

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; postmenopausal bone loss occurs at a rate of about 1-3% a year. Pharmacologic intervention is suggested by the North American Menopause Society for (1) postmenopausal women with total hip or spine T scores less than -2.5, (2) postmenopausal women with total hip or spine T scores from -2.0 to -2.5 with an additional risk factor for fracture, or (3) postmenopausal women with an osteoporotic 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. Alendronate and risedronate appear to have similar efficacy in reducing the risk of vertebral fractures when compared to raloxifene.¹¹ However, raloxifene and calcitonin have not been demonstrated to reduce the risk of nonvertebral and hip fractures at currently approved doses, while bisphosphonates are effective at reducing risk for these fracture types. When compared to estrogen, bisphosphonates do not have adverse effects on the uterus and the breast. Alendronate and risedronate are also indicated to treat osteoporosis caused by glucocorticoid in both men and women. In addition, both alendronate and risedronate are indicated for treatment to increase bone mass in men with osteoporosis. All bisphosphonates with exception of ibandronate are approved to treat Paget's disease; and they are equally efficacious. 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 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 (Fosamax plus D) as a once weekly tablet and risedronate is co-packaged with calcium as once weekly risedronate and daily calcium supplement. Ibandronate originally received FDA approval as once-daily dosing for the treatment of osteoporosis in post-menopausal women in May 2003. Ibandronate is also available in an oral once-monthly formulation and an injectable formulation that is 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. Additionally, 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. Clinical data suggest that raloxifene decreases serum total and LDL cholesterol levels; the impact of raloxifene on decreasing risks for cardiovascular disease is currently under investigation. 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; however, the evaluation of cardiovascular outcomes was not the primary objective. The Raloxifene Use for The Heart (RUTH) trial currently being conducted is designed to determine whether raloxifene lowers the risk of coronary events and reduces the risk of invasive breast cancer in women at high risk for a major coronary event. Of further note, raloxifene has been associated with a lower incidence of breast cancer and an increased risk of venous thromboembolism compared with placebo.

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.

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	N
Etidronate disodium	Didronel [®]	Procter & Gamble, Genpharm, L.P.	Y
Raloxifene	Evista [®]	Eli Lilly	N
Tiludronate	Skelid [®]	Sanofi-Synthelabo	N

Summary:

Based on the mechanism of action, the bone resorption inhibitors can be categorized into bisphosphonates (alendronate, etidronate, ibandronate, risedronate, and tiludronate) and hormones (calcitonin and raloxifene). In the bisphosphonates group, etidronate and tiludronate are only indicated for the treatment of Paget's disease. All bisphosphonates with exception of ibandronate are approved to treat Paget's disease; and they are equally efficacious. 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 frequency. Alendronate and risedronate have been studied in men and women with osteoporosis; ibandronate is only indicated for postmenopausal women. Oral ibandronate can be given once a month and IV ibandronate can be given once every three months versus once weekly oral dosing of alendronate and risedronate. Risedronate may additionally 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. Selection of a bone resorption inhibitor for the preferred list should take into consideration efficacy, dosing frequency, indications and cost.