,9,10] Although there is some suggestion that teriparatide still increases bone formation after treatment with alendronate,[9] a study in men found that, when given together, alendronate impaired the anabolic effects of teriparatide.[11] For this reason, some consider that teriparatide be started immediately after stopping bisphosphonates.[10] It has been suggested that the degree of suppression of bone turnover before treatment may dictate the response to teriparatide.[6] A study of daily or cyclical teriparatide in women with osteoporosis found that although the teriparatide-induced increase in BMD may be slightly lower in women who had previously taken alendronate than in those who had never received it, the increase in spinal BMD was still impressive. Intermittent cyclical treatment with teriparatide was found to have similar effects on BMD to those induced by daily dosage.[12]

In postmenopausal women with osteoporosis taking HRT and **corticosteroids**,[13] the addition of teriparatide significantly increased BMD of the lumbar spine; modest changes in hip bone mass were not significant.

In **men** with osteoporosis, teriparatide increased BMD in the lumbar spine and at the femoral neck;[9] risk of fracture was also reduced.[1]

1. Cappuzzo KA, Delafuente JC. Teriparatide for severe osteoporosis. *Ann Pharmacother* 2004; **38:** 294–302.
2. Madore GR, *et al.* Parathyroid hormone. *J Am Acad Orthop Surg* 2004; **12:** 67–71.
3. Brixen KT, *et al.* Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. *Basic Clin Pharmacol Toxicol* 2004; **94:** 260–70.
4. Neer RM, *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344:** 1434–41.
5. Lindsay R,*et al.* Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med* 2004; **164:** 2024–30.
6. Rubin MR, Bilezikian JP. Parathyroid hormone as an anabolic skeletal therapy. *Drugs* 2005; **65:** 2481–98.
7. 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)
8. Anonymous. Teriparatide for postmenopausal osteoporosis. *Drug Ther Bull* 2004; **42:** 93–5.
9. Quattrocchi E, Kourlas H. Teriparatide: a review. *Clin Ther* 2004; **26:** 841–54.
10. Deal C. The use of intermittent human parathyroid hormone as a treatment for osteoporosis. *Curr Rheumatol Rep* 2004; **6:** 49–58.
11. Finkelstein JS, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; **349:** 1216–26.
12. Cosman F, *et al.* Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; **353:** 566–75.
13. Lane NE, *et al.* Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. *J Clin Invest* 1998; **102:** 1627–33.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Forteo; ***Austral.:*** Forteo; ***Belg.:*** Forsteo; ***Braz.:*** Forteo; ***Canad.:*** Forteo; ***Chile:*** Forteo; ***Cz.:*** Forsteo; ***Denm.:*** Forsteo; ***Fin.:*** Forsteo; ***Fr.:*** Forsteo; ***Ger.:*** Forsteo; ***Gr.:*** Forsteo; ***Hong Kong:*** Forteo; ***Hung.:*** Forsteo; ***Irl.:*** Forsteo; ***Israel:*** Forteo; ***Ital.:*** Forsteo; ***Malaysia:*** Forteo; ***Mex.:*** Forteo; ***Norw.:*** Forsteo; ***NZ:*** Forteo; ***Philipp.:*** Forteo; ***Port.:*** Forsteo; ***S.Afr.:*** Forteo; ***Singapore:*** Forteo; ***Spain:*** Forsteo; ***Swed.:*** Forsteo; ***Switz.:*** Forsteo; ***Thai.:*** Forteo; ***UK:*** Forsteo; ***USA:*** Forteo; ***Venez.:*** Forteo.

Tiludronate

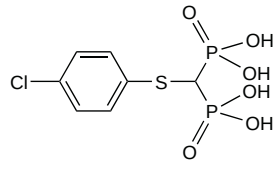
ATC — M05BA05.
ATC Vet — QM05BA05.

Tiludronic Acid *(BAN, rINN)*

Acide Tiludronique; Ácido tildrónico; Acidum Tiludronicum; ME-3737; SR-41319; Tiludronihappo; Tiludronik Asit; Tiludronsyra. {[(*p*-Chlorophenyl)thio]methylene}diphosphonic acid.

Тилудроновая Кислота

$C_7H_9ClO_6P_2S$ = 318.6.
CAS — 89987-06-4.
ATC — M05BA05.
ATC Vet — QM05BA05.



Tiludronate Disodium *(USAN)*

Tiludronate Sodium *(BANM, rINNM)*; Disodium Tiludronate; Natrii Tiludronas; Sodium Tiludronate; SR-41319B; Tiludronate de Sodium; Tiludronato sódico. Disodium dihydrogen {[(*p*-chlorophenyl)thio]methylene}diphosphonate hemihydrate.

Натрий Тилудронат

$C_7H_7ClNa_2O_6P_2S, \cdot H_2O$ = 371.6.

CAS — 149845-07-8 (anhydrous disodium tiludronate); 155453-10-4 (tiludronate disodium hemihydrate).

ATC — M05BA05.

ATC Vet — QM05BA05.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Asthenia and dizziness have been reported rarely.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including tiludronate, see under Bisphosphonates, p.1091.

Effects on the skin. As with other bisphosphonates, tiludronate has been associated with rash and pruritus. For reference to a case of massive epidermal necrosis possibly associated with tiludronate, see Hypersensitivity, under Bisphosphonates, p.1091.

Interactions

As for the bisphosphonates in general, p.1091. Indometacin may increase the bioavailability of tiludronate two to fourfold; diclofenac does not appear to have this effect. Aspirin may decrease the bioavailability of tiludronate by 50%.

Pharmacokinetics

Like other bisphosphonates tiludronate is poorly absorbed after oral doses. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The oral bioavailability of tiludronate is about 6% in the fasting state, and is reduced by about 90% when given within 2 hours of food. Plasma protein binding is about 90%, mostly to albumin. Tiludronate is not metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

Uses and Administration

Tiludronate is a bisphosphonate with similar properties to those of the bisphosphonates in general (p.1091). It inhibits bone resorption and is used for Paget's disease of bone.

It is given orally as tiludronate disodium, but doses are expressed in terms of the equivalent amount of tiludronic acid; 117 mg of tiludronate disodium is equivalent to about 100 mg of tiludronic acid. To ensure adequate absorption doses should be taken with plenty of water (at least 200 mL), at least 2 hours before or after meals. In Paget's disease of bone the usual dose is 400 mg once daily for 3 months, and this may be repeated if necessary after an interval of at least 3 to 6 months.

Tiludronate has been tried in postmenopausal osteoporosis, but results were disappointing.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Skelid; ***Austria:*** Skelid; ***Belg.:*** Skelid; ***Fin.:*** Skelid†; ***Fr.:*** Skelid; ***Ger.:*** Skelid; ***Hung.:*** Skelid; ***Neth.:*** Skelid; ***Port.:*** Skelid; ***Spain:*** Skelid; ***Swed.:*** Skelid†; ***Switz.:*** Skelid; ***UK:*** Skelid; ***USA:*** Skelid.

Zoledronate

ATC — M05BA08.

ATC Vet — QM05BA08.

Zoledronic Acid *(BAN, USAN, rINN)*

Acide Zolédronique; Ácido zoledrónico; Acidum Zoledronicum; CGP-42446; Tsoledronihappo; Zoledronik Asit; Zoledronsyra. (1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid.

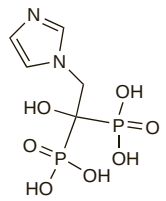
Золедроновая Кислота

$C_5H_{10}N_2O_7P_2$ = 272.1.

CAS — 118072-93-8 (anhydrous zoledronic acid); 165800-06-6 (zoledronic acid monohydrate).

ATC — M05BA08.

ATC Vet — QM05BA08.



Zoledronate Disodium *(BANM, USAN, rINNM)*

CGP-42446A; ZOL-446; Zoledronas Dinatricum; Zolédronate Disodique; Zoledronato disódico. Disodium dihydrogen (1-hydroxy-2-imidazol-1-ylethylidene)diphosphonate tetrahydrate.

Динатрий Золедронат

$C_5H_8N_2Na_2O_7P_2, 4H_2O$ = 388.1.

CAS — 165800-07-7.

ATC — M05BA08.

ATC Vet — QM05BA08.

Zoledronate Trisodium *(BANM, USAN, rINNM)*

CGP-42446B; Zoledronas Trinatricum; Zolédronate Trisodique; Zoledronato trisódico. Trisodium hydrogen (1-hydroxy-2-imidazol-1-ylethylidene)diphosphonate hydrate (5:2).

Тринатрий Золедронат

$C_5H_7N_2Na_3O_7P_2, 2 \cdot H_2O$ = 383.1.

CAS — 165800-08-8.

ATC — M05BA08.

ATC Vet — QM05BA08.

Adverse Effects and Precautions

As for Pamidronate, p.1101. It is important to ensure adequate hydration before and after doses of zoledronic acid as dehydration predisposes to deterioration in renal function.

Effect on electrolytes. Zoledronate has more potent effects on calcium than some of the other bisphosphonates, and has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in some patients.[1,2] In most cases, pre-existing conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1] Vitamin D deficiency should be treated before starting zoledronate.[1,2]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328:** 335–6.
2. Breen TL, Shane E. Prolonged hypocalcemia after treatment with zoledronic acid in a patient with prostate cancer and vitamin D deficiency. *J Clin Oncol* 2004; **22:** 1531–2.

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

Effects on the heart. For a report of a possible association between zoledronate and serious atrial fibrillation, see Effects on the Heart, under Bisphosphonates, p.1090.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, see under Bisphosphonates, p.1091. Doses may need adjusting in some patients with renal impairment (see Administration in Renal Impairment, below).

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

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Plasma concentrations of zoledronate rise rapidly after the start of an intravenous infusion. Plasma protein binding is low; it has been variously reported as 22 or 56%. Zoledronate is not metabolised, and about 23 to 55% of the dose is excreted in the urine unchanged within 24 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment (see Administration in Renal Impairment, below).

◊ References.

1. Chen T, *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; **42:** 1228–36.

Uses and Administration

Zoledronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. Zoledronic acid is given as an intravenous infusion over not less than 15 minutes.

It is used for **hypercalcaemia of malignancy**, in a single dose of 4 mg, diluted with 100 mL of sodium chloride 0.9% or glucose 5%. The treatment may be repeated if necessary after at least 7 days, at a dose of 4 mg. Individual doses should not exceed 4 mg, as there is an increased risk of adverse renal effects, including renal failure.

Zoledronic acid is given for the prevention of skeletal events in patients with advanced **bone malignancies** (p.660) at a dose of 4 mg, diluted as above, every 3 to 4 weeks.

For the treatment of **Paget's disease** of bone, zoledronic acid is given as a single intravenous infusion of 5 mg.

Zoledronic acid is also used for the treatment of **osteoporosis** in postmenopausal women; the recommended dose is a single intravenous infusion of 5 mg given once a year.

◊ Reviews.

1. Cheer SM, Noble S. Zoledronic acid. *Drugs* 2001; **61:** 799–805.
2. Theriault RL. Zoledronic acid (Zometa) use in bone disease. *Expert Rev Anticancer Ther* 2003; **3:** 157–66.
3. Neville-Webbe H, Coleman RE. The use of zoledronic acid in the management of metastatic bone disease and hypercalcaemia. *Palliat Med* 2003; **17:** 539–53.
4. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther* 2003; **25:** 2669–2708.
5. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
6. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.
7. Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. *Cancer Treat Rev* 2008; **34:** 183–92.

Administration in renal impairment. Despite the fact that renal clearance of zoledronic acid correlates to renal function, a pharmacokinetic study[1] concluded that no dosage adjustment appeared necessary in patients with mild to moderate renal impairment (creatinine clearance 50 to 80 mL/minute, and 10 to 50 mL/minute, respectively).

Licensed product information also states that no adjustment is necessary in mild to moderate renal impairment for patients with *hypercalcaemia of malignancy*, but defines this degree of impairment in terms of serum creatinine less than 400 micromoles/litre or less than 4.5 mg per 100 mL.

However, for patients with *advanced bone malignancies*, the intravenous dose of zoledronic acid should be adjusted on the basis of creatinine clearance (CC) as follows:

- CC greater than 60 mL/minute: 4 mg (no adjustment necessary)
- CC 50 to 60 mL/minute: 3.5 mg
- CC 40 to 49 mL/minute: 3.3 mg
- CC 30 to 39 mL/minute: 3 mg
- CC below 30 mL/minute: treatment not recommended

Serum creatinine should be measured before each dose and treatment withheld if renal function has deteriorated. Renal deterioration is defined as an increase of 44 micromoles/litre or 0.5 mg per 100 mL for those patients with normal baseline creatinine, and an increase of 88 micromoles/litre or 1 mg per 100 mL for those with abnormal baseline creatinine. Treatment may be restarted at the dose used before treatment interruption once the creatinine returns to within 10% of the baseline value.

For patients with *Paget's disease* or *osteoporosis*, UK licensed product information states that no dose adjustment is considered necessary for those with CC of 40 mL/minute or more; due to a lack of clinical data, treatment is not recommended for those with CC of less than 40 mL/minute.

1. Skerjanec A, *et al.* The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003; **43:** 154–62.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. Zoledronate has been shown to have a faster onset, higher response rate, and longer duration of action than pamidronate.[1] It also has a shorter infusion time than pamidronate,[1] and some consider it the treatment of choice for hypercalcaemia of malignancy.[2-4] However, zoledronate has caused severe hypocalcaemia in some patients, see Effects on Electrolytes, above.

1. Major P, *et al.* Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; **19:** 558–67.
2. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. *Oncologist* 2002; **7:** 481–91.
3. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
4. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660) not