Osteonorm; Osteostab; ***Malaysia:*** Bonefos; ***Mex.:*** Bonefos; ***Neth.:*** Bonefos; Ostac; ***Norw.:*** Bonefos; ***Philipp.:*** Bonefos; ***Pol.:*** Bonefos; Sindronat; ***Port.:*** Bonefos; Ostac; ***Rus.:*** Bonefos (Бонефос); ***S.Afr.:*** Bonephos; Ostac†; ***Singapore:*** Bonefos; ***Spain:*** Bonefos; Hemocalcin†; Mebonat†; ***Swed.:*** Bonefos; Ostac; ***Switz.:*** Bonefos; Ostac; ***Thai.:*** Bonefos; ***Turk.:*** Bonefos; ***UK:*** Bonefos; Clasteon; Loron.

Denosumab *(USAN, rINN)*

AMG-162; Dénosumab; Denosumabum.

Денозумаб

CAS — 615258-40-7.

Profile

Denosumab is a human monoclonal antibody that specifically targets the receptor activator of nuclear factor-kappa B ligand (RANKL), a mediator of the resorptive phase of bone remodelling. Denosumab is under investigation for various conditions, including osteoporosis, treatment-induced bone loss, rheumatoid arthritis, bone metastases, and multiple myeloma.

◊ References.

1. Lewiecki EM. RANK ligand inhibition with denosumab for the management of osteoporosis. *Expert Opin Biol Ther* 2006; **6:** 1041–50.
2. Body J-J, *et al.* A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 2006; **12:** 1221–8.
3. McClung MR, *et al.* Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006; **354:** 821–31.
4. Hamdy NA. Targeting the RANK/RANKL/OPG signaling pathway: a novel approach in the management of osteoporosis. *Curr Opin Investig Drugs* 2007; **8:** 299–303.
5. Lewiecki EM, *et al.* AMG 162 Bone Loss Study Group. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res* 2007; **22:** 1832–41.
6. Lipton A, *et al.* Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 2007; **25:** 4431–7.
7. Bone HG, *et al.* Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab* 2008; **93:** 2149–57.
8. Cohen SB, *et al.* Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum* 2008; **58:** 1299–1309.
9. Miller PD, *et al.* Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008; **43:** 222–9.

Etidronate

ATC — M05BA01.

ATC Vet — QM05BA01.

Etidronic Acid *(BAN, USAN, rINN)*

Acide Étidronique; Ácido etidrónico; Acidum Etidronicum; Etidronihappo; Etidronsyra. 1-Hydroxyethylidenedi(phosphonic acid).

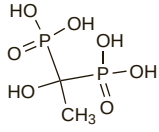
Этидроновая Кислота

$C_2H_8O_7P_2$ = 206.0.

CAS — 2809-21-4.

ATC — M05BA01.

ATC Vet — QM05BA01.



Etidronate Disodium *(USAN, rINNM)*

Dinatrii etidronas; Dinatriumetidronaatti; Dinatriumetidronat; Dinatrium-etidronát; Disodium Etidronate *(BANM)*; Disodu etydronian; Disodyum Etidronat; EHDP; Etidronas Dinatricum; Étidronate disodique; Etidronate Disodique; Etidronato disódico. Disodium dihydrogen (1-hydroxyethylidene)diphosphonate.

Динатрий Этидронат

$C_2H_6Na_2O_7P_2$ = 250.0.

CAS — 7414-83-7.

ATC — M05BA01.

ATC Vet — QM05BA01.

NOTE. Other etidronic acid sodium salts are designated as etidronate monosodium, etidronate trisodium, and etidronate tetrasodium. The name etidronate sodium is used only in *Martindale* where the salt cannot be identified more precisely.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Etidronate Disodium). A white or yellowish, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.2 to 5.2. Store in airtight containers.

USP 31 (Etidronate Disodium). A white powder that may contain lumps. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. pH of a 1% solution in water is between 4.2 and 5.2.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Unlike the newer bisphosphonates etidronate produces marked impairment of bone mineralisation at high therapeutic doses. An increase in bone pain may occur in patients with Paget's disease. Impairment of bone mineralisation may result in osteomalacia, and fractures have been reported. If a fracture occurs etidronate should be stopped until healing is complete. Hyperphosphataemia may occur, usually at high doses, but generally resolves 2 to 4 weeks after the end of therapy. There have been reports of paraesthesias, peripheral neuropathy, and confusion. Burning of the tongue, alopecia, erythema multiforme, and exacerbation of asthma have occurred rarely. Transient loss or alteration of taste has been reported mainly during and after intravenous infusion.

Effects on the blood. For a report of pancytopenia caused by etidronate therapy, see Effects on the Skin, below.

Effects on the ears. Ototoxicity, manifest as tinnitus and hearing loss, has been reported[1] in 2 patients given etidronate for osteoporosis; both patients had pre-existing otosclerosis and the authors recommended that those with ear pathology be monitored audiometrically when given bisphosphonates.

1. Yeşil S, *et al.* Further hearing loss during osteoporosis treatment with etidronate. *Postgrad Med J* 1998; **74:** 363–4.

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

Effects on the gastrointestinal tract. Oral etidronate was not associated with an increased incidence of upper gastrointestinal problems in a retrospective cohort study.[1] There was also no evidence of an increased incidence of gastrointestinal effects when given with NSAIDs or corticosteroids. Similarly, another large cohort study found no increased risk of peptic ulcer disease associated with the use of cyclical etidronate.[2] However, oesophageal ulceration has been reported with daily etidronate;[3,4] in one case possibly associated with incorrect use,[3] and in another, complicated by prior use of diclofenac, and a history of gastro-oesophageal reflux disease.[4]

1. van Staa T, *et al.* Upper gastrointestinal adverse events and cyclical etidronate. *Am J Med* 1997; **103:** 462–7.
2. Burger H, *et al.* Cyclical etidronate use is not associated with symptoms of peptic ulcer disease. *Eur J Clin Pharmacol* 2000; **56:** 319–22.
3. Macedo G, *et al.* Ulcerative esophagitis caused by etidronate. *Gastrointest Endosc* 2001; **53:** 250–1.
4. Maroy B. Ulcère géant de l'œsophage probablement dû à la prise d'étidronate. *Gastroenterol Clin Biol* 2001; **25:** 917–18.

Effects on the kidneys. Bisphosphonates are excreted by the kidneys, thus caution is advised in patients with renal impairment. When given by intravenous infusion for the treatment of hypercalcaemia of malignancy they have been reported to affect renal function adversely; hypercalcaemia or malignancy may also have contributed. For reports of renal failure associated with etidronate see under Bisphosphonates, p.1091.

Effects on mental state. Sensory hallucinations and confusion were reported in an elderly woman given daily etidronate for a week. Symptoms resolved on stopping the drug and recurred on rechallenge.[1] Mood disturbances, lack of concentration, and memory impairment were also reported in 3 patients receiving longer-term cyclical treatment; symptoms again diminished on stopping etidronate and reappeared after rechallenge.[2]

1. Burnet SP, Petrie JP. 'Wake up and smell the roses'—a drug reaction to etidronate. *Aust N Z J Med* 1999; **29:** 93.
2. Wolffenbuttel BHR, van der Klauw MM. Psychische bijwerkingen van behandeling met bisfosfonaten. *Ned Tijdschr Geneeskd* 2003; **147:** 35–7.

Effects on the respiratory system. For a report of bronchospasm induced by etidronate in an aspirin-sensitive asthmatic, see p.1091. For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, below.

Effects on the skin. A 47-year old woman with a history of auto-immune rheumatic disease developed toxic epidermal necrolysis, pancytopenia, and acute respiratory distress syndrome 7 days after starting etidronate for osteoporosis; she died of cardiorespiratory failure, secondary to the acute respiratory distress syndrome, despite aggressive supportive measures.[1]

1. Coakley G, Isenberg DA. Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. *Br J Rheumatol* 1995; **34:** 798.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare (see p.1091).

Interactions

As for the bisphosphonates in general, p.1091.

Anti-inflammatory drugs. For a lack of apparent interaction between cyclical etidronate and corticosteroids or NSAIDs see under Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

After oral doses of etidronate, absorption is variable and appears to be dose dependent. At usual doses about 1 to 6% of a dose is absorbed. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. Etidronate is rapidly cleared from the blood and has been reported to have a plasma half-life of 1 to 6 hours. It is not metabolised. About 50% is excreted in the urine within 24 hours, the remainder being sequestered to bone and slowly eliminated. The half-life of etidronate in bone exceeds 90 days. Unabsorbed etidronate appears in the faeces.

Uses and Administration

Etidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It inhibits the growth and dissolution of hydroxyapatite crystals in bone and may also directly impair osteoclast activity. It diminishes bone resorption and thus reduces bone turnover.

Etidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also given in bone disorders in which excessive bone resorption is a problem, such as Paget's disease of bone and osteoporosis. In addition, it may be used for the prevention and treatment of ectopic (heterotopic) ossification. A chelate of etidronate with radioactive technetium-99m (p.2055) is used diagnostically as a bone scanning agent and a similar compound with rhenium-186 for the palliation of bone metastases in prostate cancer (see below).

Etidronate is given as the disodium salt, by intravenous infusion over at least 2 hours, or orally, usually as a single daily dose. Food should be avoided for 2 hours before and after oral doses.

In the treatment of **Paget's disease**, etidronate disodium is given orally in a usual initial dose of 5 mg/kg daily for not more than 6 months. Doses above 10 mg/kg daily should be reserved for severe disease and should not be given for more than 3 months at a time. The maximum dose is 20 mg/kg daily. The response to etidronate may be slow in onset and may continue for several months after stopping therapy. Therefore, further treatment should only be given after a drug-free interval of at least 3 months and after evidence of relapse; it should not be given for longer than the initial treatment.

In the treatment of **hypercalcaemia of malignancy** the recommended dose of etidronate disodium by slow intravenous infusion is 7.5 mg/kg daily for 3 successive days, although infusions may be continued for up to 7 days if necessary. This daily dose should be diluted in at least 250 mL of sodium chloride 0.9% and infused over at least 2 hours. There should be at least a 7-day interval between courses of treatment. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy with oral etidronate disodium 20 mg/kg daily for 30 days may be started on the day after the last intravenous dose; treatment may be extended to a maximum of 90 days.

For the prevention and treatment of **ectopic ossification** complicating hip replacement etidronate disodium has been given orally in a dose of 20 mg/kg daily for 1 month before and 3 months after the operation. For ectopic ossification due to spinal cord injury it has been