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.

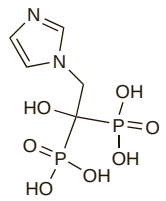
Золедроновая Кислота

$C_5H_{10}N_2O_7P_2$ = 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