INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Osteoporosis***
-April 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a review of medications with Food and Drug Administration approval for the prevention and treatment of osteoporosis. It is estimated that over 10 million Americans have osteoporosis, and over 40 million adults have osteopenia. Women are disproportionately affected by osteoporosis, with a prevalence of 16% of by the age of 50 years, and 35% by the age of 80 years.[1,2] American Indian and Alaska Native women have the highest incidence of hip fractures across all ethnic/racial populations.[3] The IHS National Core Formulary (NCF) currently includes the oral bisphosphonate, alendronate, and other medications known to have beneficial effects on bone health, including estrogen and testosterone, as well as vitamin D and calcium supplements. Following review and analysis, **no modification was made to the NCF.**

Discussion:

The **anti-resorptive** agents (those that stop bone breakdown) include oral (alendronate, risedronate, ibandronate) and IV (ibandronate, zoledronate) bisphosphonates and the RANKL ligand inhibitor, denosumab. The **anabolic agents** (those that promote bone formation) include PTH-receptor analogues (teriparatide, abaloparatide) and the sclerostin inhibitor romosozumab.[2] An estrogen agonist/antagonist, raloxifene, and calcitonin are also approved in the management of osteoporosis.

All of the approved agents for the prevention and treatment of osteoporosis have randomized controlled trials (RCTs) with evidence for increasing bone mineral density (BMD) and reduction in risk of fractures when compared to placebo. Most studies examine the impact of treatment on the incidence of vertebral, non-vertebral, and hip fractures.

Among bisphosphonates, only ibandronate lacks evidence for reduction of hip and non-vertebral fractures. It is for this reason that most guidelines exclude this agent as first-line therapy. Over a 1-3 year period, bisphosphonates reduce the fracture risk by 22-70%. All bisphosphonates are contraindicated in renal insufficiency and may cause hypocalcemia and GI side effects, as well as rare cases of osteonecrosis of the jaw (ONJ), atypical femur fractures (AFF), and ocular inflammation.[3] An adherence study in 2022 showed that IV zoledronic acid had lowest likelihood of discontinuation among all bisphosphonates (Hazard Ratio (HR) 0.73, 95% Confidence Interval (CI): 0.61-0.88).[4]

Denosumab can be used in patients with renal insufficiency, and reduces fracture risk by 20-68%. The American College of Obstetrics and Gynecology (ACOG), the American College of Physicians, and the Osteoporosis International recommend it be offered as a first-line agent, while the American Academy of Clinical Endocrinologists reserves this designation for patients at very high risk of fracture.[1-3, 5-6] This medication requires administration by a healthcare provider, and is given subcutaneously (SC) every 6 months. Risks include hypersensitivity reactions, and ONJ/AFF at similar rates to bisphosphonates. Discontinuation is associated with rapid BMD loss and increased fracture risk, thus it is recommended to follow treatment with an alternative anti-resorptive agent.[3]

A 2019 network meta-analysis of RCTs including over 5,000 patients compared denosumab head to head with bisphosphonates. BMD at the spine was greater in the denosumab group at 24 months (mean difference 1.74, 95% CI 1.05-2.43) but there was no difference in fracture risk.[7]

The PTH-analogues teriparatide and abaloparatide reduce fracture risk by 35-77% and 43-86% respectively. Guidelines agree that these agents should be offered as first-line therapy only in patients at very high risk of fracture. They are administered as daily injections for 2 years and must be followed by treatment with anti-resorptive therapy, as discontinuation is similarly associated with rapid loss of BMD. Both agents must be avoided in patients with hypercalcemia, active kidney stones, and increased risk of osteosarcoma.[3]

A 2023 network meta-analysis of RCTs and observational studies did not find a difference in risk of any clinical fracture between bisphosphonates and denosumab, but did detect a reduction in risk of any clinical fracture for both PTH-analogues when compared to bisphosphonates (abaloparatide vs bisphosphonates HR 0.35, 95% CI: 0.15-0.81), (teriparatide vs bisphosphonates HR 0.64, 95% CI: 0.43-0.95). Participant withdrawal due to adverse events was higher in the abaloparatide group vs bisphosphonates (HR 1.75, 95% CI: 1.17-2.61).[3]

Romosozumab is approved for use in postmenopausal women, but has not yet been approved for use in men in the US. This agent reduces vertebral and non-vertebral fractures by 36 and 73% respectively. It requires 12 months of therapy

with monthly two-shot dosing, administered SC by a healthcare professional. It is associated with hypersensitivity reactions, and has similar risk of hypocalcemia, ONJ, and AFF as bisphosphonates and denosumab. There is a black box warning for romosozumab due to increased risk for MI, Stroke, and CV death (HR 1.87, 95% CI: 1.11-3.14) for romosozumab compared to alendronate.[9] For this reason, most guidelines do not list it a first-line agent and only recommend its use in patients with very high risk of fracture and low risk of CV disease.[1-2, 5, 10]

Raloxifene reduces the risk of vertebral fractures by 30-50% and can be used to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis. It does not reduce the risk of non-vertebral and hip fractures, and is associated with increased risk of deep venous thrombosis. For this reason, it is not considered first-line therapy and is only recommended under special circumstances.[1, 4]

Calcitonin reduces the risk of vertebral fracture by 30%, but does not reduce the risk of non-vertebral fractures. This agent is not considered first-line due to its limited efficacy compared to other available agents.[3]

Findings:

Several specialty guidelines recommend the use of oral and IV bisphosphonates, denosumab, and the PTH-analogues as first-line options for the prevention and treatment of osteoporosis. However, concerns remain about the long-term safety and efficacy of denosumab and the PTH-analogues, especially with regard to the observed rapid BMD loss and increased risk of fractures after these agents are discontinued. Furthermore, reports from both the U.S. National Institute of Health and the Institute for Clinical and Economic Review agree that treatment with these agents does not meet the generally accepted cost thresholds for quality adjusted life-years.[11-12]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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