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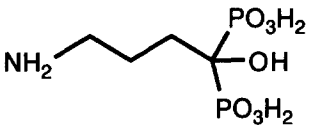
New Drugs—Reports of New Drugs Recently Approved by the FDA

Alendronate



Structure
$C_4H_{13}NO_7P_2$

(4-Amino-1-hydroxybutylidene)bisphosphonic acid
[CAS 66376-36-1]

Supply: Monosodium salt trihydrate, mp 233–235 °C (dec.), $C_4H_{12}NNaO_7P_2$: $3H_2O$ [CAS 12168-17-5].

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Mechanism of action: All bisphosponates are taken up rapidly by the skeleton and inhibit osteoclast-mediated bone resorption.[1,2,3] Mechanism of antiresorptive activity is not fully understood; possible mechanisms include direct inhibition of osteoclast activity or inhibition of osteoblasts from producing osteoclast-stimulating activity.[3,4,5].

Therapeutic category: Osteoporosis (10 mg), Paget's disease (40 mg).

Synthesis: This compound can be synthesized by several different ways. 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid can be prepared by the reaction of 4-amino-butyric acid with a mixture of phosphorous acid and phosphorous trichloride in the presence of methanesulfonic acid, followed by the neutral hydrolysis of the phosphonylated reaction mixture in 90% yield. The mono sodium salt of alendronic acid can be obtained by adjusting the pH to 4.3 during the crystallization process.[6]

Summary: Alendronate is a potent aminobisphosphonate derivative which has shown efficacy in postmenopausal osteoporosis,[4,9] Paget's disease,[8] and malignant hypercalcemia.[8] In hyperparathyroid rats, alendronic acid reduces bone loss, while in ovariectomized rats, alendronic acid prevents and reverses estrogen deficiency-induced bone changes. In ovariectomized baboons, alendronic acid decreases the rate of bone turnover, while increasing bone strength and volume. In rats, alendronic acid is more potent at inhibiting bone resorption than etidronic acid and has a higher safety margin. After sequestration into bone, the half-life is estimated to be more than 10 years, however, biological effects diminish post-treatment.[3,5,10] Unlike earlier bisphosphonate compounds, alendronate contains an amino group side-chain, which imparts greater potency and specificity.[1] As an inhibitor of bone resorption, alendronate is 200 to 1000 times more potent than etidronate and approximately 100 times as potent as clodronate or tiludronate (Averbuch[2,5] 1993, Tuzerillo.[5–] Alendronate localizes preferentially at active sites of bone resportion, and bone resorption has been inhibited at doses that have no effect on bone mineralization (Averbuch[2,7] 1993, Harris 1993). Results from two three-year pivotal trials with 994 postmenopausal women with osteoporosis support the conclusion that alendronate builds healthy bone. In patients treated with daily alendronate, 10 mg for 3 years, a progressive increase from baseline in bone mineral density occured at the spine (8.2%) and hip (7.2%), compared with patients treated with placebo, in whom bone mineral density decreased between 0.65 and 1.16%. Oral alendronate significantly decreases biochemical markers of bone turnover in post menopausal women to levels simiar to those found in healthy premenopausal women. Bone biopsy results indicate that the quality of new bone formed in treated patients is normal. In postmenopausal women with osteoporosis, alendronic acid significantly reduces the number of patients with new vertebral fractures by nearly 50%, reduces the number of vertebral

fractures per patient, reduces the apparent severity of vertebral fractures, and reduces height loss compared to placebo. Alendronate was licensed to Merck & Co., Inc. by Istituto Gentili SPa of Pisa, Italy in 1988 and is approved in 28 other countries.

Manufacturer: Merck & Co., Inc.

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