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

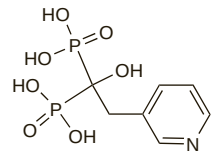
Risedronaatti; Risedronat; Risedronatum.
ATC — M05BA07.
ATC Vet — QM05BA07.

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.

Effects on the musculoskeletal system. From the initial marketing of risedronate until June 2003, the FDA had received 6 reports of severe bone, joint, or muscle pain. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[1]

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

1. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; **165:** 346–7.

Effects on the respiratory system. For a report of bronchiolitis obliterans organising pneumonia induced by risedronate, see p.1091.

Hypersensitivity. Allergic reactions to bisphosphonates are rare, see p.1091. Angioedema, generalised rashes, and bullous skin reactions, some severe, have been reported with risedronate.

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Like other bisphosphonates, risedronate is poorly absorbed orally. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The mean bioavailability is 0.63% in the fasting state, and is reduced by 30% when given 1 hour before breakfast, and by 55% when given half an hour before breakfast. Plasma protein binding is about 24%. Risedronate is not metabolised. About half of the absorbed portion is excreted in the urine within 24 hours; the remainder is sequestered to bone for a prolonged period. Unabsorbed drug is eliminated unchanged in the faeces.

Absorption. Absorption of a single dose of risedronate was comparable when given 0.5 to 1 hour before breakfast or 2 hours after an evening meal in a study in healthy subjects.[1] The pharmacokinetics of risedronate are dose-proportional after a single oral dose.[2]

1. Mitchell DY, *et al.* The effect of dosing regimen on the pharmacokinetics of risedronate. *Br J Clin Pharmacol* 1999; **48:** 536–42.
2. Mitchell DY, *et al.* Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. *J Clin Pharmacol* 2000; **40:** 258–65.

Uses and Administration

Risedronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p.1091). It inhibits bone resorption and is used either alone or with calcium, or with calcium and vitamin D for the prevention and treatment of postmenopausal osteoporosis. It is also used for the treatment of osteoporosis in men. Risedronate is also used for prevention and treatment of corticosteroid-induced osteoporosis, and for the treatment of Paget's disease of bone.

Risedronate is given orally as the sodium salt. The specific instructions given in Adverse Effects and Precautions, above should be followed to minimise gastrointestinal adverse effects and permit adequate absorption. The recommended dosage for **Paget's disease** of bone is 30 mg of risedronate sodium once daily for 2 months. Treatment may be repeated once if necessary after an interval of a further 2 months. The recommended dosage for the treatment or prevention of postmenopausal or corticosteroid-induced **osteoporosis** is 5 mg daily. Alternatively, for postmenopausal osteoporosis, 35 mg may be taken once weekly, 75 mg may be taken on 2 consecutive days of each month, or 150 mg may be taken once a month. For men with osteoporosis, the recommended dose is 35 mg once weekly.

◊ General references.

1. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161:** 353–60.
2. Dunn CJ, Goa KL. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* 2001; **61:** 685–712.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23:** 1409–21.
4. White NJ, Perry CM. Risedronate once a week. *Treat Endocrinol* 2003; **2:** 415–20.

Administration. A procedure for the extemporaneous preparation of an oral solution from risedronate tablets has been proposed,[1] for use in patients who cannot swallow whole tablets or require feeding tubes.

1. Dansereau RJ, Crail DJ. Extemporaneous procedures for dissolving risedronate tablets for oral administration and for feeding tubes. *Ann Pharmacother* 2005; **39:** 63–7.

Administration in renal impairment. Renal clearance of risedronate significantly correlated to renal function in a pharmacokinetic study,[1] although the authors concluded that generally no dosage adjustment appears necessary for patients with mild to moderate renal impairment (creatinine clearance (CC) greater than 20 mL/minute). Licensed product information states that no dosage adjustment is necessary when CC is greater than 30 mL/minute; however, use of risedronate is contra-indicated in patients with severe renal impairment (CC less than 30 mL/minute), due to a lack of clinical data.

1. Mitchell DY, *et al.* Effect of renal function on risedronate pharmacokinetics after a single oral dose. *Br J Clin Pharmacol* 2000; **49:** 215–22.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Risedronate improves bone mineral density (BMD) and reduces the risk of both vertebral and non-vertebral fractures in **postmenopausal** osteoporosis;[1-4] effects are maintained for at least 5 years.[5] In **corticosteroid-induced** osteoporosis, risedronate increases BMD at the lumbar spine, femoral neck, and trochanter.[3,6] Risedronate is also used to treat **men** with osteoporosis. In a controlled study in elderly men after a stroke, those given risedronate had increased BMD and a decreased risk of hip fracture.[7] In a prospective controlled study, 12 months of daily risedronate significantly increased BMD at the lumbar spine, femoral neck, and hip, and significantly reduced the incidence of new vertebral fractures in men with primary or secondary osteoporosis.[8]

A once-monthly regimen of risedronate was found to be similar in efficacy and safety to the once-daily regimen.[9]

1. Sickels JM, Nip C-S. Risedronate for the prevention of fractures in postmenopausal osteoporosis. *Ann Pharmacother* 2002; **36:** 664–70.
2. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161:** 353–60.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23:** 1409–21.
4. Wells G, *et al.* Risedronate 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 16/04/08).
5. Sorensen OH, *et al.* Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003; **32:** 120–6.
6. Dougherty JA. Risedronate for the prevention and treatment of corticosteroid-induced osteoporosis. *Ann Pharmacother* 2002; **36:** 512–16.
7. Sato Y, *et al.* Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med* 2005; **165:** 1743–8.
8. Ringe JD, *et al.* Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 2006; **26:** 427–31.
9. Delmas PD, *et al.* Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. *Bone* 2008; **42:** 36–42.

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. Risedronate has been found to improve pagetic bone lesions,[1] and to be more effective than etidronate.[2]

1. Brown JP, *et al.* Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. *Bone* 2000; **26:** 263–7.
2. Miller PD, *et al.* A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; **106:** 513–20.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Actonel; Ductonar; Rentop; Ribastamin; Ridron; Risedon; ***Austral.:*** Actonel; ***Austria:*** Actonel; ***Belg.:*** Actonel; ***Braz.:*** Actonel; Risedross; ***Canad.:*** Actonel; ***Chile:*** Actonel; ***Cz.:*** Actonel; Norsed; Risendros; ***Fin.:*** Optinate; ***Fr.:*** Actonel; ***Ger.:*** Actonel; ***Gr.:*** Actonel; ***Hong Kong:*** Actonel; ***Hung.:*** Actonel; ***India:*** Actonel; Risofos; ***Indon.:*** Actonel; Osteonate; ***Irl.:*** Actonel; ***Israel:*** Actonel; ***Ital.:*** Actonel; Optinate; ***Jpn:*** Benet; ***Malaysia:*** Actonel; ***Mex.:*** Actonel; Seralis; ***Neth.:*** Actonel; ***Norw.:*** Optinate; ***Philipp.:*** Actonel; ***Pol.:*** Actonel; ***Port.:*** Actonel; Norsed; ***S.Afr.:*** Actonel; ***Singapore:*** Actonel; ***Spain:*** Acrel; Actonel; ***Swed.:*** Optinate; Optinate Septimum; ***Switz.:*** Actonel; ***Thai.:*** Actonel; ***Turk.:*** Actonel; ***UK:*** Actonel; ***USA:*** Actonel; ***Venez.:*** Actonel.

Multi-ingredient: ***Arg.:*** Ribastamin Duo; Ridron Pack; ***Austral.:*** Actonel Combi; ***Fr.:*** Actonelcombi; ***Hung.:*** Actonel Trio; ***Irl.:*** Actonel Combi; ***Neth.:*** Actokit; ***Swed.:*** Optinate Combi; ***UK:*** Actonel Combi; ***USA:*** Actonel with Calcium.

Strontium Ranelate *(rINNM)*

FK-481; Ranelate de Strontium; Ranelato de estroncio; S-12911; Strontii Ranelas. 2-(2-Carboxy-4-cyano-5-[*N,N*-di(carboxymethyl)amino]thiophen-3-yl) acetic acid distrontium salt.

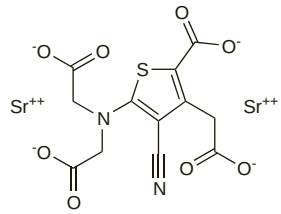
Стронций Ранелат

$C_{12}H_6N_2O_8SSr_2$ = 513.5.

CAS — 135459-87-9.

ATC — M05BX03.

ATC Vet — QM05BX03.



Adverse Effects and Precautions

Common adverse effects of strontium ranelate include gastrointestinal disturbances, headache, dermatitis, and eczema. Disturbances in consciousness, memory loss, and seizures may occur. Treatment with strontium ranelate has been associated with an increased incidence in venous thromboembolism including pulmonary embolism, and should be given with caution to those patients considered at risk or with a history of thromboembolic disorders. Transient reversible increases in creatine kinase activity have been reported. Hypersensitivity reactions, including rash, pruritus, urticaria, angioedema, and Stevens-Johnson syndrome have occurred. Drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, has also been reported. Strontium may interfere with certain methods used for the determination of serum and urinary calcium.

Strontium ranelate should not be given with food or antacids—see Interactions, below.

Hypersensitivity. As of November 2007, the EMEA had received reports of 16 cases of drug rash with eosinophilia and systemic symptoms (DRESS), a serious and life-threatening condition, in patients treated with strontium ranelate. Two fatalities were reported. Reactions appeared within 3 to 6 weeks of starting therapy, with skin rash, accompanied by fever, swollen glands, eosinophilia, and effects on the liver, kidneys, and lungs. Patients are advised to stop treatment with strontium ranelate if a rash occurs and to seek medical advice; treatment should not be restarted.[1] Similar advice, and a reminder that the drug should also be used with caution in patients with risk factors for venous thromboembolism, was issued in June 2008 by the Australian regulatory authorities; although there had been no fatalities, they had seen 16 reports of rash, one accompanied by fever and one by eosinophilia.[2]

1. EMEA. EMEA recommends changes in the product information for Protelos/Osseor due to the risk of severe hypersensitivity reactions (issued 16th November 2007). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease_Protelos_41745807en.pdf (accessed 21/01/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Severe skin reactions and venous thromboembolism with strontium ranelate (Protos). *Aust Adverse Drug React Bull* 2008; **27:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0806.pdf (accessed 17/07/08)

Interactions

Food, milk, and calcium-containing compounds may reduce the bioavailability of strontium ranelate; antacids containing aluminium or magnesium may reduce its absorption. Such products should be given at least 2 hours apart from, and, in the case of antacids, preferably after, strontium ranelate. Because of possible complex formation, strontium ranelate should not be given with oral tetracyclines or quinolones.

Pharmacokinetics

Strontium ranelate has an absolute bioavailability of about 25% after an oral dose; calcium or food reduces the bioavailability by about 60 to 70%. Peak plasma concentrations are achieved 3 to 5 hours after an oral dose. Plasma protein binding is low. Strontium ranelate has a high affinity for bone tissue. It is not metabolised, and has a half-life of about 60 hours. Excretion occurs via the kidneys and gastrointestinal tract.

Uses and Administration

Strontium ranelate is claimed to stimulate bone formation as well as reduce bone resorption. It is given orally in the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. The recommended dose is 2 g daily by mouth, given preferably at night and at least 2 hours after food.

◊ References.

1. Marie PJ. Strontium ranelate: new insights into its dual mode of action. *Bone* 2007; **40** (suppl 1): S5–S8.
2. Fonseca JE. Rebalancing bone turnover in favour of formation with strontium ranelate: implications for bone strength. *Rheumatology (Oxford)* 2008; **47** (suppl 4): iv17–iv19.

Administration in renal impairment. Strontium excretion occurs via the kidneys and clearance decreases as creatinine clearance (CC) decreases. UK licensed product information states that no dosage adjustment of strontium ranelate is required in patients with mild to moderate renal impairment (CC 30 to 70 mL/minute). However, it is not recommended for those with severe renal impairment (CC below 30 mL/minute) because of a lack of pharmacokinetic data in these patients; continuation of treatment in patients developing severe renal impairment should be considered on an individual basis.