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Drug Class Update: Bone Metabolism Drugs

Date of Review: December 2024

Date of Last Review: September 2019
Dates of Literature Search: 05/23/2019 – 08/02/2024

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Review new comparative evidence for the bone metabolism agents including bisphosphonates, abaloparatide, denosumab, romosozumab, and teriparatide for management of osteoporosis in women and men to ensure Oregon Medicaid prior authorization (PA) criteria are consistent with current guidelines.

Plain Language Summary:
- As people get older, their bones become weaker and more brittle. In some people, this can lead to a condition called osteoporosis, in which bones break easily (fracture), even after a minor injury, like a little bump or fall. The bones in the hip, spine, and wrist are most frequently affected by osteoporosis. Women who have gone through menopause are more likely to get osteoporosis than other people. However, up to 1 in every 3 men over the age of 50 years will break a bone due to osteoporosis.
- Alendronate, ibandronate, risedronate, and zoledronic acid belong to the class of medicines called bisphosphonates. Bisphosphonates are the first choice for osteoporosis treatment for people at high risk of fracture. These medicines help strengthen bones and decrease the risk of hip and spine fractures. These medicines have not been shown to make a difference in the risk of breaking an arm or wrist bone.
- Bisphosphonates can be taken as tablets once a day, once a week, or once a month depending on the medicine. Ibandronate and zoledronic acid can also be given by a healthcare provider as an injection every 3 months or once a year. No studies have shown that one of these medicines is more effective than another for making bones stronger. Selection of a medication should be based on patient preferences after a discussion with their provider.
- For most people, bisphosphonates are safe and well tolerated. Side effects can include heartburn, indigestion, pain or stiffness in the muscles or joints, headache, and feeling tired. A rare side effect of bisphosphonates is a break or crack in the middle of thigh bone, known as atypical femoral fracture. This injury can cause pain in the leg and may gradually feel worse over time. Another rare side effect is called osteonecrosis of the jaw, in which a section of the jaw is slow to heal, usually after a tooth is pulled or other dental work has been done.
- If people cannot take a bisphosphonate, another drug called denosumab may be ordered by their provider. Denosumab must be given by an injection under the skin every 6 months at the provider's office. This medicine can increase the risk of getting an infection or causing a drop in blood calcium levels in people with advanced kidney disease.
- People at very high risk of breaking a bone, who have had a fracture, or cannot take oral medicines, may receive an injectable medication such as teriparatide, abaloparatide, or romosozumab. These medicines make bones stronger and prevent fractures. Studies have shown these injectable medicines are better than bisphosphonates for decreasing the risk of spinal fractures in people at high risk for fracture, but they should not be continued for more than

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1 or 2 years, depending upon the medicine. Teriparatide and abaloparatide should not be used in people at high risk of bone cancer. Romosozumab should not be given to people who have had a stroke or heart attack.

- Oregon Medicaid pays for most forms of oral alendronate, ibandronate, and risedronate. Providers must explain why someone needs an injectable medicine such as zoledronic acid, denosumab, abaloparatide, teriparatide or romosozumab before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. Is there new comparative evidence that including bisphosphonates, abaloparatide, denosumab, romosozumab, and teriparatide differ in efficacy or effectiveness for osteoporosis?
2. Is there any new comparative evidence the bone metabolism agents differ in harms?
3. Are there specific subpopulations (ethnicity, demographics, disease severity, comorbidities, gender, fracture risk) for which one agent is better tolerated or more effective than other available agents?

Conclusions:

- Since the previous bone metabolism class update in 2019, 5 systematic reviews[1-5] and 7 clinical guidelines[6-12] have been published for management of osteoporosis.
- A 2022 systematic review and meta-analysis evaluated the efficacy and safety of zoledronic acid versus alendronate in patients with osteoporosis.[1] Pooled estimates demonstrated that there was no difference between alendronate and zoledronic acid in increasing the bone mineral density (BMD) of the lumbar spine after 1 year (standard mean difference [SMD] = - 0.03, 95% confidence interval [CI] -0.15 to 0.09) or after 2 years (SMD = 0.16, 95% CI -0.12 to 0.43), and the BMD of the total hip after 1 year (SMD = -0.08, 95% CI -0.31 to 0.14) or after 2 years (SMD = 0.05, 95% CI -0.21 to 0.32; moderate-quality evidence for all outcomes).[1] Higher total adverse event (AE) rates (relative risk [RR] = 2.27, 95% CI 1.60 to 3.21) were recorded within 3 days of zoledronic acid infusion, but some AE rates were lower, particularly gastrointestinal (GI) AEs (RR=0.6, 95% CI 0.44 to 0.83), were noted after 3 days of zoledronic acid infusion compared with alendronate (moderate-quality evidence for both outcomes).[1]
- A 2020 systematic review and meta-analysis compared the safety and efficacy of teriparatide with bisphosphonates for management of postmenopausal osteoporosis.[2] Three bisphosphonates (risedronate, alendronate, and zoledronic acid) were compared to teriparatide. The teriparatide group had a lower total occurrence of vertebral fractures (RR = 0.55, 95% CI 0.40 to 0.77; P = 0 .001) and nonvertebral fractures (RR = 0.65, 95% CI 0.46 to 0.90; P = 0.009) compared with the bisphosphonate group over 12 to 36 months (moderate-quality evidence for both outcomes).[2] Compared bisphosphonates, teriparatide group improved BMD at the femoral neck at the final follow-up (MD= 0.85%, 95% CI 0.65 to 1.06; moderate-quality evidence).[2] No difference was found between the teriparatide and bisphosphonate groups in rates of AEs (RR=1.05, 95% CI 0.9 to 1.22; P =0.516; moderate-quality evidence).[2]
- A 2021 systematic review compared the efficacy and safety of romosozumab with teriparatide for the treatment of postmenopausal osteoporosis.[3] Based on a meta-analysis of 4 RCTs (n=1304), moderate-quality evidence showed that compared with teriparatide, romosozumab increased the BMD of the lumbar spine, total hip, and femoral neck, with a lower incidence of injection-site reactions.[3] A meta-analysis of 2 RCTs did not find a difference in the incidence of death and other serious adverse events (SAEs) between romosozumab and teriparatide (moderate-quality evidence for both outcomes).[3]
- A 2023 systematic review explored the safety and efficacy of oral bisphosphonates (risedronate, ibandronate, and alendronate), denosumab, and teriparatide in management of secondary osteoporosis due to continuous use of glucocorticoids.[4] Teriparatide and denosumab were superior to bisphosphonates at increasing the BMD of the lumbar spine (teriparatide: MD=3.98%, 95% CI 3.61 to 4.175; P=0.00001; denosumab: MD=2.07%, 95% CI 0.97 to 3.17; P=0.0002; high-quality evidence for both outcomes).[4] Teriparatide was superior to bisphosphonates for increasing hip BMD (MD = 2.39%, 95% CI 1.47 to 3.32, P<0.00001; high-quality evidence).[4] There was no statistically significant difference in SAEs or AEs found between bisphosphonates, denosumab, and teriparatide; high-quality evidence).[4]

- A 2024 meta-analysis evaluated the comparative safety of denosumab versus bisphosphonates in patients with primary osteoporosis.[5] In comparison to bisphosphonates, denosumab had less withdrawal due to AEs (RR = 0.49, 95% CI 0.34 to 0.71), more infections (RR=1.14, 95% CI 1.02 to 1.27), more upper respiratory tract infections (RR = 1.56, 95% CI 1.08 to 2.25), less vertebral fractures (RR= 0.54, 95% CI 0.31 to 0.93), and less abdominal pain (RR=0.44, 95% CI 0.22 to 0.87; moderate-quality evidence for all outcomes).[5]
- In November 2021, the Canadian Agency for Drugs and Technology in Health (CADTH) published recommendations for the Canadian Agency for Drugs and Technology in Health (CADTH.[6] CADTH criteria for romosozumab include:
    - Patients with a history of bone fracture and who are at high risk for future fracture, defined as a 10-year fracture risk ≥ 20% as defined by the Fracture Risk Assessment (FRAX) tool.[6]
    - The patient must be treatment-naive to osteoporosis medications, except for calcium and/or vitamin D.[6]
    - Maximum duration of treatment is 12 months.[6]
    - Romosozumab should not be prescribed concurrently with other osteoporosis medications, except for calcium and/or vitamin D.[6]
- In May 2022, the National Institute for Health and Care Excellence (NICE) issued recommendations for the use of romosozumab in postmenopausal persons with severe osteoporosis.[7] Romosozumab is recommended as an option in those at high risk of fracture if they have had a major bone fracture (spine, hip, forearm or humerus fracture) within the previous 24 months.[7]
- In August 2024, NICE published guidance for the use of abaloparatide for treating osteoporosis.[8] Abaloparatide is recommended as an option for treating osteoporosis in postmenopausal persons at very high risk of fracture.[8] Very high risk fracture is defined as a fracture probability based on the FRAX tool that exceeds the threshold for intervention by 60%.[8]
- In February 2020, the Endocrine Society published an update to 2019 guidance for pharmacologic management of osteoporosis in postmenopausal persons.[9] The primary objective was to assess new evidence for romosozumab for bone fracture prevention in people at very high risk for bone fracture (i.e., low T-score < −2.5 or multiple vertebral fractures).[9] Two new recommendations are:
    - Romosozumab is recommended for up to 1 year to reduce risk of vertebral, hip, and nonvertebral fractures (strong recommendation; moderate-quality evidence).[9]
    - After a completed course of romosozumab, treatment with antiresorptive osteoporosis therapies is recommended to maintain BMD and reduce fracture risk (strong recommendation; moderate-quality evidence).[9]
- The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) issued a guidance update in 2020 for diagnosis and treatment of osteoporosis in postmenopausal persons.[10] Strength of recommendations and quality of evidence for diagnosis and treatment of osteoporosis in postmenopausal women are summarized in **Table 3**.
- The Osteoporosis Canada 2023 Group published guidance for interventions to optimize fracture prevention in postmenopausal females and males aged 50 years and older with the presence of risk factors for osteoporosis.[11] Although most studies were performed in postmenopausal females, the evidence available in males with primary or hypogonadal osteoporosis shows similar effects to females on fractures with bisphosphonates and denosumab.[11] Therefore, the evidence from females was used for males but rated as moderate certainty from some indirectness.[11] **Table 4** summarizes the recommendations and quality of evidence from the analysis conducted by the Osteoporosis Canada 2023 group.
- The 2017 American College of Rheumatology (ACR) guidance for prevention and treatment of glucocorticoid-induced osteoporosis for patients with rheumatic or nonrheumatic conditions was updated in 2022.[12] For adults beginning or continuing greater than 3 months of glucocorticoid treatment, ACR strongly recommends initial assessment of fracture risks with clinical fracture assessment, BMD with vertebral fracture assessment or spinal x-ray, and FRAX Tool assessment if 40 years of age or older.[12] For adults at medium, high, or very high fracture risk, ACR strongly recommends pharmacologic treatment.[12]. Choice of oral or intravenous (IV) bisphosphonates, denosumab, or parathyroid hormone analogs should be made by shared decision-making.[12] Anabolic

agents are conditionally recommended as initial therapy for those with high and very high fracture risk.[12] **Table 5** provides a summary of the 2022 ACR recommendations and certainty of evidence for glucocorticoid-induced osteoporosis assessment and treatment.

- In December 2022, TYMLOS (abaloparatide) received an expanded FDA indication to increase bone density in men with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy.[13]
- Two new biosimilar products received FDA-approval in March 2024:
    - A PROLIA biosimilar, JUBBONTI (denosumab-bbdz) received FDA-approval for treatment of postmenopausal women with osteoporosis at high risk for fracture, treatment to increase bone mass in men with osteoporosis at high risk for fracture, treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture, treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and treatment to increase bone mass in women at high risk for fracture receiving aromatase inhibitor therapy for breast cancer.[14]
    - An XGEVA biosimilar, WYOST (denosumab-bbdz) received FDA-approval for prevention of skeletal-related events in patients with multiple myeloma and it patients with bone metastases from solid tumors, treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.[15]
- The black boxed warning for the risk of osteosarcoma was removed from the teriparatide label in November 2020. In December 2021, the black boxed warning for the risk of osteosarcoma with abaloparatide was removed from the label. However, these warnings are still part of the "Warnings and Precautions" section for both medications.[13,16] Abaloparatide and teriparatide should be avoided in patients are at increased baseline risk of osteosarcoma.
- In January 2024, a black boxed warning regarding the risk of severe hypocalcemia in patients with advanced kidney disease was added to the denosumab label.[17] Patients with advanced chronic kidney disease, including dialysis-dependent patients, are at greater risk of severe hypocalcemia following denosumab administration.[17] Other new FDA safety alerts for this drug class are summarized in **Table 6**.
- There was no new evidence to demonstrate one agent is better tolerated or more effective than other available agents for specific subpopulations (gender, demographics, disease severity, comorbidities, fracture risk).

Recommendations:

- No changes to the Practitioner-Managed Prescription Drug Plan (PMPDP) are recommended.
- Revise prior authorization (PA) criteria for bone metabolism agents to align with recently published guidelines and FDA safety alerts (**Appendix 4**).
- After review drug costs in the executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy:

- The Pharmacy and Therapeutics Committee last reviewed bone metabolism agents at the July 2019 meeting. The monoclonal antibody, romosozumab, approved by the United States (US) FDA for the treatment of osteoporosis in postmenopausal women at high risk for fracture was maintained as a non-preferred agent on the PMPDP with PA criteria. In addition, new comparative evidence for existing bone metabolism agents (e.g., bisphosphonates, teriparatide, abaloparatide, and denosumab) for management of osteoporosis and Paget disease was reviewed.
- Preferred drugs on the PMPDP for bone metabolism agents include oral formulations of alendronate, ibandronate and risedronate. Nonpreferred drugs including raloxifene, denosumab, abaloparatide, romosozumab, and teriparatide are subject to PA review. In the third quarter (July 1 to September 30) of 2024, most of the Oregon Health Plan (OHP) Fee-For-Service (FFS) utilization for bone metabolism drugs was due to preferred oral alendronate (99%) and preferred oral ibandronate (1%). The PDL status of the bone metabolism agents is presented in **Appendix 1.** PA criteria are presented in **Appendix 4**.

Background:
Osteoporosis is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, compromised bone strength, and increased risk of fracture.[18] Osteoporosis occurs as part of the aging process or secondary to nutritional deficiency, metabolic disorders or utilization of certain medications. Long-term intake of antiepileptic drugs, aromatase inhibitors, gonadotropin releasing-hormones, glucocorticoids, lithium, thiazolidinediones and proton pump inhibitors is associated with increased risk for secondary osteoporosis.[18] Lifestyle factors that adversely impact the risk for osteoporosis include low calcium intake, vitamin D deficiency, excess vitamin A intake, inadequate physical activity, smoking and alcohol abuse.[18] Other factors that increase the risk for osteoporosis include people with low body weight (< 57.6 kg), rheumatic disease, hyperparathyroidism, malabsorption, diabetes, or inflammatory bowel disease.[19]

Post-menopausal women are at highest risk for osteoporosis.[18] For fracture at any site in women, after adjusting for BMD, weight, and other covariates, non-Hispanic white and Hispanic-American women have the highest risk for fracture, followed by women of Alaska Native/ American Indian, Black/African American, and Asian ethnicity (North American).[20] Although osteoporosis is more prevalent in women, it is estimated that up to one third of new osteoporotic fractures occur in men.[21] In 9 industrialized countries (US, Canada, Australia, Japan, United Kingdom, France, Germany, Italy, and Spain) osteoporosis prevalence at the total hip or hip/spine ranged from 9 to 38% for women and 1 to 8% for men, based on World Health Organization (WHO) criteria.[22] In these countries, osteoporosis affects up to 49 million individuals.[22] Osteoporosis poses a heavy financial burden on patients, with annual direct medical costs estimated at 17 to 20 billion dollars in the US.[23] When projecting to 2040 population estimates, approximately 279 million US women aged 50 years or more will have a 10-year probability of a major osteoporotic fracture.[24]

According to WHO diagnostic classification, osteoporosis is defined by BMD at the hip or lumbar spine that is less than or equal to 2.5 standard deviations (SD) below the mean BMD of a young-adult reference population (i.e., T-score ≤ -2.5).[25] **Table 1** provides a classification of osteopenia and osteoporosis based upon WHO criteria. Measurement of bone density at the hip and lumbar spine with Dual-Energy X-Ray Absorptiometry (DXA) is a surrogate marker used to diagnose osteoporosis. In addition to providing diagnostic information, low BMD is recognized as a major risk factor for fractures.[26] A meta-analysis of prospective cohort studies found that for every one SD decrease in BMD at the femoral neck in women was associated with a relative risk of 2.6 (95% CI 2.0 to 3.5) for hip fracture and 1.6 (95% CI 1.4 to 1.8) for all fractures.[27] A one SD decrease in lumbar spine BMD was associated with a relative risk of 2.3 (95% CI 1.9 to 2.8) for vertebral fracture and 1.5 (95% CI 1.4 to 1.7) for all fractures.[27] The US Preventative Services Task Force (USPSTF) recommends screening women at average risk with a BMD measurement at age 65 years and screening younger women whose fracture risk is equal to or greater than that of a 65-year old white woman with no additional risk factors.[28] The USPSTF concluded that there is insufficient evidence to assess the balance of benefits and harms for screening for osteoporosis in men.[28]

Table 1. World Health Organization Classification of Osteopenia and Osteoporosis[29]

Category	T-Score
Normal	-1.0 or above
Osteopenia	Between -1.0 and -2.5
Osteoporosis	-2.5 or below
Severe Osteoporosis	-2.5 or below with fragility fracture

Bone fractures are the clinical consequence of osteoporosis.[18] Risk of fracture can be assessed with the FRAX Tool, which estimates the 10-year probability of hip fracture and major osteoporotic fracture (spine or forearm fracture) using 9 clinical risk factors including femoral neck BMD.[30] The most common fractures

associated with osteoporosis are vertebral (27%), wrist (19%), hip (14%), and pelvic (7%).[31] Hip fractures result in serious disability related to difficulty with ambulation, inability to perform activities of daily living, and are associated with increased nursing home and rehabilitation hospital admissions.[32] Approximately 20% of patients who experience hip fractures die within a year of injury.[18] According to the FDA, radiographic vertebral fracture is the accepted primary endpoint for fracture trials supporting an osteoporosis indication.[33] Osteoporosis is also diagnosed when an individual experiences a fragility fracture in a location associated with osteoporosis. A fragility fracture is a low-energy fracture that would not normally be expected to result in a broken bone, such as a fall from standing height or less.

Throughout life, older bone is resorbed by osteoclasts and replaced with new bone made by osteoblasts.[34] This process is known as remodeling and is targeted to a particular site that is in need for repair by osteocytes.[34] Osteocytes make RANK-ligand, a cytokine required for osteoclast formation.[20] Osteoclasts breakdown and remove damaged bone. When this system is out of balance, bone loss occurs. Two categories of drugs are used to slow bone loss in osteoporosis: anti-resorptive (osteoclast inhibition) and anabolic (osteoblast stimulation) medications. Anti-resorptive agents include bisphosphonates (e.g., alendronate, ibandronate, risedronate, and zoledronic acid), selective estrogen receptor modulators (raloxifene, bazedoxifene), and denosumab. The parathyroid hormone agonists, teriparatide and abaloparatide, are anabolic agents. Parathyroid hormone regulates calcium homeostasis and stimulates osteoblasts to form new bone.[20] Romosozumab has dual actions, both stimulating bone formation and inhibiting bone resorption.

Hormonal therapies used to manage osteoporosis include estrogen and calcitonin. Estrogen/progestin therapy is approved by the FDA for prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause.[20] Calcitonin prevents bone breakdown, which increases bone density.[20] Calcitonin reduces vertebral fracture occurrence by about 30% in those with prior vertebral fractures but does not reduce the risk of non-vertebral fractures.[20] Because more effective drugs are available for prevention of bone loss and reduction of fracture risk, calcitonin is considered second-line therapy reserved for women in whom alternative osteoporosis treatments are not suitable.[20] A summary of the FDA-approved medications, formulations, and approved populations for management of osteoporosis is provided in **Table 2**.

Table 2. Food and Drug Administration-Approved Drugs for Osteoporosis[35]

Generic Name (BRAND NAME)	Formulation	Approved For*
Bisphosphonates		
Alendronate (FOSAMAX)	Tablet	Women and Men
Ibandronate (BONIVA)	Tablet and Intravenous Injection	Women
Risedronate (ACTONEL, ATELVIA)	Tablet	Women and Men
Zoledronic Acid (RECLAST)	Intravenous Infusion	Women and Men
Estrogen-Related Therapies		
Estrogen (multiple formulations)	Tablet and Transdermal	Women
Raloxifene (EVISTA)	Tablet	Women
Conjugated estrogen/bazedoxifene (DUAVEC)	Tablet	Women
Parathyroid Hormone Analogs		
Abaloparatide (TYMLOS)	Subcutaneous Injection	Women and Men
Teriparatide (FORTEO)	Subcutaneous Injection	Women and Men

RANK-ligand Inhibitor		
Denosumab (PROLIA)	Subcutaneous Injection	Women and Men
Sclerostin Inhibitor		
Romosozumab (EVENITY)	Subcutaneous Injection	Women
Calcitonin Salmon		
Calcitonin (FORTICAL, MIACALCIN)	Nasal Spray, Intramuscular or Subcutaneous Injection	Women
* Study populations included postmenopausal women and men ≥ 50 years of age		

The primary goal of osteoporosis management is to reduce risk of fracture.[36] Guidance from the Endocrine Society (2019) recommends oral bisphosphonates (e.g., weekly alendronate, weekly or monthly risedronate, or monthly ibandronate) as first-line therapy for initial treatment of osteoporosis in post-menopausal women with the following risk factors:

- history of a fracture of the hip or spine; or
- T-score ≤ -2.5, in the lumbar spine, femoral neck, or total hip; or
- T-score between -1 and -2.5 and a 10-year probability ≥ 20% for major osteoporosis fracture or ≥ 3% for hip fracture based on the FRAX tool estimates.[36]

Randomized clinical trials have demonstrated a reduction of vertebral and hip fractures in women who took alendronate, risedronate, and zoledronic acid.[36] Ibandronate reduces the incidence of vertebral fractures, but has not shown to reduce the risk of nonvertebral fractures in postmenopausal women.[36] Alendronate, risedronate, and zoledronic acid have also shown to decrease vertebral fractures in men over 50 years of age and in patients with glucocorticoid-induced osteoporosis.[37] Oral bisphosphonates are contraindicated in people with esophageal disorders (i.e., esophageal stricture, esophageal varices, Barrett's esophagus, achalasia, dysphagia) or known malabsorption due to gastric bypass surgery.[36] Two IV agents are available for people who cannot tolerate oral bisphosphonate therapy: zoledronic acid given once a year and ibandronate given every 3 months.[36] Due to concerns about renal toxicity, bisphosphonates are indicated only for patients with an estimated glomerular filtration rate (eGFR) greater than 30 mL/min for risedronate and ibandronate and greater than 35 mL/min for alendronate and zoledronic acid.[36]

Two rare adverse effects, osteonecrosis of the jaw and atypical femur fractures, are associated with bisphosphonate use.[36] Osteonecrosis of the jaw is more frequently associated with high-dose IV bisphosphonate treatment for cancer (96% of cases reported).[20] For patients taking oral bisphosphonates to manage osteoporosis, the incidence of osteonecrosis of the jaw is estimated to be between 1/10,000 and 1/100,000 and is only slightly higher than the incidence of osteonecrosis of the jaw in the general population.[20] The risk of osteonecrosis of the jaw appears to increase with bisphosphonate treatment beyond 5 years.[20] The incidence of atypical femur fracturs is very low in the general untreated population.[20] Higher risk is associated with Asian ethnicity (North American), lateral bowing of the femur, autoimmune disease, and glucocorticoid use.[20] Atypical femur fractures have been reported in people taking bisphosphonates, denosumab, and romosozumab.[20]

In postmenopausal women with osteoporosis who are at high risk for osteoporotic fractures, denosumab 60 mg subcutaneously (SC) every 6 months is recommended as an alternative to bisphosphonates as initial treatment.[36] Denosumab prevents the formation of osteoclasts by inhibiting the RANK-ligand cytokine. This leads to decreased bone resorption and increased bone mass.[20] Denosumab has been shown to decrease hip, vertebral, and nonvertebral fractures compared with low doses of calcium and vitamin D.[37] Denosumab is FDA-approved to treat postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with osteoporosis at high risk for fracture, to treat glucocorticoid-induced osteoporosis in men and women at high risk

for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[17] Denosumab must be administered by a healthcare professional, it is not licensed for patient self-administration.

In contrast to the bisphosphonates, denosumab may be administered to patients with chronic kidney disease and those with eGFR 35 mL/min or less, if monitored by a nephrologist.[36] The denosumab label carries a black boxed warning that patients with advanced kidney disease are at increased risk for severe hypocalcemia associated with denosumab administration and should be closely monitored.[17] Since denosumab is a monoclonal antibody that suppresses the immune system, its use is associated with elevated risk for serious infections. Denosumab can also have adverse effects on bone and calcium metabolism including atypical femoral fractures and osteonecrosis of the jaw.[17] Osteonecrosis of the jaw has been reported in more than 2% of studied cancer patients taking high doses of denosumab (XGEVA).[20] Discontinuation of denosumab treatment is associated with rapid bone loss that may result in multiple vertebral fractures, especially in patients with a prior vertebral fracture.[20] For this reason, a drug holiday is not appropriate with denosumab. The FDA recommends during periods of suspended denosumab treatment alternate antiresorptive therapy should be considered to maintain gains in bone density.[17] Following denosumab with alendronate has been shown to preserve bone mass, while following denosumab with teriparatide has been associated with bone loss at some skeletal sites.[20]

In postmenopausal women with osteoporosis at high risk of fracture and a low risk of venous thromboembolism (VTE), the selective estrogen receptor modulators raloxifene or bazedoxifene are recommended if bisphosphonates or denosumab are not appropriate.[36] Raloxifene has been shown to reduce the risk of vertebral, but not non-vertebral fractures.[32] Although it reduces breast cancer risk, raloxifene increases the incidence of hot flashes and VTE. Bazedoxifene is only licensed in the US as a combination therapy with conjugated estrogens for the treatment of hot flushes or prevention of osteoporosis in patients for whom other treatments for osteoporosis are not suitable.[36] The combination of conjugated estrogens and bazedoxifene results in an increase in spinal BMD at 1 year compared with conjugated estrogens and a progestin, but less breast tenderness and more amenorrhea.[36] Bazedoxifene in combination with conjugated estrogens has not been shown to reduce the risk of fracture.[36] The 2017 Endocrine Society guidelines recommend estrogen/progestin therapy to prevent fractures in some postmenopausal women at high risk for fractures and less 60 years of age or less than 10 years past menopause who are experiencing vasomotor or climacteric symptoms and cannot take bisphosphonates or denosumab.[38]

For postmenopausal women with osteoporosis who are at very high risk of fracture (i.e., T-score ≤ -3.0 in the absence of fractures or T-score ≤ -2.0 plus a fragility fracture, or multiple fragility fractures) initial treatment with an anabolic agent (teriparatide or abaloparatide) is recommended.[36] In clinical trials, teriparatide and abaloparatide decreased the incidence of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.[13,16] Teriparatide is FDA-approved for the treatment of postmenopausal women at high risk for fracture, men with osteoporosis who have high risk of fracture, treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture, and individuals whose condition has not improved with other osteoporosis therapy.[16] Abaloparatide is FDA-approved for use in postmenopausal women with osteoporosis at high risk for fracture and men with osteoporosis at high risk for fracture, or in patients who have failed or are intolerant to other available osteoporosis therapy.[13]

Due to an increase in the risk of osteosarcoma in growing rodents treated with high doses of teriparatide, the FDA limited treatment duration with teriparatide to 24 months when it was initially approved.[16] However, increased osteosarcoma has not been observed in humans during 15 years of post-marketing studies with teriparatide.[20] The revised teriparatide label now states that use for more than 2 years during a patient's lifetime can be considered if the patient remains at or has returned to having a high risk for fracture.[16] Teriparatide and abaloparatide use should be avoided in settings of increased risk for osteosarcoma including Paget disease, prior radiation therapy involving the skeleton, open epiphyses, history of bone metastases or malignancies, and hereditary disorders

predisposing to osteosarcoma.[13,16] Because the safety and efficacy of abaloparatide have not been evaluated beyond 2 years of treatment, the manufacturer does not recommend use of abaloparatide for more than 2 years during a patient's lifetime.[13]

In 2020, the Endocrine Society updated treatment guidance for osteoporosis in high-risk postmenopausal women to include romosozumab.[9] Romosozumab inhibits sclerostin, a cytokine secreted by osteocytes that blocks bone formation. As a result of romosozumab administration bone formation is increased and bone resorption decreased. Romosozumab treatment is recommended for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures.[9] The recommended dosage is 210 mg SC once a month for 12 months by a health care provider.[9] Duration of romosozumab therapy is limited to 1 year because the bone-forming effect of romosozumab wanes after 12 doses.[39] Follow-on therapy with denosumab and, to a lesser degree, alendronate, preserve or continue to accrue BMD benefits following romosozumab therapy.[20] Romosozumab received FDA approval for treatment of osteoporosis in postmenopausal women at high risk for fracture with a boxed warning stating that it may increase risks for myocardial infarction, stroke, and cardiovascular death.[39] There is a concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification.[40] Women at high risk of cardiovascular disease and stroke should not be considered for romosozumab therapy pending further studies on cardiovascular risk associated with this medication.[9]

Bone density monitoring via DXA can be used to monitor the effects of pharmacologic therapy. While there are a number of approaches to monitoring therapy, there is no consensus on the optimal approach.[41] The American College of Physicians (ACP) recommends against monitoring during therapy, as many women treated with antiresorptive therapy have a reduction in fracture even when BMD does not increase.[42] In general, stability or an increase in BMD is considered to be response to osteoporosis therapy. Significant BMD loss should result in an evaluation of factors contributing to suboptimal therapeutic effect (e.g. adherence) and an assessment of alternative treatment strategies. A minimal clinically important difference has not been identified for changes in BMD associated with medication therapy.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Efficacy and Safety of Zoledronic Acid and Alendronate in the Treatment of Osteoporosis
A 2022 systematic review and meta-analysis evaluated the efficacy and safety of zoledronic acid versus alendronate in patients with osteoporosis.[1] Literature was searched through April 2022 for comparative studies, including RCTs and cohort studies.[1] Eight trials including 1863 participants were identified.[1] Six studies were RCTs and 2 studies were non-randomized parallel comparative studies.[1] The mean age of the patients ranged from 57 to 71 years and 79.5% of the patients were female.[1] The dose of oral alendronate was 70 mg once weekly, and the dose for zoledronic acid was a 5 mg IV infusion administered once yearly.[1] Study

durations ranged from 12 months (4 RCTs), 24 months (3 RCTs), and 36 months for one trial.[1] Six studies compared changes in BMD and 5 studies compared AEs between treatment with zoledronic acid versus alendronate.[1]

Using the Cochrane risk-of-bias tool, 2 trials had a low risk of bias, 3 trials had an unclear risk of bias and one trial had a high risk of bias.[1] Two trials did not clearly report the random sequence generation, 1 trial did not correctly conceal the allocation, 1 trial did not clearly describe the method used for allocation concealment, and 4 trials did not adequately describe the blinding of the outcome assessment.[1] Three trials included bias from using sample sizes of fewer than 100 in each group.[1] The risk of bias of the 2 cohort studies was assessed with Newcastle-Ottawa Scale (NOS). The NOS is used to assess quality of non-randomized studies in meta-analyses. Highest scores are awarded up to 9 points.[43] The 2 studies in this analysis were scored 8 and 9 points, respectively.[1]

Six trials (n=1103) reported data on BMD changes in the lumbar spine after 1 year of treatment, and the pooled estimates did not show a difference between alendronate and zoledronic acid (SMD = −0.03, 95% CI −0.15 to 0.09; P =0.64, I^2=41%; moderate-quality evidence).[1] Pooled estimates from 3 trials (n=597) reported data on lumbar spine BMD changes after 2 years which also did not show a difference between the 2 groups (SMD = 0.16, 95% CI −0.12 to 0.43; P=0.26, I^2=63%; moderate-quality evidence).[1] Five trials (n=889) reported data on total hip BMD changes after 1 year of treatment, and the pooled estimates did not show a difference between alendronate and zoledronic acid (SMD = −0.08, 95% CI −0.31 to 0.14; P=0.4, I^2=64%; moderate-quality evidence).[1] Three trials (n=598), reported data on total hip BMD changes after 2 years, and the pooled estimates showed no difference between the 2 groups (SMD = 0.05, 95% CI −0.21 to 0.32; P=0.7I2, I^2=61; moderate-quality evidence.).[1]

Four trials (n=1256) reported data on safety outcomes, including total AEs, GI AEs (defined as symptoms such as diarrhea, constipation, gastroesophageal reflux, nausea, dyspepsia, flatulence, and abdominal pain), musculoskeletal AEs, influenza-like symptoms, and SAEs. Pooled estimates showed that the alendronate group had lower rates of total AEs (RR=2.27, 95% CI 1.60 to 3.21; P<0.00001) musculoskeletal AEs (RR=4.45, 95% CI 2.90 to 6.83; P<0.00001), and influenza-like symptoms (RR=3.97, 95% CI 2.89 to 5.46; P<0.00001) within 3 days of administration, compared with the zoledronic acid group (moderate-quality evidence for all assessments).[1] The zoledronic acid group had lower rates of GI AEs (RR=0.6, 95% CI 0.44 to 0.83; P=0.002; moderate-quality evidence)) after the third day of infusion, and had similar rates of GI AEs (RR=1.10, 95% CI 0.4 to 3.0; P=0.85; moderate-quality evidence) within 3 days of administration, compared with the alendronate group.[1] The frequency of SAEs was similar in both treatment groups (RR=0.92, 95% CI 0.68 to 1.24; P=0.57; moderate-quality evidence).[1]

In summary, pooled estimates demonstrated that compared with alendronate, zoledronic acid showed no difference in increasing the BMD of the lumbar spine after 1 year or 2 years and the BMD of the total hip after 1 year or 2 years.[1] Higher total AE rates were recorded within 3 days of zoledronic acid infusion, but some AE rates were lower, particularly GI AEs, were noted after 3 days of zoledronic acid infusion compared with oral alendronate taken once a week.[1]

Teriparatide Versus Bisphosphonates for Management of Postmenopausal Osteoporosis

A 2020 systematic review and meta-analysis compared the safety and efficacy of teriparatide with bisphosphonates for management of postmenopausal osteoporosis.[2] Literature was searched through March 2019 for eligible RCTs.[2] Fourteen RCTs with sample sizes ranging from 17 to 680 participants met inclusion criteria.[2] Three bisphosphonates (risedronate, alendronate, and zoledronic acid) were compared to teriparatide. The follow-up duration ranged from 12 to 36 months.[2] The mean age of the participants in the included studies ranged from 60.9 to 75.9 years.[2] Outcomes included occurrence of vertebral and nonvertebral fractures, BMD in the lumbar and femoral neck, and rate of AEs. Three trials were categorized as having an unclear overall risk of bias, and 6 were categorized as having an unclear risk of bias regarding allocation concealment.[2] Two studies were categorized as having a high risk of bias regarding allocation concealment.[2]

Six studies (n=3862) reported the occurrence of vertebral fractures.[2] The teriparatide group had a lower total occurrence of vertebral fractures than the bisphosphonate group (RR= 0.55, 95% CI 0.40 to 0.77; P =0.001; moderate-quality evidence).[2] Six studies (n=2419) reported the occurrence of nonvertebral fractures.[2] The teriparatide group had a lower total occurrence of nonvertebral fractures than the bisphosphonate group (RR=0.65, 95% CI 0.46 to 0.90; P =0.009; moderate-quality evidence).[2]

Eight trials (n=714) provided data about the BMD in the lumbar spine at the final follow-up.[2] Compared with the bisphosphonate group, the teriparatide group improved BMD in the lumbar spine (MD= 1.03%, 95% CI 0.65 to 1.40; P=0.000); moderate-quality evidence.[2] Five studies (n=1084) reported the mean BMD in the femoral neck.[2] Compared with the bisphosphonate group, teriparatide increased the mean BMD in the femoral neck at the final follow-up (MD= 0.85%, 95% CI 0.65 to 1.06; moderate quality evidence).[2] Nine studies (n=2981) reported the incidence of AEs.[2] There was no difference between the teriparatide and bisphosphonate groups in terms of reported AEs (RR = 1.05, 95% CI 0.90 to 1.22; P =0.516; moderate quality evidence).[2]

Romosozumab versus Teriparatide for the Treatment of Postmenopausal Osteoporosis

A 2021 systematic review compared the efficacy and safety of romosozumab with teriparatide for the treatment of postmenopausal osteoporosis.[3] Literature was searched through June 2019.[3] Four RCTs (n=1304) with a duration of 1 year met inclusion criteria.[3] The RCTs were rated at low risk of bias.[3] All patients were over 60 year of age.[3] The primary endpoint was the percentage change in BMD of lumbar spine and total hip from baseline at 6 and 12 months. The secondary endpoints included the percentage change in BMD of femoral neck at 6 and 12 months and the incidence of AEs at 12 months.

Four studies assessed lumbar spine BMD of 620 patients through 12 months and 2 studies assessed 514 patients through 6 months.[3] The results indicated that compared with teriparatide, romosozumab showed better effects in improving BMD of lumbar spine at 6 months (MD = 3.54%, 95% CI 3.13 to 3.94; P<0.001) and at 12 months (MD = 4.93%, 95% CI 4.21 to 5.64; P<0.001; moderate-quality evidence).[3] Four studies assessed total hip BMD of 570 patients through 12 months and 514 patients through 6 months.[3] Compared with teriparatide, romosozumab improved the total hip BMD at 6 months (MD = 2.27%, 95% CI 0.62 to 3.91; P=0.007), and at 12 months (MD = 3.17%, 95% CI 2.68 to 3.65; P<0.001; moderate-quality evidence).[3] The BMD of femoral neck was reported in 2 RCTs, including 514 patients at 6 and 12 months.[3] The percentage change of BMD from baseline in the romosozumab group was improved more than with teriparatide at the femoral neck at 6 and 12 months (MD = 2.30%, 95% CI 0.51 to 4.08; P = 0.01; and MD = 3.04%, 95% CI 2.29 to 3.78, P<0.001, respectively; moderate-quality evidence).[3]

Two studies evaluated the incidence of AEs.[3] At 12 months, injection-site reactions were observed less frequently with romosozumab compared with teriparatide (RR = 2.84, 95% CI 1.22 to 6.59; P=0.02; high-quality evidence).[3] At 12 months, no difference in the incidence of SAEs (RR = 0.78, 95% CI 0.46 to 1.33; P=0.37) or death (RR = 0.61, 95% CI 0.08 to 4.62; P=0.63) were reported between the two groups (moderate-quality evidence for both outcomes).[3]

In summary, based on a meta-analysis of 4 RCTs, romosozumab can increase the BMD of lumbar spine, total hip, and femoral neck, with a lower incidence of injection-site reactions compared with teriparatide.[3] There was no difference in the incidence of death and other serious adverse events.[3]

Denosumab, Teriparatide, and Oral Bisphosphonates in Management of Glucocorticoid-Induced Osteoporosis

A 2023 systematic review explored the safety and efficacy of oral bisphosphonates (risedronate, ibandronate, and alendronate), denosumab, and teriparatide in management of osteoporosis due to continuous use of glucocorticoids.[4] Literature was searched through March 5, 2022 for comparative RCTs lasting at least 12 months.[4] The primary endpoints included vertebral fractures, serious AEs and percentage change in the BMD of the lumbar spine. Secondary endpoints included nonvertebral fractures, AEs, and percent change in the BMD of the hip.[4] Ten RCTs (n=2923) met inclusion criteria.[4] The risk of bias assessment showed low bias

for the included studies.[4] The RCTs ranged from 12 to 36 months in duration, with studies in the denosumab arm all occurring within 12 months.[4] Patients had an average age of 52.8 years, with a range from 35.8 to 78.5 years.[4]

The pooled results of 3 trials involving 209 subjects in the denosumab group indicated that denosumab was superior to oral bisphosphonates at increasing lumbar spine BMD (MD=2.07%, 95% CI 0.97 to 3.17; P=0.0002; high-quality evidence).[4] There was no statistical difference between denosumab and oral bisphosphonates in preventing lumbar vertebral fractures (RR=0.76, 95% CI 0.38 to 1.52; high-quality evidence).[4] The pooled results also indicated that oral bisphosphonates were superior to denosumab at increasing total hip BMD (MD = -0.43%, 95% CI − 0.72 to 0.15; P=0.003; high-quality evidence).[4] No studies evaluated the impact of denosumab on new nonvertebral fractures.[4]

The pooled results of the teriparatide group involving 4 trials of 948 subjects showed that teriparatide was superior to oral bisphosphonates at increasing the lumbar spine BMD (MD=3.89%, 95% CI 3.61 to 4.17; P=0.00001; high-quality evidence).[4] The pooled results of 7 trials involving 1375 subjects in the teriparatide group showed that teriparatide was superior to oral bisphosphonates at reducing new vertebral fractures (MD=0.11%, 95% CI 0.04 to 0.31; P=0.0001, high-quality evidence).[4] Teriparatide was not statistically different from oral bisphosphonates at preventing nonvertebral fractures (RR=1.12, 95% CI 0.75 to 1.67; high-quality evidence).[4] The pooled results of 3 trials involving 856 subjects showed that teriparatide was superior to oral bisphosphonates at increasing the total hip BMD (MD=2.39%, 95% CI 1.47 to 3.32; P<0.00001; high-quality evidence).[4]

Denosumab and teriparatide did not differ in the incidence of AEs (denosumab: RR=1.30, 95% CI 0.75 to 2.33 and teriparatide: RR=1.12, 95% CI 0.65 to 1.94; high-quality evidence).[4] Denosumab and teriparatide did not differ in the incidence of SAEs (denosumab: RR=0.98, 95% CI 0.72 to 1.33; teriparatide: RR=0.66, 95% CI 0.42 to 1.04; high-quality evidence).[4]

Safety of Denosumab Versus Bisphosphonates in Primary Osteoporosis

A 2024 systematic review evaluated the comparative safety of denosumab versus bisphosphonates.[5] Literature was searched through December 2023 for RCTs that compared AEs between denosumab and different bisphosphonates the in patients with primary osteoporosis over 12 to 24 months.[5] Eleven RCTs (n=5545) met inclusion criteria.[5] Seven RCTs compared oral alendronate 35 to 70 mg once a week to denosumab, 2 RCTs compared oral ibandronate 100 to 150 mg once monthly to denosumab, and one study compared IV zoledronic acid 5 mg once a year to denosumab. In all RCTs, denosumab was administered as 60 mg SC every 6 months. All trials had a moderate risk of bias (e.g., reporting bias linked to secondary endpoints and selection bias linked to random allocation).[5]

People who received denosumab experienced less withdrawal due to AEs (RR=0.49; 95% CI 0.34 to 0.71; P=0.0002; moderate-quality evidence) compared to patients who received bisphosphonates.[5] However, no differences in the rates of any AEs, SAEs, or death were found.[5] People who received denosumab experienced more infections than those who received bisphosphonates (RR=1.14; 95% CI 1.02 to 1.27; P=0.02; moderate-quality evidence.[5] No differences were observed between denosumab and bisphosphonates in malignancies, GI disorders, and musculoskeletal disorders.[5] Those who received denosumab experienced fewer vertebral fractures than those who received bisphosphonates (RR=0.54; 95% CI 0.31 to 0.93; P=0.03; moderate-quality evidence).[5] No differences between the two groups were observed in the rates of clinical, major osteoporotic, or nonvertebral fractures.[5] The relatively short duration of the RCTs may have resulted in the absence of reported cases of osteonecrosis of the jaw in 4 trials involving 2215 patients and 3 cases of atypical femoral fractures in 2 trials involving 1357 patients.[5]

After review, 36 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Canadian Agency for Drugs and Technologies in Health: Romosozumab Recommendations

In November 2021, CADTH published recommendations for the use of romosozumab in postmenopausal osteoporosis.[6] CADTH criteria for romosozumab:

- Patients with a history of osteoporotic fracture who are at high risk for future fracture, defined as a 10-year osteoporotic fracture risk ≥ 20% as defined by the FRAX tool.[6]
- The patient must be treatment-naive to osteoporosis medications, except for calcium and/or vitamin D.[6] Note: The currently available evidence demonstrating reduced risk of fracture with romosozumab compared with alendronate is in predominantly treatment-naive patients. There is insufficient evidence to support initiating romosozumab in treatment-experienced patients. The bone-forming mechanism of action of romosozumab also support its use in patients who have not been previously treated with osteoporosis medications.[6]
- Maximum duration of treatment is 12 months.[6]
- Romosozumab should not be prescribed concurrently with other osteoporosis medications except for calcium and/or vitamin D.[6] Note: There is no evidence supporting concurrent treatment with romosozumab and other osteoporosis medications. Concurrent therapy was not permitted in the primary clinical trial, except with calcium and vitamin D.[6]

National Institute for Health and Care Excellence: Romosozumab for Treating Severe Osteoporosis

In May 2022, NICE issued recommendations for the use of romosozumab in severe osteoporosis.[7] Current treatments for people with severe osteoporosis after menopause include bisphosphonates, denosumab or teriparatide.[7] Romosozumab is recommended as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if they have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture).[7]

National Institute for Health and Care Excellence: Abaloparatide for Treating Osteoporosis After Menopause

In August 2024, NICE published guidance for the use of abaloparatide for treating osteoporosis after menopause.[8] People with a very high fracture risk may be offered romosozumab or teriparatide, which can only be taken for a limited time.[8] After taking them, people should have an antiresorptive treatment (such as an oral bisphosphonate) to maintain the BMD gained during anabolic treatment.[8] Romosozumab and teriparatide are not suitable for everyone. For example, romosozumab is not used for people with a history of myocardial infarction or stroke.[8] The NICE committee agreed that, despite current treatment options, there was still an unmet need for people with a very high risk of fracture when romosozumab or teriparatide are not suitable.[8] One consideration is that abaloparatide does not need to be refrigerated (unlike teriparatide) and is taken daily, which some people may prefer over taking a monthly treatment (such as romosozumab).[8] The committee determined abaloparatide is recommended as an option for treating osteoporosis after menopause in women, trans men and non-binary people, only if they have a very high risk of fracture.[8] Very high risk fracture is defined as a fracture probability based on the FRAX tool that exceeds the threshold for intervention by 60%.[8]

Endocrine Society: Pharmacological Management of Osteoporosis in Postmenopausal Women

In February 2020, the Endocrine Society published an update to the 2019 guidance for pharmacologic management of osteoporosis in postmenopausal women.[9] The primary objective was to include evidence assessing the safety and efficacy of romosozumab for fracture prevention in postmenopausal women at very high risk for osteoporotic fracture.[9] The Endocrine Society recommends romosozumab as first-line therapy in patients with multiple vertebral fractures or hip fracture and BMD in the osteoporotic range (severe osteoporosis).[9] This agent also could be considered in individuals who have failed antiresorptive treatments.[9] Two new recommendations were added to the 2019 guidance:

- In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (i.e., low T-score < −2.5 and fractures) or multiple vertebral fractures, the Endocrine Society recommends romosozumab treatment for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures (strong recommendation; moderate-quality evidence).[9] Note: Women at high risk of cardiovascular disease and stroke should not be considered for romosozumab pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke.[44]
- In postmenopausal women with osteoporosis who have completed a course of romosozumab, the Endocrine Society recommends treatment with antiresorptive osteoporosis therapies to maintain bone mineral density gains and reduce fracture risk (strong recommendation; moderate-quality evidence).[9]

American Association of Clinical Endocrinologists/American College of Endocrinology: Diagnosis and Treatment of Postmenopausal Osteoporosis
The AACE and ACE issued a guidance update in 2020 for diagnosis and treatment of postmenopausal osteoporosis.[10] Key updates include:

- Postmenopausal women with osteoporosis can be stratified according to high-risk and very-high-risk features, which includes prior fractures. Stratification of the patient drives the choice of the initial agent as well as the duration of therapy.[10]
- The new anabolic agent romosozumab is included in the treatment algorithm.[10]
- Transitions from therapeutic agents, including denosumab, are further elucidated.[10]

Head-to-head trial data are limited for the bone metabolism agents.[10] Four agents (alendronate, risedronate, zoledronate, and denosumab) have evidence for "broad-spectrum" antifracture efficacy (spine, hip, and nonvertebral fracture risk reduction) and should, in the absence of contraindications, be considered as initial options for most patients who are candidates for treatment.[10] Those who have "high fracture risk" (for example, postmenopausal women with no prior fractures and moderately low T-scores) can be started on oral agents.[10] Injectable agents such as abaloparatide, denosumab, romosozumab, teriparatide, or zoledronate can be considered as initial therapy for those who are at very high fracture risk (for example, older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores), those who have gastrointestinal problems and might not tolerate or absorb oral medication, and for patients who have trouble remembering to take oral medications or coordinating an oral bisphosphonate with other oral medications or daily routine.[10] Patients taking the anabolic agents or denosumab are advised to transition to an oral bisphosphonate when the course of therapy is complete to avoid bone loss after stopping those drugs.[10] Anabolic (teriparatide, abaloparatide) and dual-action (romosozumab) agents may be preferable for patients at very high risk of fracture as initial therapy.[10] For women at high risk of spine fracture but not at risk for hip or nonvertebral fractures, raloxifene may be appropriate and has an additional benefit of reducing the risk of breast cancer.[10] **Table 3** summarizes the recommendations and quality of evidence for the AACE/ACE 2020 guidance for pharmacologic therapy in postmenopausal women with osteoporosis.

Table 3. 2020 AACE/ACE Guidance for Treatment of Postmenopausal Osteoporosis in Women[10]

Recommendations	**Strength of Recommendation; Quality of Evidence**
Who Needs Pharmacologic Therapy?	
Pharmacologic therapy is strongly recommended for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine.	Very Strong; High

Pharmacologic therapy is strongly recommended for patients with a T-score of −2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius.	Very Strong; High
Pharmacologic therapy is strongly recommended for patients with a T-score between −1.0 and −2.5 if the FRAX (or if available, trabecular bone score [TBS]-adjusted FRAX®) 10-year probability for major osteoporotic fracture is ≥ 20% or the 10-year probability of hip fracture is ≥ 3% in the United States.	Very Strong; High
Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than −3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk.	Strong; High
What Medication Should Be Used to Treat Osteoporosis?	
Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic patients with high fracture risk.	Very Strong; High
Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk.	Very Strong; High
Ibandronate or raloxifene may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy.	Strong; High
If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive agent.	Very Strong; High
Until the effect of combination therapy on fracture risk is better understood, AACE/ACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis.	Very Strong; High
Follow treatment with an anabolic agent (e.g., abaloparatide, romosozumab, teriparatide) with a bisphosphonate or denosumab to prevent bone density decline and loss of fracture efficacy.	Very Strong; High
Monitoring Treatment	
Obtain a baseline axial (lumbar spine and hip; 1/3 radius if indicated) DXA and repeat DXA every 1 to 2 years until findings are stable. The 1/3 radius may be considered as an alternate site when the lumbar spine/hip are not evaluable or as an additional site in patients with primary hyperparathyroidism. Continue with follow-up DXA every 1 to 2 years or at a less frequent interval, depending on clinical circumstances.	Strong; Moderate
Consider alternative therapy or reassessment for causes of secondary osteoporosis in patients who have recurrent fractures or significant bone loss while on therapy. Although a single fracture while on therapy is not necessarily evidence of treatment failure, consider 2 or more fragility fractures are evidence of treatment failure.	Strong; High
Duration of Treatment	
Limit treatment with abaloparatide and teriparatide to 2 years and follow abaloparatide or teriparatide therapy with a bisphosphonate or denosumab.	Very Strong; High
Limit treatment with romosozumab to 1 year and follow with a drug intended for long-term use, such as a bisphosphonate or denosumab.	Strong; High
For oral bisphosphonates, consider a bisphosphonate holiday after 5 years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional 5 years if fracture risk remains high.	Strong; Moderate

For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in patients with very high fracture risk.	Strong; Moderate
For zoledronic acid, consider a bisphosphonate holiday after 3 years in high-risk patients or until fracture risk is no longer high, and continue for up to 6 years in very-high-risk patients.	Very Strong; High
The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change of the DXA machine, or an increase in bone turnover markers.	Very Strong; High
A holiday is not recommended for non-bisphosphonate antiresorptive drugs and treatment with such agents should be continued for as long as clinically appropriate.	Very Strong; High
Abbreviations: AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FRAX = fracture risk assessment tool	

Osteoporosis Canada 2023 Guidance

Developed by the Osteoporosis Canada 2023 Guideline Update Group, this updated guideline is intended to assist primary health care professionals in screening community-dwelling postmenopausal females and males aged 50 years and older for the presence of risk factors for osteoporosis and fractures, and provide interventions to optimize skeletal health and fracture prevention.[11] Although most studies were performed in postmenopausal females, the evidence available in males with primary or hypogonadal osteoporosis shows similar effects to females on fractures with bisphosphonates and denosumab; therefore, the evidence from females was used for males but rated as moderate certainty from some indirectness.[11] Overall, bisphosphonate therapy for 3 years results in 20 to 30 fewer vertebral, 10 fewer nonvertebral, and 3 fewer hip fractures per 1000 people than no treatment.[45] Compared with placebo, there may be very few harms with short-term (≤ 3 years) use of oral bisphosphonate therapy, including gastrointestinal events such as esophagitis and ulcers (< 1% difference), and transient flu-like symptoms with zoledronic acid infusions, as well as very uncertain evidence for an increased risk of atrial fibrillation.[46] The benefits of denosumab are similar to those of zoledronic acid, but there may be greater harms with denosumab: 7% more serious adverse events (such as infections requiring hospital admission) than with placebo[47] and 14% and 7% more when compared with alendronate and zoledronic acid, respectively.[48] Delayed dosing or discontinuation of denosumab is associated with rapid bone loss and may lead to vertebral fractures.[49]

In females with higher risk of fractures (e.g., recent severe vertebral fracture, or > 1 vertebral fracture and T-score ≤ −2.5), there is high-certainty evidence that anabolic therapy (teriparatide or romosozumab) results in greater reductions in vertebral, nonvertebral and hip fractures than bisphosphonates (35, 18 and 5 fewer, respectively, per 1000 people).[50] This evidence is indirect in males and therefore of moderate certainty.[11] Stopping anabolic treatment without subsequent antiresorptive therapy risks the loss of bone density gains.[11] For most people, the negative aspects of teriparatide, romosozumab or denosumab (such as injection schedules and the risks associated with and need for transition therapy when stopping the medication) probably outweigh the benefits compared with bisphosphonates.[11] However, for people at higher risk of fractures, the benefits may outweigh these downsides.[11] Recommendations and certainty of evidence for osteoporosis assessment and treatment are summarized in **Table 4**.

Table 4. Recommendations for Osteoporosis Assessment and Treatment[51]

Recommendations	**Strength Of Recommendation and Certainty of Evidence**
Fracture Risk Assessment and Treatment Initiation	
We recommend initiating pharmacotherapy in postmenopausal females and males aged ≥ 50 years who: a) have had previous hip, vertebra or ≥ 2 osteoporosis-related fractures *OR*	Strong recommendation. -High-certainty evidence (females: a and c)

b) have a 10-yr major osteoporotic fracture risk ≥ 20% *OR* c) are aged ≥ 70 years and have a T-score ≤ −2.5 (femoral neck, total hip or lumbar spine).	-Moderate-certainty evidence (females: b; males: a, b and c)
We suggest initiating pharmacotherapy in postmenopausal females and males aged ≥ 50 years who: a) have a 10-yr major osteoporotic fracture risk between 15% and 19.9% *OR* b) are aged < 70 years and have a T-score ≤ −2.5 (femoral neck, total hip or lumbar spine). Remark: The risk of subsequent fracture is greatest shortly after a fracture, and greater consideration should be given to a fracture in the last 2 years.	Conditional recommendation. -Moderate-certainty evidence (females) -Very low-certainty evidence (males)
Pharmacologic Interventions	
For people who meet criteria for initiation of pharmacotherapy, we recommend bisphosphonates (alendronate, risedronate or zoledronic acid). Remark: Oral bisphosphonates may be preferred, as access to an infusion center may be a barrier to zoledronic acid.	Strong recommendation. -High-certainty evidence (females) -Moderate-certainty evidence (males)
For people meeting criteria for initiation of pharmacotherapy who have contraindications, substantial intolerance or barriers to bisphosphonates, we suggest denosumab. Remark: Despite the benefits of denosumab, a careful assessment of indications is required because of the risk of rapid bone loss and vertebral fractures with delayed dosing or discontinuation of denosumab. It is important to communicate the need for commitment to long-term therapy and the need to transition to alternative antiresorptive therapy if discontinuing denosumab. Denosumab may be preferred when there is a high burden of oral medications, gastrointestinal intolerance, contraindication to oral bisphosphonates or barriers to accessing intravenous zoledronic acid.	Conditional recommendation. -High-certainty evidence (females) -Moderate--certainty evidence (males)
For people meeting criteria for initiation of pharmacotherapy who have had a recent severe vertebral fracture, or > 1 vertebral fracture, AND a T-score ≤ −2.5, we suggest seeking advice from a consultant with expertise in osteoporosis about anabolic therapy (teriparatide or romosozumab). Remark: “Recent fracture” is defined as a fracture occurring within the past 2 year, and “severe vertebral fracture” as vertebral body height loss of > 40%. Clinicians may seek advice from radiologists to clarify the degree of severity of the vertebral fracture. The choice of anabolic therapy may depend on feasibility of injection schedule.	Conditional recommendation. -High-certainty evidence (females) -Moderate-certainty evidence (males)
For postmenopausal females initiating pharmacotherapy who have contraindications or substantial intolerance to, or who choose not to take other suggested therapies, we suggest raloxifene rather than no treatment. Remark: Raloxifene should be used only in those who are not at high risk of venous thromboembolism.	Conditional recommendation; moderate-certainty evidence

American College of Rheumatology: Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

The 2017 ACR guidance for prevention and treatment of glucocorticoid-induced osteoporosis for patients with rheumatic or nonrheumatic conditions receiving greater than 3 months treatment with glucocorticoids ≥ 2.5 mg daily was updated in 2022.[12] For adults beginning or continuing greater than 3 months of glucocorticoid treatment, ACR strongly recommends initial assessment of fracture risks with clinical fracture assessment, BMD with vertebral fracture assessment or spinal x-ray, and FRAX Tool assessment if ≥ 40 years old.[12] For adults at medium, high, or very high fracture risk, ACR strongly recommends pharmacologic treatment.[12] Choice of oral or IV bisphosphonates, denosumab, or parathyroid hormone analogs should be made by shared decision-making.[12]

Anabolic agents are conditionally recommended as initial therapy for those with high and very high fracture risk.[12] Notably, most evidence reviewed in this guideline is downgraded for indirectness because 1) identified studies in glucocorticoid-induced osteoporosis rely on the surrogate fracture risk marker, BMD, because they were not powered for fracture outcomes and 2) available fracture data were exclusively or predominantly from general osteoporosis studies.[12] A summary of the ACR recommendation and certainty of evidence is presented in **Table 5**.

Table 5. ACR Recommendations for Assessment and Treatment of Glucocorticoid-Induced Osteoporosis[12]

Recommendation	Strength of Recommendation; Certainty of Evidence
Fracture Risk Assessment	
For all adults (≥18 years old) initiating or continuing GC therapy ≥ 2.5 mg/day for > 3 months, we strongly recommended initial clinical fracture risk assessment including symptomatic and asymptomatic fracture history, FRAX (age ≥ 40 only), and BMD with VFA or spine x-rays over no assessment.	Strong; Low
For adults continuing chronic GC ≥ 2.5 mg/day but < 7.5 mg/day and assessed as low fracture risk, who were not recommended to start therapy, or moderate fracture risk who chose not to start OP therapy (except calcium and vitamin D), we strongly recommend fracture risk reassessment every 1 to 2 years.	Strong; Low
For adults continuing chronic GC ≥2.5 mg/day and assessed as moderate, high, or very high fracture risk who are continuing OP therapy ≥1 year, we strongly recommend fracture risk re-assessment every 1 to 2 years over no risk reassessment.	Strong; Low
For adults stopping GC and remaining at moderate, high, or very high fracture risk, we strongly recommend continuing OP therapy.	Strong; Low
Treatment For Adults Taking Prednisone ≥ 2.5 mg/day for > 3 months	
For adults ≥ 40 years with high or very high fracture risk, we strongly recommend OP therapy over no treatment. Agents to use include oral bisphosphonates, IV bisphosphonates, denosumab, raloxifene, abaloparatide, teriparatide, or romosozumab.	Strong; Low
For adults ≥40 years with very high fracture risk, we conditionally recommend abaloparatide or teriparatide over anti-resorptive (denosumab, bisphosphonate) treatment.	Conditional; Low
For adults ≥40 years with high fracture risk, we conditionally recommend denosumab, abaloparatide, or teriparatide over bisphosphonate treatment.	Conditional; Low
For adults ≥40 years with high or very high fracture risk, we strongly recommend oral bisphosphonate over no treatment.	Strong; Low
For adults ≥40 years with high or very high fracture risk, we conditionally recommend using romosozumab or raloxifene in patients intolerant of other agents.	Conditional; Very Low
For adults ≥40 years with high or very high fracture risk, we conditionally recommend against using two different OP medications.	Conditional; Very Low
For adults ≥40 years with moderate fracture risk, we conditionally recommend against romosozumab except for in patients intolerant of other agents, due to risk of myocardial infarction, stroke, or death.	Conditional; Very Low
Adults <40 years with moderate fracture risk, we conditionally recommend oral or IV bisphosphonates, denosumab, or abaloparatide/teriparatide therapy.	Conditional; Low to Very Low
Adults <40 years with moderate fracture risk, we conditionally recommend against using romosozumab due to risk of myocardial infarction, stroke, or death.	Conditional; Very Low

For adults taking OP therapy and discontinuing GC therapy, with no new fragility fracture and a current BMD T-score ≥ −2.5, we strongly recommended stopping current OP therapy and continuing calcium and vitamin D. However, sequential therapy is strongly recommended after stopping denosumab, teriparatide, abaloparatide or romosozumab.	Strong; Low
Treatment For Adults Receiving High-Dose GC (Initial Dose ≥ 30 mg/day for > 30 days Or Cumulative Dose ≥ 5 g In 1 Year)	
We conditionally recommend treating with abaloparatide/teriparatide over anti-resorptives.	Conditional; Low
Oral bisphosphonates are strongly recommended over no treatment.	Strong; Low
IV bisphosphonates and denosumab are conditionally recommended over no treatment.	Conditional; Low
Raloxifene and romosozumab are conditionally recommended in those intolerant of other agents.	Conditional; Low
Children Ages 4–17 Years Treated with GCs for >3 Months (Low and Moderate Risk)	
We conditionally recommend against starting oral or IV bisphosphonates due to low risk of OP fractures in this age group.	Conditional; Very Low
Children Ages 4-17 Years with An Osteoporotic Fracture Who Are Continuing Treatment With GCs at a Dose of ≥ 0.1 Mg/Kg/Day For > 3 Months (High Risk)	
We conditionally recommend treating with an oral or IV bisphosphonate.	Conditional: Very Low
Abbreviations: ACR = American College of Rheumatology; bone mineral density; FRAX = Fracture Risk Assessment; GC = glucocorticoid; IV = intravenous; OP = osteoporosis; VFA = vertebral fracture assessment	

New Formulations and Indications:

- December 2022: TYMLOS (abaloparatide) received an expanded FDA indication to increase bone density in men with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy.[13] Prior to the expanded indication, abaloparatide was only approved for use in women. The safety and efficacy of abaloparatide in men were evaluated in a 12 month, double blind, placebo-controlled RCT conducted in 228 patients aged 42 to 85 years.[13] At baseline, the mean T-scores were -2.1 at the lumbar spine, -2.1 at the femoral neck, and -1.7 at the total hip.[13] Patients took daily supplemental calcium (500 to 1000 mg) and vitamin D (400 to 800 IU) during the trial.[13] The primary endpoint was the percent change from baseline in lumbar spine BMD at 12 months in patients treated with abaloparatide 70 mg SC once a day compared to placebo.[13] Treatment with abaloparatide for 12 months increased BMD compared to placebo at the lumbar spine (difference: 7.3%, 99% CI 5.1 to 9.6); total hip (difference: 2.1%, 99% CI 1.0 to 3.2) , and femoral neck (difference: 2.8%, 99% CI 1.4 to 4.2).[13] Reported AEs in men included injection site reactions (i.e., erythema, swelling, pain),dizziness, arthralgia, abdominal distension, diarrhea, nausea, and bone pain.[13]

- March 2024: A PROLIA biosimilar, JUBBONTI (denosumab-bbdz) received FDA-approval for treatment of postmenopausal women with osteoporosis at high risk for fracture, treatment to increase bone mass in men with osteoporosis at high risk for fracture, treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture, treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and treatment to increase bone mass in women at high risk for fracture receiving aromatase inhibitor therapy for breast cancer.[14] The dose is 60 mg SC every 6 months administered by a health care provider.[14] Like PROLIA, JUBBONTI carries a black box warning for the risk of severe hypocalcemia in patients with advanced kidney disease.[14]

New FDA Safety Alerts:

Table 6. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles
Denosumab	PROLIA[17]	4/2020	Warnings and Precautions	Following discontinuation of denosumab treatment, fracture risk increases, including the risk of multiple vertebral fractures. Treatment with denosumab results in significant suppression of bone turnover and cessation of denosumab treatment results in increased bone turnover above pretreatment values 9 months after the last dose of denosumab. Bone turnover then returns to pretreatment values 24 months after the last dose of denosumab.
Denosumab	PROLIA[17]	5/2022	Warnings and Precautions	The safety and effectiveness of PROLIA in pediatric patients have not been established. PROLIA is not approved for use in pediatric patients. In clinical trials, hypercalcemia has been reported in pediatric patients with osteogenesis imperfecta treated with denosumab products. Some cases required hospitalization and were complicated by acute renal injury.
Denosumab	PROLIA[17]	1/2024	Boxed Warning	**Severe Hypocalcemia in Patients with Advanced Kidney Disease** Patients with advanced chronic kidney disease (eGFR <30 mL/min/1.73 m^2), including dialysis-dependent patients, are at greater risk of severe hypocalcemia following denosumab administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia in these patients. Prior to initiating denosumab in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with denosumab in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD.
Teriparatide	FORTEO[16]	11/2020	**Removed** Boxed Warning Regarding Risk of Osteosarcoma. Warnings and Precautions Section Updated.	Osteosarcoma has been reported in patients treated with teriparatide in the post-marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of teriparatide use. Avoid teriparatide use in patients with at increased baseline risk of osteosarcoma including: • Open epiphyses (pediatric and young adult patients) (Teriparatide is not approved in pediatric patients.) • Metabolic bone diseases other than osteoporosis, including Paget's disease of the bone. • Bone metastases or a history of skeletal malignancies.

				• Prior external beam or implant radiation therapy involving the skeleton.
Abaloparatide	TYMLOS[13]	12/2021	**Removed** Boxed Warning Regarding Risk of Osteosarcoma. Warnings and Precautions Section Updated.	Osteosarcoma has been reported in patients treated with a PTH-analog in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of abaloparatide and/or use of a PTH-analog. Avoid abaloparatide use in patients with (these patients are at increased baseline risk of osteosarcoma): • Open epiphyses (pediatric and young adult patients) (abaloparatide is not approved in pediatric patients). • Metabolic bone diseases other than osteoporosis, including Paget's disease of the bone. • Bone metastases or a history of skeletal malignancies. • Prior external beam or implant radiation therapy involving the skeleton. • Hereditary disorders predisposing to osteosarcoma.

Randomized Controlled Trials:
A total of 196 citations were manually reviewed from the initial literature search. After further review, 196 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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15. WYOST (denosumab-bbdz) subcutaneous injection. Prescribing Information. Princeton, NJ; Sandoz, Inc. March 2024.
16. FORTEO (teriparatide) subcutaneous injection. Prescribing Information. Indianapolis, IN. Eli Lilly and Company. July 2024.
17. PROLIA (denosumab) subcutaneous injection. Prescribing Information. Thousand Oaks, CA; Amgen Inc. Marc 2024.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
risedronate sodium	ACTONEL	ORAL	TABLET	Y
alendronate sodium	ALENDRONATE SODIUM	ORAL	TABLET	Y
alendronate sodium	FOSAMAX	ORAL	TABLET	Y
ibandronate sodium	IBANDRONATE SODIUM	ORAL	TABLET	Y
risedronate sodium	RISEDRONATE SODIUM	ORAL	TABLET	Y
calcitonin, salmon, synthetic	CALCITONIN-SALMON	INJECTION	VIAL	N
calcitonin, salmon, synthetic	MIACALCIN	INJECTION	VIAL	N
ibandronate sodium	IBANDRONATE SODIUM	INTRAVEN	SYRINGE	N
calcitonin, salmon, synthetic	CALCITONIN-SALMON	NASAL	SPRAY/PUMP	N
alendronate sodium	ALENDRONATE SODIUM	ORAL	SOLUTION	N
raloxifene HCl	EVISTA	ORAL	TABLET	N
alendronate sodium/vitamin D3	FOSAMAX PLUS D	ORAL	TABLET	N
raloxifene HCl	RALOXIFENE HCL	ORAL	TABLET	N
risedronate sodium	ATELVIA	ORAL	TABLET DR	N
risedronate sodium	RISEDRONATE SODIUM DR	ORAL	TABLET DR	N
alendronate sodium	BINOSTO	ORAL	TABLET EFF	N
teriparatide	FORTEO	SUBCUT	PEN INJCTR	N
teriparatide	TERIPARATIDE	SUBCUT	PEN INJCTR	N
abaloparatide	TYMLOS	SUBCUT	PEN INJCTR	N
romosozumab-aqqg	EVENITY	SUBCUT	SYRINGE	N
romosozumab-aqqg	EVENITY (2 SYRINGES)	SUBCUT	SYRINGE	N
denosumab	PROLIA	SUBCUT	SYRINGE	N
zoledronic acid/mannitol-water	RECLAST	INTRAVEN	PGGYBK BTL	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	INTRAVEN	PGGYBK BTL	
zoledronic ac/mannitol/0.9NaCl	ZOLEDRONIC ACID	INTRAVEN	PIGGYBACK	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	INTRAVEN	PIGGYBACK	
pamidronate disodium	PAMIDRONATE DISODIUM	INTRAVEN	VIAL	
zoledronic acid	ZOLEDRONIC ACID	INTRAVEN	VIAL	
denosumab	XGEVA	SUBCUT	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 02, 2024

1	Osteoporosis, Postmenopausal/ or Osteoporosis/ or osteoporosis.mp.	107186
2	Risedronate Sodium/	1281
3	Alendronate/	4153
4	ibandronate.mp.	1149
5	Calcitonin/	16331
6	Raloxifene Hydrochloride/	2838
7	Teriparatide/	2333
8	Denosumab/	2593
9	zoledronic acid.mp.	6044
10	pamidronate.mp.	3330
11	abaloparatide.mp.	302
12	romosozumab.mp.	530
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	36841
14	1 and 13	10756
15	limit 14 to humans	9612
16	limit 15 to (clinical trial, phase iii or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or systematic review)	1467
17	limit 16 to yr.="2019 -Current"	196

Appendix 3: Key Inclusion Criteria

Population	Postmenopausal women and men ≥ 50 years of age with osteoporosis
Intervention	Bisphosphonates, denosumab, abaloparatide, teriparatide, and romosozumab
Comparator	Bisphosphonates, denosumab, abaloparatide, teriparatide, and romosozumab
Outcomes	Changes in bone mineral density at lumbar spine, hip or femoral neck and incidence of vertebral and nonvertebral fractures.
Timing	6 to 36 months, depending on medication
Setting	Outpatient

Bone Metabolism Agents

Goal(s):

- To ensure appropriate drug use and safety of bone metabolism agents by authorizing utilization in specified patient populations.

Length of Authorization:

- 12 to 24 months

Requires PA:

- Non-preferred drugs for pharmacy claims
- Physician administered claims for romosozumab

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Definition for Very High Risk of Fracture

Osteoporosis in post-menopausal women and men at very high risk of fracture with: • Multiple fragility fractures OR • T score ≤ - 2.0 plus a fragility fracture OR • T-score ≤ - 3.0 in the absence of fractures OR • Fractures sustained while on approved osteoporosis therapy OR • Fractures while on medications causing skeletal harm (e.g. long-term glucocorticoids) OR • High risk for falls or history of injurious falls and very high fracture probability with a FRAX Score > 30% for major osteoporosis fracture or > 4.5%
Abbreviation: FRAX = Fracture Risk Assessment Tool

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of cancer-related issues?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Is this a request for continuation of therapy for those previously approved by the FFS program for abaloparatide, teriparatide, or romosozumab?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed to receive benefit from an oral bisphosphonate (alendronate, risedronate, or ibandronate), have contraindications to these treatments, or have very high risk of fracture (Table 1)? (document contraindication, if any)	**Yes:** Go to #7	**No:** Go to #5
5. Is the request for a non-preferred bisphosphonate, calcitonin or zoledronic acid?	**Yes:** Go to #6	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of oral bisphosphonate.
6. Will the prescriber consider a change to a preferred product? <u>Note</u>: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months.
7. Is the request for denosumab?	**Yes:** Go to #8	**No:** Go to #11

Approval Criteria		
8. Is denosumab being prescribed for one of the following reasons: • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Treatment to increase bone mass in men with osteoporosis at high risk for fracture • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer	**Yes:** Go to #9	**No:** Pass to RPh; Deny; medical appropriateness
9. Have labs been obtained to assess renal function?	**Yes:** Document date and results here_____ Go to #10	**No:** Pass to RPh; Deny; medical appropriateness
10. If estimated glomerular filtration rate (eGFR) is less than 30 mL/min is there documentation of a calcium monitoring plan? Note: Denosumab has a black box warning regarding the risk of severe hypocalcemia following denosumab administration in patients with advanced chronic kidney disease (eGFR <30 mL/min), including dialysis-dependent patients. Treatment with denosumab in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of chronic kidney disease.	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness
11. Is the request for raloxifene in a postmenopausal woman with osteoporosis?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Is the patient at increased risk for thromboembolism (DVT or PE) or stroke due to coronary heart disease?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Inform prescriber boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months
13. Is the request for teriparatide or abaloparatide?	**Yes:** Go to #14	**No:** Go to #16
14. Is the is the patient at very high risk for fracture (see **Table 1**)?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Does the patient meet one of the following conditions: a. Concomitant bisphosphonate; or b. Pediatric or young adult with open epiphyses; or c. History of osteosarcoma or skeletal malignancies; or d. Metabolic bone disease other than osteoporosis, such as Paget's disease; or e. Underlying hypercalcemic disorders; or f. Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 24 months (depending on when therapy was initiated.) Note: Teriparatide and abaloparatide are only FDA approved for a total duration of therapy of 2 years but use for more than 2 years during a patient's lifetime can be considered if the patient remains at or has returned to having a high risk for fracture.
16. Is the request for romosozumab and is the patient a postmenopausal woman with osteoporosis and T-score ≤ -2.5 or a history of fracture?	**Yes:** Go to #17	**No:** Pass to RPh; Deny; medical appropriateness

Approval Criteria		
17. Has the patient had a myocardial infarction or stroke within the past year?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months maximum. Note: FDA has only approved use of romosozumab for a total of 12 months. If continued osteoporosis therapy is warranted, continue therapy with an anti-resorptive agent (e.g. bisphosphonates or denosumab).

Renewal Criteria		
1. Is the request to continue romosozumab beyond 1 year of total therapy?	**Yes**: Pass to RPh; Deny; medical appropriateness.	**No**: Go to # 2
2. Is the request to continue abaloparatide or teriparatide beyond 2 years of total therapy?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness**.**
3. Does the prescriber attest that the patient remains at or has returned to having a high risk for fracture?	**Yes:** Approve for 12 months. Document provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: *12/24 (DM); 7/19; 3/18; 7/16; 9/10*
Implementation: *1/1/25; 11/1/19; 4/16/18; 8/16, 1/1/11*