



Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Bone Resorption Inhibitors

Overview:

Bone resorption inhibitors are used for bone diseases in ambulatory populations, such as treatment and prevention of osteoporosis and treatment of Paget's disease. Osteoporosis is associated with reduced bone mass accompanied by deterioration of the skeleton, which leads to an increased risk of fracture. The incidence of osteoporosis increases after menopause and postmenopausal bone loss occurs at a rate of about 1-3% a year. Pharmacologic intervention is suggested by the National Osteoporosis Foundation for:

- (1) patients with total hip or spine T scores less than -2.5 ,
- (2) postmenopausal women or men age 50 and older with femoral neck, total hip or spine T scores from -1.0 to -2.5 with an additional risk factor for fracture, or
- (3) patients with an osteoporotic hip or vertebral fracture.

Paget's disease of the bone is a chronic progressive disorder of the adult skeleton. The disease usually occurs after age 40 and is characterized by increased bone remodeling, bone hypertrophy, and abnormal bone structure, leading to pain and deformity.

Bisphosphonates (alendronate, etidronate, risedronate, ibandronate, and tiludronate) bind to hydroxyapatite in bone and inhibit bone resorption by decreasing the number and activity of osteoclasts. Alendronate, ibandronate, and risedronate are approved to treat and prevent osteoporosis; however, alendronate and risedronate appear to have similar efficacy in reducing the risk of vertebral fractures when compared with raloxifene.¹¹ Alendronate and risedronate are also indicated to treat glucocorticoid-induced osteoporosis in both men and women and are indicated for treatment to increase bone mass in men with osteoporosis. Bisphosphonates have also been shown to reduce the risk of nonvertebral and hip fractures, while calcitonin and raloxifene have been ineffective in reducing the risk for these fracture types. When compared with estrogen, bisphosphonates do not have adverse effects on the uterus and breast.

Additionally, all bisphosphonates are equally efficacious, and with the exception of ibandronate, are approved to treat Paget's disease. One disadvantage of the oral bisphosphonates is that the agents must be taken on an empty stomach, and the patient must remain sitting upright for 30 minutes.

Alendronate and risedronate are available as both once daily and once weekly tablets. Risedronate is also available as a once monthly tablet and is available in tablets taken on two consecutive days for once monthly dosing. Because it is recommended for patients to take adequate amounts of calcium and vitamin D to achieve the maximum effect of bisphosphonates, alendronate is formulated with vitamin D as a once weekly tablet and risedronate is co-packaged with calcium as once weekly risedronate and a daily calcium supplement. Ibandronate was originally approved as a once-daily regimen in May 2003. Since then, ibandronate has also become available in an oral once-monthly formulation as well as an injectable formulation administered once every three months. Less frequent dosing is a desirable quality of these products.

Raloxifene acts as an estrogen receptor agonist by reducing bone resorption and increasing bone mineral density. Raloxifene is indicated for the prevention and treatment of osteoporosis in postmenopausal women. In addition, raloxifene is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, and for the reduction in risk of invasive breast cancer in postmenopausal women at high-risk for invasive breast cancer. Unlike estrogen, raloxifene does not stimulate the endometrium; however, it should be noted that hot flashes are the most common side effect of raloxifene. Results from the Raloxifene Use for The Heart (RUTH) trial, which evaluated the effects of raloxifene on cardiovascular events and invasive breast cancer in women at high risk for coronary heart disease, established that raloxifene significantly reduces the risk of invasive breast cancer, but is not associated with a reduced risk of coronary events. Therefore, though raloxifene has been shown to decrease serum total and LDL cholesterol levels, clinical data indicate these favorable changes in lipid profiles do not translate into reduced coronary risks. Additionally, while a secondary analysis of data from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial showed that raloxifene significantly reduced the risk of cardiovascular events in a subset of women with increased cardiovascular risk, the evaluation of cardiovascular outcomes was not the primary objective.

Calcitonin slows bone loss by inhibiting osteoclast-mediated bone resorption and is indicated for the treatment of osteoporosis in females greater than five years past menopause. Calcitonin injection is approved for the treatment of Paget's disease of the bone. Calcitonin does not seem to be as clinically efficacious as other agents; however, it does seem to decrease bone pain associated with compression fractures. The available products are Miacalcin and Fortical. These

two products are not interchangeable due to different manufacturing processes. However, the active ingredient for both products is the same.

Prolia™ (denosumab) recently received FDA approval, and is the first and only drug in a new class of agents known as RANK Ligand (RANKL) Inhibitors. RANKL is a soluble protein essential for the formation, function, and survival of osteoclasts. Prolia™ prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors, thereby inhibiting osteoclast formation, decreasing bone resorption and increasing bone mass and strength. Prolia™ is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture; defined as a history of osteoporotic fracture or multiple risk factors for fracture; or those who have failed or are intolerant to other available osteoporosis therapy. Prolia™ is to be given as a single subcutaneous injection by a healthcare professional once every six months.

GENERIC NAME	BRAND NAME	MANUFACTURER	GENERIC
Alendronate	Fosamax®	Merck, various	Y
Alendronate; Cholecalciferol	Fosamax® Plus D	Merck	N
Risedronate	Actonel®	Procter & Gamble	N
Risedronate with Calcium	Actonel® with Calcium	Procter & Gamble	N
Ibandronate	Boniva®	Roche	N
Calcitonin-salmon	Miacalcin®, Fortical®	Novartis, Upsher- Smith, various	Y (Miacalcin)
Etidronate disodium	Didronel®	Procter & Gamble, Genpharm, L.P.	Y
Raloxifene	Evista®	Eli Lilly	N
Tiludronate	Skelid®	Sanofi-Synthelabo	N
Denosumab	Prolia™	Amgen	N

Summary:

Bisphosphonates (alendronate, etidronate, risedronate, ibandronate, and tiludronate) inhibit bone resorption by decreasing the number and activity of osteoclasts. All bisphosphonates are equally efficacious, and with the exception of ibandronate, are approved to treat Paget's disease. Etidronate and tiludronate are indicated for the treatment of Paget's disease only. Alendronate, risedronate, and ibandronate are indicated for the treatment and prevention of osteoporosis; the differences between alendronate, risedronate, and ibandronate are their indications and dosing frequencies. Additionally, alendronate and risedronate have been studied in men and women with osteoporosis, while ibandronate is only indicated for use in postmenopausal women. Oral ibandronate and oral risedronate can be given once a month, IV ibandronate once every three months,

and alendronate once weekly. Risedronate may also be taken on two consecutive days as a total of two tablets each month. A head-to-head study comparing alendronate and risedronate demonstrated that alendronate is superior in improving bone turnover markers. However, the result does not translate to reduction of fractures.

Calcitonin is indicated for the treatment of Paget's disease and osteoporosis; however, calcitonin does not seem to be as clinically efficacious as other agents. Raloxifene is an estrogen modulator indicated for the treatment and prevention of osteoporosis in postmenopausal women, reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, and reduction in risk of invasive breast cancer in postmenopausal women at high-risk for invasive breast cancer. Denosumab is a RANKL inhibitor indicated for the treatment of osteoporosis in postmenopausal women with high risk for fracture; defined as a history of osteoporotic fracture or multiple risk factors for fracture; or those who have failed or are intolerant to other available osteoporosis therapy. Selection of a bone resorption inhibitor for the preferred list should take into consideration efficacy, dosing frequency, indications, and cost.