

INTRODUCTION

- Osteoporosis is the most common bone disease and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture (*Cosman et al 2014*). The National Osteoporosis Foundation (NOF) estimated that in 2010, 12 million people in the United States had osteoporosis, and more than 2 million osteoporosis-related fractures occur annually, with more than 70% of these occurring in women. Age is an important risk factor for bone loss; by age 60, half of white women have osteopenia or osteoporosis (*Camacho et al 2016*).
- According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person. Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score (*World Health Organization 1994, 2007*).
- Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis, and low bone mass is the primary indicator of fracture risk (*Camacho et al 2016*). Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death (*Cosman et al 2014*).
- To decrease the risk of fractures, the general population should be advised to consume 1200 mg of calcium and 800 to 1000 mg of vitamin D per day from dietary sources or supplements. All individuals should also participate in regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Strategies for preventing falls should be implemented when needed. Smoking cessation and avoidance of excessive alcohol intake are other initiatives to prevent osteoporosis (*Camacho et al 2016, Cosman et al 2014*).
- Bisphosphonates are used to prevent and treat postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis, and Paget's disease. There are several bisphosphonates approved for treatment of Paget's disease and malignancy-induced bone conditions, but not for osteoporosis. These agents include Aredia (pamidronate) zoledronic acid (*Zometa*) and Didronel (etidronate) (*Micromedex 2020*).
- Other agents used to treat osteoporosis include calcitonin (Miacalcin), an estrogen agonist/antagonist (Evista), the parathyroid hormone analogs (Forteo, *Bonsity*, and Tymlos), the receptor activator of nuclear factor K-B ligand inhibitor (Prolia), and the sclerostin inhibitor (Evenity). These agents also have other indications, such as: reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis; reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; treatment of Paget's disease; treatment of hypercalcemia; treatment of glucocorticoid-induced osteoporosis at high risk of fracture; treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer; and treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Another parathyroid hormone analog is Natpara, which is an injectable form of recombinant parathyroid hormone. Natpara is FDA approved for the treatment of hypocalcemia in patients with hypoparathyroidism as an adjunct to calcium and vitamin D supplementation (*Micromedex 2020*).
- Other agents in the estrogen agonist/antagonist class include Clomid or Serophene (clomiphene), tamoxifen, Fareston (toremifene), and Ospheña (ospemifene). These agents have different indications, including: to induce ovulation in appropriately selected anovulatory women desiring pregnancy; the treatment and prevention of breast cancer; and treatment of women experiencing moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause (*Micromedex 2020*). These agents will not be discussed in this review.
- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab (Prolia), is also available as Xgeva. This product is approved to prevent skeletal-related events in patients with bone metastases from solid tumors, treat hypercalcemia of malignancy refractory to bisphosphonates, and treat adults with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (*Micromedex 2020*). It will not be further discussed in this review. The Food and Drug Administration (FDA) has approved estrogen/hormone therapy for the prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. The Women's Health Initiative (WHI) found that 5 years of hormone therapy in the form of Prempro (conjugated estrogen/medroxyprogesterone) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% (*Writing Group for the WHI 2002*). However, the study also reported increased risks of myocardial infarction, stroke, invasive

breast cancer, pulmonary emboli, and deep vein thrombosis during 5 years of treatment. It is now recommended to use estrogen/hormone therapy in the lowest effective doses for the shortest duration necessary. Thus, these agents are not recommended for long-term prevention and will not be further discussed in this review.

- Medispan Class: Bone Density Regulators; Hormone Receptor Modulators

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bisphosphonates	
Actonel (risedronate)	✓
Atelvia (risedronate, delayed release tablet)	✓
Binosto (alendronate, effervescent tablet)	-
Boniva (ibandronate)	✓
Didronel (etidronate)*	✓
Fosamax (alendronate)	✓
Fosamax Plus D (alendronate/cholecalciferol)	-
Reclast (zoledronic acid)	✓
Calcitonin	
Miacalcin (calcitonin salmon) nasal solution*	✓
Estrogen Agonist-Antagonist	
Evista (raloxifene)	✓
Parathyroid Hormone Analogs	
Forteo, Bonsity (teriparatide)	-
Natpara (recombinant parathyroid hormone)**	-
Tymlos (abaloparatide)	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors	
Prolia (denosumab)	-
Sclerostin Inhibitor	
Evenity (romosozumab)	-

*Brand etidronate and calcitonin nasal spray are no longer marketed; products only available generically

**In September 2019, the manufacturer recalled this product due to concerns of the presence of rubber particulates. According to a January 21, 2020 update from the manufacturer, there is an expected delay of at least 1 year before the product becomes available in the US (*Takeda Pharmaceuticals 2020*).

(*Drugs @FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	alendronate* (Binosto, Fosamax, Fosamax Plus D)	etidronate (Didronel)	ibandronate* (Boniva)	risedronate* (Actonel, Atelvia)*	zoledronic acid* (Reclast)
Treatment of postmenopausal osteoporosis	✓		✓	✓	✓
Prevention of postmenopausal osteoporosis	✓ (Fosamax only)		✓ (tablets only)	✓ (Actonel only)	✓
Treatment to increase bone mass in men with osteoporosis	✓			✓ (Actonel only)	✓

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Treatment of glucocorticoid-induced osteoporosis	✓ (Fosamax only)			✓ (Actonel only)	✓
Prevention of glucocorticoid-induced osteoporosis				✓ (Actonel only)	✓
Treatment of Paget's disease	✓ (Fosamax only)	✓		✓ (Actonel only)	✓
Treatment of heterotopic ossification due post hip replacement or spinal cord injury		✓			

* Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of Actonel, Reclast and Boniva (tablets) for the treatment of osteoporosis are based on clinical data of 3 years duration. The safety and effectiveness of Atelvia and Boniva injection for the treatment of osteoporosis are based on clinical data of 1 year duration. The safety and effectiveness of Binosto and Fosamax/Fosamax PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

(Prescribing information: Actonel 2019, alendronate solution 2019, Atelvia 2015, Binosto 2019, Boniva injection 2019, Boniva tablets 2016, etidronate 2017, Fosamax 2019, Fosamax Plus D 2019, Reclast 2017)

Table 3: FDA Approved Indications for Calcitonins, Estrogen Agonist-Antagonist, and Receptor Activator of Nuclear Factor K-B Ligand Inhibitor

Indication	Evista (raloxifene)	Evenity (romosozumab)	Miacalcin (calcitonin)	Prolia (denosumab)
Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause for whom alternative treatments are not suitable			✓	
Treatment of postmenopausal osteoporosis	✓			
Treatment of postmenopausal osteoporosis at high risk of fracture		✓		✓
Prevention of postmenopausal osteoporosis	✓			
Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis	✓			
Reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer	✓			
Treatment of Paget's disease			✓ (injection only)	
Treatment of hypercalcemia			✓ (injection only)	
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture				✓
Treatment to increase bone mass in men receiving androgen deprivation therapy for prostate cancer				✓
Treatment to increase bone mass in women receiving adjuvant aromatase inhibitor therapy for breast cancer				✓
Treatment to increase bone mass in men with osteoporosis at high risk for fracture				✓
Treatment of osteoporosis in patients who have failed or are intolerant to other therapies		✓		

(Prescribing Information: Calcitonin salmon nasal spray 2019, Evenity 2019, Evista 2019, Miacalcin injection 2018, Prolia 2019)

Table 4: FDA Approved Indications for Parathyroid Hormone Analogs

Indication	Forteo, Bonsity (teriparatide)	Natpara (recombinant parathyroid hormone)	Tymlos (abaloparatide)
Adjunct to calcium and vitamin D for hypocalcemia due to hypoparathyroidism		✓	
Treatment of postmenopausal osteoporosis at high risk of fracture	✓		✓
Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture	✓		
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture	✓		

(Prescribing Information: **Bonsity** 2019, **Forteo** 2019, **Natpara** 2018, **Tymlos** 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Bisphosphonates

- Clinical trials for bisphosphonates included within this review evaluate their efficacy in increasing BMD and/or decreasing bone turnover markers (BTMs). Regardless of whether a patient is being treated for osteoporosis or has osteopenia and is receiving preventative treatment, the goal of therapy is to increase BMD and reduce the risk of fractures. Since both the treatment and prevention of osteoporosis focus on the same therapeutic outcomes, the data supporting the use of bisphosphonates for these indications has been summarized together.
- Head-to-head trials have resulted in conflicting data when comparing the efficacy among bisphosphonates. Data from trials and a meta-analysis specifically examining fractures indicate that bisphosphonates are efficacious and significantly lower the risk of developing fractures in both vertebral and nonvertebral areas, compared to placebo in both men and women (*Black et al 1996, Kanis et al 2005, Liu et al 2018, Lyles et al 2007, Ringe et al 2009, Sawka et al 2005*). Several meta-analyses have found that etidronate is effective for reducing the risk of vertebral fractures but not non-vertebral fractures when compared to placebo or calcium and vitamin D in postmenopausal women with osteoporosis (*Cranney et al 2001, Wells et al 2008*). Some evidence suggests that alendronate results in greater increases of BMD when compared to risedronate (*Bonnick et al 2006, Reid et al 2006, Reid et al 2008*). In an observational study, treatment with risedronate resulted in a greater reduction in the risk of nonvertebral and hip fractures compared to alendronate (*Silverman et al 2007*). In a small randomized trial (N = 50), once weekly alendronate demonstrated similar efficacy to daily risedronate (*Sarioglu et al 2006*). Zoledronic acid and alendronate 70 mg weekly had comparable increases in lumbar BMD over 1 year in a study with postmenopausal women with osteoporosis and over 2 years in a study of men with osteoporosis (*McClung et al 2007, Orwoll et al 2010*). Ibandronate was shown to reduce vertebral fractures more than alendronate and risedronate in 1 trial; however, 2 other trials demonstrated similar efficacy with ibandronate vs alendronate (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
 - Clinical trials have also established the efficacy of alendronate, risedronate, and zoledronic acid in patients with glucocorticoid-induced osteoporosis (*Mok et al 2008, Okada et al 2008, Reid et al 2009*). In a meta-analysis of 10 trials of alendronate in glucocorticoid-induced osteoporosis, the risk of fracture was not significantly affected despite significant improvements in BMD of the lumbar spine and femoral neck (*Wang et al 2018*). Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. One such trial demonstrated that zoledronic acid is more effective than risedronate for the treatment of Paget's disease (*Reid et al 2005*).

- Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another and should be considered first-line for the treatment and prevention of osteoporosis.
- In terms of safety, a meta-analysis measuring bisphosphonate gastrointestinal (GI) adverse events (AEs) concluded that patients treated with zoledronic acid had a higher probability of any GI AE and nausea. However, etidronate had the highest probability of discontinuation due to GI AEs compared to the other oral formulations, risedronate was associated with a greater incidence of serious GI AEs, and alendronate was associated with a greater incidence of upper GI and esophageal AEs. Ibandronate was not included in the analysis (*Tadrous et al 2014*).
- Alendronate effervescent tablets (Binosto) have been shown to be bioequivalent to alendronate tablets (Fosamax). Therefore, clinical efficacy for this product is taken from clinical trials conducted for alendronate 10 mg per day and 70 mg per week (*Binosto prescribing information 2016*).
- In a Phase 3 non-inferiority trial comparing oral ibandronate 100 mg to intravenous ibandronate 1 mg, both therapies led to comparable gains in BMD after 12 months in all evaluable subgroups (*Hagino et al 2018*).
- A systematic review evaluated the efficacy and safety of bisphosphonates in Paget's disease. The analysis included 20 studies (N = 3168). A total of 10 studies specifically compared bisphosphonates (etidronate, tiludronate, ibandronate, pamidronate, olpadronate, alendronate, risedronate, zoledronate) to placebo, and found that bisphosphonates tripled the proportion (31% vs 9%) of patients whose bone pain disappeared (risk ratio [RR], 1.97; 95% CI, 1.29 to 3.01). Results were similar across all bisphosphonates evaluated (*Corral-Gudino et al 2017*).
- The effectiveness of etidronate for the treatment of heterotopic ossification due post hip replacement or spinal cord injury has been demonstrated through several studies (*Banovac et al 1993, Banovac et al 2000, Stover et al 1976[a], Stover et al 1976[b], Thomas et al 1985*).

Calcitonin

- There is a lack of substantial clinical trial data for calcitonin; the body of evidence is primarily comprised of small observational trials (*Cadarette et al 2008, Chestnut et al 2000, Cranney et al 2002[b], Downs et al 2000, Hwang et al 2006, Kanis et al 1974, Woodhouse et al 1977*).
- Injectable calcitonin has demonstrated beneficial effects in the treatment of Paget's disease. Calcitonin therapy resulted in bone and symptom relief, increased mobility, and decreased alkaline phosphate and other BTMs. In addition, calcitonin has been shown to cause disease regression in some patients (*kaufa et al 1974, Woodhouse et al 1977*).
- Nasal calcitonin achieved significant increases in BMD at the lumbar spine compared to placebo after 6 months of therapy, which was maintained for up to 2 years. Effects on BMD at the forearm and hip have produced mixed results with some trials demonstrating improvement, or preservation, and others demonstrating no improvement (*Chestnut et al 2000, Downs et al 2000*). Furthermore, a meta-analysis of 30 clinical trials demonstrated that calcitonin significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for nonvertebral fractures (*Hwang et al 2006*).

Estrogen Agonist-Antagonist

- Several placebo-controlled trials have demonstrated that treatment with raloxifene in postmenopausal women with osteoporosis significantly increases BMD. In addition, raloxifene demonstrated beneficial effects on lipid profile parameters (*Eastell et al 2009, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Siris et al 2005, Tanaka et al 2011*). In the MORE trial, raloxifene decreased the risk of vertebral fractures compared to placebo, with no observed difference in the rate of nonvertebral fractures (*Kung et al 2003*). There was also no difference in nonvertebral fracture rate during a 7 year follow-up of the MORE trial (*Siris et al 2005*). These data are supported by results of a meta-analysis of seven placebo-controlled trials, in which the reduction in the risk of vertebral fractures associated with raloxifene was inconsistent between 2 clinical trials, and neither trial demonstrated a reduction in the risk in nonvertebral fractures (*Eastell et al 2009*). When compared to bisphosphonate therapy, increases in BMD were significantly greater with alendronate compared to raloxifene (*Recker et al 2007*).
- In addition to evaluating the efficacy of raloxifene on bone, the MORE trial evaluated its efficacy in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. As a secondary end point, raloxifene reduced the incidence of newly diagnosed invasive breast cancer compared to placebo (*Cummings et al 1999*). In addition, the CORE trial evaluated the efficacy of 4 additional years of raloxifene treatment on the incidence of invasive breast cancer, and over a total of 8 years, the incidence of invasive breast cancer and estrogen receptor-positive breast cancer was reduced by 66% and 76%, respectively, with raloxifene compared to placebo. In the placebo-controlled RUTH trial, raloxifene significantly reduced the risk of invasive breast cancer, as well as vertebral fractures, and did not significantly

affect the risk of coronary heart disease. Raloxifene, however, was associated with a higher risk of venous thromboembolism and fatal stroke (*Barrett-Connor et al 2006*).

- Raloxifene has also been compared head-to-head with the antineoplastic agent tamoxifen in reducing the risk of invasive breast cancer. In the STAR trial, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive and noninvasive breast cancer, with a lower risk of thromboembolic events and cataracts after a median of 3.9 years. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar between the 2 treatments (*Vogel et al 2006*). However, in a trial with a median follow-up of 6.75 years, tamoxifen was shown to significantly reduce the risk of invasive breast cancer compared to raloxifene. At this time, raloxifene significantly reduced the risk of invasive uterine cancer, uterine hyperplasia, and thromboembolic events. There was no difference in mortality rate between raloxifene and tamoxifen at the end of 3.9 years (*Vogel et al 2010*).
- In terms of safety data, raloxifene was most commonly associated with hot flashes and leg cramps. Several clinical trials reported thromboembolic events (*Bachmann et al 2011, Barrett-Conner et al 2006, Cadarette et al 2008, Cranney et al 2002[a], Cummings et al 1999, Eastell et al 2009, Ensrud et al 2006, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Martino et al 2004, Recker et al 2007, Siris et al 2005, Tanaka et al 2011, Vogel et al 2006, Vogel et al 2010*).

Parathyroid Hormone Analogs

- A 2-year, placebo-controlled trial (N = 437) evaluating teriparatide in increasing bone mass in men with primary or hypogonadal osteoporosis was terminated early when a long-term toxicology trial noted an increase in the incidence of osteosarcoma in rats receiving teriparatide. After a median duration of 11 months, teriparatide significantly increased BMD at the lumbar spine and femoral neck compared to placebo (*Orwoll et al 2003*). In a follow-up of this trial, no serious safety concerns with teriparatide were observed (*Kaufman et al 2005*). Teriparatide has been compared to the bisphosphonate alendronate for the treatment of men with primary or hypogonadal osteoporosis. Specifically, when compared to alendronate and the combination of teriparatide plus alendronate, teriparatide significantly increased BMD at the posteroanterior spine, lateral spine, and femoral neck (*Finkelstein et al 2003*).
- Teriparatide also significantly increased BMD at the lumbar spine and total hip compared to alendronate in patients with glucocorticoid-induced osteoporosis. Additionally, significantly fewer patients receiving teriparatide had a vertebral fracture after 36 months (*Langdahl et al 2009, Saag et al 2007, Saag et al 2009*). Teriparatide was also compared to risedronate in men with glucocorticoid-induced osteoporosis. At 18 months, teriparatide was more effective at increasing BMD at the lumbar spine than risedronate (*Gluer et al 2013*).
- Teriparatide has been most extensively evaluated for the treatment of osteoporosis in postmenopausal women (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Hwang et al 2006, Kendler et al 2018, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Yuan et al 2019*). The double-blind, double-dummy, multicenter, randomized, controlled VERO trial enrolled 1360 postmenopausal women with at least 2 moderate or 1 severe vertebral fracture and a BMD T score ≤ -1.50 (*Kendler et al 2018*). Patients were randomly assigned to receive 20 mcg of teriparatide once daily plus oral weekly placebo or 35 mg risedronate once weekly plus daily placebo injections for 24 months. The primary outcome was new radiographic vertebral fractures. Results revealed that new vertebral fractures occurred in 28 (5.4%) patients in the teriparatide group and 64 (12%) patients in the risedronate group (risk ratio, 0.44; 95% confidence interval [CI], 0.29 to 0.68; $p < 0.001$). Clinical fractures were also significantly reduced with teriparatide (4.8% vs 9.8%; $p = 0.0009$). The EUROFORS trial was a prospective, 2-year trial in which all patients received teriparatide for the first year of treatment. After 12 months, patients were divided into 2 substudies. In Substudy 1, for the second year of treatment, patients were randomized to teriparatide, the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on teriparatide for the second year of treatment. After the first year of treatment, teriparatide significantly increased BMD at the lumbar spine, total hip, and femoral neck. The benefits of teriparatide appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued teriparatide for a total of 2 years achieved significant increases in BMD after 24 months. Within Substudy 1, during the second year of treatment, BMD at the lumbar spine, total hip, and femoral neck continued to increase significantly with teriparatide. BMD at the lumbar spine did not change in patients who were switched to raloxifene; however, BMD at the total hip and femoral neck significantly increased. Patients who were switched to no active treatment had a significant decrease in BMD at the lumbar spine, no change in BMD at the total hip, and a significantly increased BMD at the femoral neck (*Eastell et al 2009, Minne et al 2008, Obermayer-Pietsch et al 2008*). In addition to significant increases in BMD, placebo-controlled trials demonstrate that teriparatide significantly reduces the risk of vertebral and nonvertebral fractures (*Body et al 2002, Lindsay et al 2004, Neer et al 2001*). Data also suggest that teriparatide in combination with a

bisphosphonate may result in significant increases in BMD compared to monotherapy with either teriparatide or a bisphosphonate (*Cosman et al 2009, Cosman et al 2011*). In another study of 12 months duration, combined teriparatide plus denosumab were compared to either treatment alone. Combination therapy was associated with significantly greater BMD increases at the posterior-anterior spine, femoral neck, and hip than either drug alone (*Leder et al 2014, Tsai et al 2013*).

- A systematic review and meta-analysis of 23 RCTs examining upper limb and hip fractures found a significant reduction in hip fractures with teriparatide compared to either placebo or other medications (odds ratio [OR], 0.44; 95% CI, 0.22 to 0.87; $p=0.019$); however, no difference was seen in reduction of humerus, forearm, or wrist fractures (*Diez-Perez et al 2019*). A second systematic review of 17 studies showed that teriparatide reduced vertebral and nonvertebral fractures when compared to placebo but did not reduce wrist and hip fractures (*Chen et al 2019*). Additionally, there was no difference in fracture risk reduction between teriparatide and other medications.
- In terms of safety data, no clinically significant concerns related to teriparatide were observed; however, treatment was associated with a higher rate of hypercalcemia compared to placebo and bisphosphonate therapy. No cases of osteosarcoma were reported (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Finkelstein et al 2003, Finkelstein et al 2006, Hwang et al 2006, Kaufman et al 2005, Langdahl et al 2009, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Orwoll et al 2003, Saag et al 2007, Saag et al 2009*).
- The efficacy of abaloparatide was compared with teriparatide and placebo in the 18-month randomized controlled ACTIVE trial in 2463 postmenopausal women with osteoporosis. Treatment with abaloparatide resulted in a significant reduction in new morphometric vertebral and nonvertebral fractures vs placebo, while treatment with teriparatide also resulted in a significant reduction in new morphometric vertebral fractures vs placebo. For reduction in nonvertebral fractures, treatment with abaloparatide was not statistically different from teriparatide. The incidence of hypercalcemia was significantly lower with abaloparatide vs teriparatide (*Miller et al 2016*). The ACTIVEExtend open-label extension trial evaluated 6 months of follow-up therapy with alendronate 70 mg once weekly in both the abaloparatide and placebo groups, and demonstrated that the treatment cycle with abaloparatide for 18 months followed by alendronate reduced new morphometric vertebral fractures by 87%, nonvertebral fractures by 52%, clinical fractures by 45%, and major osteoporotic fractures by 58% vs placebo and alendronate (*Cosman et al 2017*).
- Several RCTs have examined the effect of recombinant parathyroid hormone on BMD. In 2 RCTs, recombinant parathyroid hormone significantly increased BMD at 12 and 18 months in postmenopausal women with osteoporosis compared to placebo; however, 1 of these RCTs found a decrease in BMD at the forearm at 18 months (*Greenspan et al 2007, Hodsmann et al 2003*). There are several studies examining the effect of recombinant parathyroid hormone on BMD in patients with hypoparathyroidism, but these studies generally include small sample sizes or lack a comparator arm. Results have been inconsistent in showing an increase in BMD, and 2 of these studies have shown a decrease in BMD at the hip, spine, whole body, or radius (*Cusano et al 2013, Rubin et al 2016, Sikjaer et al 2011*).

Receptor Activator of Nuclear Factor K-B Ligand Inhibitors

- The safety and efficacy of denosumab for the treatment of bone loss in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer were established in a 2 year, double-blind, placebo-controlled, randomized trial enrolling 252 women (*Ellis et al 2008*). Patients were randomized to subcutaneous denosumab every 6 months ($n = 127$) or placebo ($n = 125$) for a total of 4 doses; all patients received supplemental calcium and vitamin D. Overall, denosumab increased BMD at the lumbar spine at 12 and 24 months by 5.5% and 7.6%, respectively, compared to placebo ($p < 0.0001$ at both time points). BMD at the lumbar spine was significantly higher with denosumab compared to placebo after 12 months (4.8% vs -0.7%; treatment difference, 5.5%; 95% CI, 4.8 to 6.3; $p < 0.0001$). Furthermore, after 2 years, denosumab increased BMD at the lumbar spine (-1.4% placebo, +4.8% denosumab), total hip (-1.0% placebo, +3.8% denosumab), and femoral neck (-0.8% placebo, +2.8% denosumab).
- A double-blind, placebo-controlled, Phase 3 trial evaluated denosumab vs placebo in 3420 postmenopausal women with early hormone-receptor positive breast cancer receiving treatment with aromatase inhibitors (*Gnant et al 2015*). Women were randomized to denosumab 60 mg every 6 months or placebo. The primary outcome measure of time to first fracture was significantly delayed in the denosumab group compared to placebo (hazard ratio [HR], 0.50; 95% CI, 0.39 to 0.65; $p < 0.0001$). The incidence of AEs was similar in both treatment groups.
- When compared to placebo, denosumab significantly prolonged bone-metastasis-free survival (composite of time to first occurrence of bone metastasis and death from any cause) in men with non-metastatic prostate cancer (treatment difference, 4.2 months; HR, 0.85; 95% CI, 0.73 to 0.98; $p = 0.028$). There was no difference in overall survival observed

between the 2 treatment groups. In this trial, BMD evaluations were not performed; however, it was noted that biochemical markers of bone turnover significantly decreased with denosumab compared to placebo ($p < 0.001$ for all). Of note, the FDA-approved dosing was not evaluated in this trial; denosumab was administered once monthly (*Smith et al 2012*). The ADAMO trial showed that denosumab therapy administered every 6 months continued to increase BMD in men with low BMD throughout the second year of treatment (*Langdahl et al 2015*).

- Of the available clinical trial data evaluating the safety and efficacy of denosumab in postmenopausal women with osteoporosis who are at high risk of fracture, only one placebo-controlled trial (the FREEDOM trial) demonstrated a reduction in the risk of fracture with denosumab. In this trial, after 36 months, there were significant reductions with denosumab compared to placebo in the incidence of new vertebral (2.3% vs 7.2%; relative risk [RR], 0.32; 95% CI, 0.26 to 0.41; $p < 0.001$), nonvertebral (6.5% vs 8%; RR, 0.80; 95% CI, 0.67 to 0.95; $p = 0.01$), and hip fractures (0.7% vs 1.29%; RR, 0.6; 95% CI, 0.31 to 0.97; $p = 0.04$) (*Cummings et al 2009*). A 3-year extension trial maintained patients randomized to denosumab on active treatment for a total of 6 years and crossed over the placebo patients to denosumab treatment for a total of 3 years. For patients on denosumab for 6 years, BTMs were maintained at lower than pretreatment levels and BMD continued to increase. Fracture incidence in the long-term group remained low and below the rates reported in the FREEDOM placebo group. For the cross-over group, data obtained were consistent with FREEDOM observations (ie, rapid and marked reduction in BTMs, large increases in BMD, low fracture rates, favorable benefit/risk profile) (*Bone et al 2013*). A 7-year extension of FREEDOM, for a total of 7 to 10 years of exposure to denosumab, further confirmed a low fracture incidence rate with low rates of AEs (*Bone et al 2017*). Additionally, BMD at the lumbar spine, total hip, femoral neck, and radius continued to increase, suggesting no plateau to BMD benefits with denosumab.
- A meta-analysis/systematic review of clinical trials of denosumab in osteopenic and osteoporotic postmenopausal women with low bone mass sought to evaluate the effect of denosumab on BTMs and BMD. In this analysis, AEs, including fracture risk, were also evaluated as secondary endpoints. Due to missing or unavailable data, it was not possible for the investigators to evaluate the efficacy of denosumab based on change in baseline BMD. Treatment with denosumab was associated with increased BMD at the lumbar spine and hip, as well as decreased BTMs. Regarding secondary outcomes, denosumab did not demonstrate a significant reduction in fracture risk (OR, 0.74; 95% CI, 0.33 to 0.64; $p = 0.45$) (*Anastaskilakis et al 2009*).
- The efficacy of denosumab for increasing BMD is also supported by 3 dose-ranging, placebo-controlled trials, as well as a head-to-head trial with the bisphosphonate, alendronate (*Brown et al 2009*, *Lewiecki et al 2007*, *McClung et al 2006*, *Miller et al 2008[b]*). The 3 dose-ranging trials demonstrated that 48 months of denosumab therapy significantly increased BMD at all measured skeletal sites (lumbar spine, total hip, and distal 1/3 radius) ($p < 0.001$), and achieved potent and sustained reductions of BTMs compared to placebo (*Cummings et al 2009*). In a small subset of patients who discontinued treatment with denosumab, subsequent decreases in BMD at measured skeletal sites were observed. When compared to alendronate, changes in BMD at the total hip were also significantly greater with denosumab at 12 months (3.5% vs 2.6%; $p < 0.0001$) (*Brown et al 2009*). In a second meta-analysis comparing denosumab to weekly alendronate, no difference in fracture risk was demonstrated (OR, 1.42; 95% CI, 0.84 to 2.40; $p = 0.19$); however, both treatments were associated with significantly increased BMD at distal radius, total hip, lumbar spine, and femoral neck after 6 months (*Lin et al 2012*). In a 12-month trial comparing denosumab to monthly ibandronate therapy, treatment with denosumab resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate (*Recknor et al 2013*).
- A systematic review and meta-analysis assessed the efficacy and safety of denosumab compared to other anti-osteoporosis agents (eg, bisphosphonates, teriparatide) in patients previously treated with other medications (*Fontalis et al 2018*). Results demonstrated the superiority of denosumab in augmenting BMD at all skeletal sites studied (treatment difference in total hip [primary outcome], 1.59%; 95% CI, 1.01 to 2.17) compared to controls, whereas the overall incidence of serious AEs was not increased ($p = 0.42$). Similar results were demonstrated in another meta-analysis comparing denosumab to bisphosphonates for the treatment of postmenopausal osteoporosis. In this analysis, denosumab significantly increased the change in total hip, femoral neck, and lumbar spine BMD when compared to bisphosphonates. Denosumab did not yield any increased benefit for reducing fracture risk when compared to bisphosphonates and both denosumab and bisphosphonate therapy demonstrated a similar incidence of AEs and withdrawals due to AEs (*Wu et al 2018*).
- The impact of denosumab compared to risedronate on BMD was evaluated in 795 patients with glucocorticoid-induced osteoporosis. At 24 months, the increase in lumbar spine and total hip BMD was significantly higher with denosumab compared to risedronate in patients on glucocorticoids for less than 3 months (mean percentage change: 4.5% for the

lumbar spine, 3.1% for the total hip, and 2.5% for the femoral neck) as well as for those taking glucocorticoids for greater than 3 months (mean percentage change: 3.2% for the lumbar spine, 2.5% for the total hip, and 1.8% for the femoral neck). The incidence of discontinuation of treatment due to AEs was 7.9% with denosumab and 9.6% with risedronate. Fractures were reported in 8.8% in the denosumab group (4.4% vertebral, 5.3% non-vertebral) and 9.1% of patients taking risedronate (6.9% vertebral, 3.8% non-vertebral). The incidence of infection was approximately 36% in both groups (Saag et al 2019).

- A systematic review and meta-analysis assessed the effect of denosumab vs bisphosphonate treatment on BMD, fractures and safety in patients with glucocorticoid-induced osteoporosis. Collective data from 3 clinical trials demonstrated that one year of denosumab therapy increased lumbar (2.32%, 95% CI, 1.73% to 2.91%, $p < 0.0001$) and hip (1.52%, 95% CI, 1.1% to 1.94%, $p < 0.0001$) BMD more than bisphosphonates. The analysis found similar rates of fracture incidence, AEs and, infection between both treatments (Yanbeiy and Hansen 2019).
- In terms of safety data, no clinically significant concerns related to denosumab were observed; the safety profile of denosumab appears similar to that of bisphosphonates (Anastaskilakis et al 2009, Brown et al 2009, Cummings et al 2009, Lewiecki et al 2007, Lin et al 2012, McClung et al 2006, Miller et al 2008[b], Smith et al 2012).

Sclerostin Inhibitors

- The efficacy of romosozumab in postmenopausal women with osteoporosis was demonstrated in 2 clinical trials. When compared with placebo, romosozumab significantly decreased vertebral and clinical fractures; however, there was no statistically significant difference in nonvertebral fractures between patients receiving placebo or romosozumab (Cosman et al 2016). In a trial comparing 24 months of alendronate with 12 months of romosozumab followed by 12 months of alendronate, a significant reduction in new vertebral fracture risk was observed in the romosozumab treatment group at 24 months. Additionally, patients receiving romosozumab followed by alendronate had a lower risk of new vertebral fracture, clinical fracture, hip fracture, and nonvertebral fracture, which was significant compared to the alendronate only group (Saag et al 2017).
- An RCT examining the use of romosozumab in men > 50 years of age with osteoporosis and a history of fragility fracture showed a significant increase in BMD at the spine and hip compared to placebo (Lewiecki et al 2018).

Comparative Efficacy

- From the Agency for Healthcare Research and Quality (AHRQ) evaluation (Crandall et al 2012), the following conclusions were reached:
 - Calcitonin was excluded because the reviewers found that it should no longer be considered appropriate therapy for osteoporosis.
 - There is a high level of evidence from randomized controlled trials (RCTs) that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
 - There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis; there is moderate evidence that teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
 - There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.
 - There is insufficient evidence from head-to-head trials with bisphosphonates to support the superiority of one agent over the others for the prevention of fractures.
 - The evidence is insufficient regarding the use of combination therapy or sequential use of osteoporosis therapies in relation to fracture outcomes.
 - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men.
 - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies.
 - About half of patients appeared to show persistence with osteoporosis treatment at 1 year.
 - Adverse effects of concern identified from the report included the following:
 - A relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
 - Evidence is high for an increased risk for venous thromboembolic events (eg, pulmonary embolism) and vasomotor symptoms (eg, hot flashes) with raloxifene therapy.
 - Evidence is insufficient regarding the risk of esophageal cancer with bisphosphonates.

- Evidence is high regarding the risk for alendronate and mild upper GI events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn).
- Evidence is high that the prevention and treatment of osteoporosis with bisphosphonates remains a relatively minor contributor to the development of osteonecrosis of the jaw.
- The risk remains low for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis compared with the numbers of osteoporotic fractures prevented by bisphosphonate therapy.
- Evidence is high for rashes, injection site reactions, and infection with denosumab.
- A 2016 surveillance report of the document summarized new evidence with respect to AEs that were not reported in the original report. (*Agency for Healthcare Research and Quality 2016*). These include risk of:
 - Cerebrovascular accident, myocardial infarction, GI events, death, arrhythmia, dyspnea, and hypertension with teriparatide.
 - Headache, dizziness, arthritis/arthralgia, and hypotension with raloxifene.
 - Dermatological conditions and falls with denosumab.
- There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments. In 2 clinical trials, bisphosphonate and parathyroid hormone analog therapy demonstrated significantly greater increases in BMD at the lumbar spine compared to nasal calcitonin-salmon (*Downs et al 2000, Hwang et al 2006*).
- A network meta-analysis found that zoledronic acid significantly increased BMD in lumbar spine and teriparatide decreased fracture rates in men with osteoporosis when compared to other agents such as alendronate, ibandronate, and risedronate (*Chen et al 2015*).
- A network meta-analysis performed indirect comparisons to determine the likelihood of each drug being the most preferable for various outcomes (*Yang et al 2016*). Among products included in this study, the most preferred agents for various outcomes were teriparatide in nonvertebral fractures; denosumab, zoledronic acid, and alendronate in hip fractures; teriparatide in wrist fractures; and raloxifene, alendronate, and denosumab for AEs.
- A systematic review and meta-analysis demonstrated teriparatide to be superior to alendronate in increasing lumbar spine BMD in patients with postmenopausal osteoporosis. The results of the meta-analysis showed no significant difference in the change from baseline in femoral neck BMD or incidence of vertebral and/or nonvertebral fractures between the 2 therapies (*Wang et al 2017[a]*).
- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) evidence report included a network meta-analysis of 3 RCTs to evaluate the comparative safety and efficacy of teriparatide, abaloparatide, and zoledronic acid for treatment of osteoporosis in postmenopausal women at high risk for fracture. The analysis determined that teriparatide and abaloparatide were not significantly different from each other or zoledronic acid in reducing morphometric vertebral or nonvertebral fractures, and safety issues had little influence on the net benefit for each therapy compared to each other (*CTAF 2017*).
- A systematic review and meta-analysis demonstrated significantly lower risk of vertebral fractures with alendronate and risedronate in men with osteoporosis, but not with injectable calcitonin or denosumab vs controls. For bisphosphonates as a treatment category, meta-analyses demonstrated a significantly lower risk of vertebral fractures and possible nonvertebral fractures vs controls (*Nayak et al 2017*).
- A network meta-analysis identified parathyroid hormone therapy (teriparatide) and zoledronic acid as agents with the highest probability of satisfactory performance in preventing vertebral fractures in postmenopausal women in the final relative ranking of interventions among 10 osteoporosis agents, including oral bisphosphonates, denosumab, raloxifene, and strontium ranelate. For prevention of clinical vertebral fractures, zoledronic acid was determined to be the most effective, with denosumab as a second option, when compared to placebo. There were no significant differences between therapies identified with respect to adverse effects (*Wang et al 2017[b]*).
- A prospective cohort study of 32 patients with glucocorticoid-induced osteoporosis found that denosumab 60 mg subcutaneously every 6 months was superior to alendronate 35 mg orally once weekly in increasing lumbar spine BMD at 12 months ($p < 0.05$) (*Iseri et al 2018*).
- A systematic review of 6 RCTs found significant improvement in bone strength in postmenopausal women with osteoporosis receiving denosumab compared to bisphosphonates at 12 months in 4 of the 6 studies; however, bone turnover marker was consistently lower in patients receiving denosumab (*Chandran et al 2019*).
- A systematic review and meta-analysis of 16 trials (N=18,940) evaluated the impact of bone anabolic therapies (teriparatide, abaloparatide, romosozumab) compared to bisphosphonates or placebo on fractures (primary outcome), BMD, and bone markers in patients with postmenopausal osteoporosis. Abaloparatide ranked better than other active

treatments for reduction in vertebral and non-vertebral fractures. For the secondary outcome of increase in BMD, romosozumab ranked highest for all BMD locations compared to other active treatments. Compared to other treatments, teriparatide had the greatest impact on bone formation markers. However, about 30% of the trials in this analysis were found to have a high risk of bias (*Hernandez 2019*).

CLINICAL GUIDELINES

- To prevent and/or treat osteoporosis in postmenopausal women and men, national guidelines recommend adequate calcium and vitamin D intake, weight bearing exercise, cessation of smoking, and limiting alcohol intake (*ACOG 2012 [reaffirmed in 2019], Adler et al 2016, Buckley et al 2017, Camacho et al 2016, Conley 2020, Cosman et al 2014, Eastell et al 2019, Qaseem et al 2017, Watts et al 2012*).
- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Cosman et al 2014, Eastell et al 2019, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*).
 - Bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) are generally considered first-line therapy. Clinical trials have not consistently shown one agent to be more effective than another. Because etidronate is not approved for the indication of prevention or treatment of osteoporosis, many guidelines do not recommend its use (*ACOG 2012, Adler et al 2016, Camacho et al 2016, Cosman et al 2014, Qaseem et al 2017, Watts et al 2012*).
 - While some national guidelines recommend denosumab as an alternative to bisphosphonates (*ACOG 2012, Eastell et al 2019*), the American Association of Clinical Endocrinologists (AAACE) recommends denosumab as an optional first-line treatment in postmenopausal women (*Camacho et al 2016*).
 - Teriparatide is generally reserved for patients at high risk for fractures, or unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Eastell et al 2019, Watts et al 2012*). The Endocrine society has recommended abaloparatide or teriparatide as treatment options in postmenopausal women at very high risk of fracture (*Eastell et al 2019*).
 - Although calcitonin and raloxifene are approved for osteoporosis, they are not considered first-line therapies due to AEs, less evidence of efficacy, and/or route of administration.
 - A recent guideline from the American Society for Bone and Mineral Research (ASBMR) specifically geared toward secondary fracture prevention in patients 65 years of age and older recommends the following for pharmacologic therapy (*Conley et al 2020*):
 - Oral alendronate or risedronate as first-line treatment (considered well-tolerated and available at a low cost). Intravenous zoledronic acid or subcutaneous denosumab are recommended if oral bisphosphonates cannot be used.
 - Patients at high-risk (specifically after vertebral fractures): consider anabolic therapies in consultation with a specialist.
 - Optimal duration of treatment is unknown but general recommendation is 3 to 5 years due to potential risk of rare adverse events that increase with longer duration of treatment.
 - Consider risks and monitor for atypical femoral fractures and osteonecrosis of the jaw.
- Patients with chronic kidney disease (CKD) grades 3a to 3b with parathyroid hormone in the normal range and osteoporosis and/or high risk of fracture should receive treatment similar to that of the general population (*Ketteler et al 2018*).
- According to the Endocrine Society guideline for Paget's disease, treatment with bisphosphonates is recommended for most patients with active or symptomatic Paget's disease who are at risk of future complications. A single 5 mg dose of intravenous zoledronic acid is recommended as the preferred initial agent in patients with no contraindications (*Singer et al 2014*).

SAFETY SUMMARY

- **Contraindications**
 - Bisphosphonates
 - **Oral agents:** Abnormalities of the esophagus that delay esophageal emptying (eg, stricture or achalasia)
 - **Oral agents:** Inability to stand or sit upright for at least 30 minutes (at least 60 minutes for ibandronate)
 - Hypocalcemia
 - **Clinically overt osteomalacia (etidronate)**

- **Creatinine clearance <35 mL/min or acute renal impairment (zoledronic acid)**

- Alendronate oral solution
 - Patients at increased risk of aspiration
- Raloxifene
 - Active or past history of venous thromboembolism
 - Pregnancy or nursing mothers
- Denosumab
 - Hypocalcemia
 - Pregnancy or nursing mothers
- Romosozumab
 - Hypocalcemia

- **Warnings/precautions**

- Bisphosphonates
 - Caution should be used in patients with active GI problems (except zoledronic acid)
 - Reports of severe and occasionally incapacitating bone, joint, and/or muscle pain
 - Osteonecrosis of the jaw
 - Caution should be used in aspirin-sensitive patients (zoledronic acid)
 - Caution should be used in patients who must restrict sodium intake (alendronate effervescent tablets)
 - Hypocalcemia must be corrected prior to use
 - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
 - Patients receiving Atelvia should not be treated with Actonel, as both products contain the same active ingredient
 - Renal toxicity may occur in patients with pre-existing renal impairment receiving ibandronate injection
- Raloxifene
 - **Boxed warning:** Increased risk of venous thromboembolism and death from stroke
 - Venous thromboembolism: increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Discontinue 72 hours prior to and during prolonged immobilization
 - Death due to stroke
 - Should not be used for the primary or secondary prevention of cardiovascular disease
 - Not recommended in premenopausal women
 - Caution should be used in patients with hepatic impairment
 - Concomitant use with systemic estrogens is not recommended
 - Hypertriglyceridemia; serum triglycerides should be monitored throughout treatment for women with a history of marked hypertriglyceridemia receiving treatment with raloxifene and oral estrogen or estrogen plus progestin
- Parathyroid Hormone Analogs
 - **Boxed warning:** Parathyroid hormone analogs should not be used in patients at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, prior external beam or implant radiation involving the skeleton, and in pediatric and young adult patients with open epiphyses)
 - Cumulative lifetime use of abaloparatide and/or teriparatide > 2 years not recommended
 - Recombinant parathyroid hormone should only be used in patients that are unable to be controlled on calcium and vitamin D
 - Orthostatic hypotension
 - Caution should be used in patients with active or recent urolithiasis
 - Hypercalcemia
 - Hypocalcemia following discontinuation of recombinant parathyroid hormone
- Calcitonin
 - Potential increased risk of malignancies
 - Circulating antibodies and abnormal urine sediment
 - Hypocalcemia
 - Nasal spray: Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status recommended at beginning of treatment, periodically during the course of therapy, and at any time nasal symptoms occur
- Denosumab

- Atypical, low-energy, or low trauma fractures of the femoral shaft
- Osteonecrosis of the jaw
- Severe musculoskeletal pain
- An increased risk for multiple vertebral fractures has been reported following discontinuation of denosumab
- Increased risk for serious infections in patients on concomitant immunosuppressant agents or with impaired immune systems
- Patients receiving Prolia should not be treated with Xgeva, as both products contain the same active ingredient
- Hypersensitivity reactions, including anaphylaxis, may occur
- Hypocalcemia must be corrected prior to use. Concomitant use of calcium-lowering drugs or calcimimetic drugs may increase risk of hypocalcemia.
- Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
- Dermatologic reactions, including dermatitis, rash, and eczema have been reported, and may require discontinuation of the drug
- Significant suppression of bone remodeling may occur and may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing
- Romosozumab
 - **Boxed warning:** There may be an increase in risk of myocardial infarction, stroke, and cardiovascular death. Romosozumab should not be used in patients with a stroke or myocardial infarction within the past year and should be discontinued if events occur during therapy.
 - Major adverse cardiac events may occur
 - Hypersensitivity reactions may occur
 - Hypocalcemia must be corrected prior to use
 - Osteonecrosis of the jaw
 - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
 - Use should be limited to 12 monthly doses
- **AEs**
 - Bisphosphonates
 - The most common AEs are headache and GI effects such as abdominal pain, diarrhea, constipation, nausea, and dyspepsia.
 - Raloxifene
 - The most common AEs (> 2%) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating.
 - Teriparatide
 - The most common AEs (> 10%) include nausea, arthralgia, and pain.
 - Abaloparatide
 - The most common AEs (≥ 2%) include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.
 - Recombinant parathyroid hormone
 - The most common AEs (> 10%) include paresthesia, hypocalcemia, headache, hypercalcemia, hypoaesthesia, diarrhea, vomiting, arthralgia, nausea, hypercalciuria, and extremity pain.
 - Calcitonin
 - Nasal spray: The most common AEs (≥ 3%) include rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache.
 - Injection: The most common AEs include nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2 to 5%).
 - Denosumab
 - The most common AEs (> 5%) include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, cystitis, nasopharyngitis, bronchitis, and headache. Pancreatitis has also been reported in clinical trials.
 - Romosozumab
 - The most common AEs (≥ 5%) include arthralgia and headache.

● Drug Interactions

- Bisphosphonates

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- Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with absorption of oral bisphosphonates
- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) increase GI AEs with oral bisphosphonates
- **Olestra, mineral oils, orlistat and bile acid sequestrants may impair the absorption of vitamin D (alendronate/cholecalciferol).**
- Raloxifene
 - Cholestyramine, warfarin, highly protein-bound drugs, ampicillin, and amoxicillin.
- Teriparatide and recombinant parathyroid hormone
 - Hypercalcemia may predispose patients to digitalis toxicity; caution recommended in patients on digoxin
- Calcitonin
 - Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations
- **Risk Evaluation and Mitigation Strategy (REMS)**
 - Denosumab has a REMS program with the goal of mitigating the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions (*REMS Website 2020*).
 - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe denosumab.
 - Recombinant parathyroid hormone has a REMS program with the goal of increasing awareness and mitigating the risk of osteosarcoma (*REMS Website 2020*).
 - All prescribers and dispensing pharmacies must be certified through the REMS program.

DOSING AND ADMINISTRATION

- Bisphosphonates
 - Oral bisphosphonates should be taken at least 30 minutes (60 minutes for ibandronate) before the first food or drink of the day and swallowed whole in an upright position and with a full glass of plain water. Patients should not lie down for 30 minutes (60 minutes for ibandronate) after ingestion.
 - Exception: Delayed-release risedronate should be taken immediately after breakfast
 - Supplemental calcium and vitamin D are recommended if dietary intake is inadequate; however, calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with bisphosphonate absorption and should be administered at a different time of the day.
- Calcitonin
 - Unopened nasal spray bottle should be stored in the refrigerator. Once opened, it should be stored at room temperature and discarded after 35 days.
 - Injection should be stored in the refrigerator. If the volume of the injection exceeds 2 mL, intramuscular (IM) injection is preferable, and the total dose should be distributed across multiple injection sites.
- Parathyroid Hormone Analogs
 - Teriparatide prefilled pens should be refrigerated at all times and injected into the thigh or abdominal wall.
 - Abaloparatide prefilled pens should be refrigerated before use then stored at room temperature for up to 30 days after first use. The injection should be into the periumbilical region of abdomen at approximately the same time every day.
 - Recombinant parathyroid hormone must be reconstituted prior to administration using a mixing device and should be administered using the Q-Cliq pen delivery device into the thigh, rotating thighs each day. Reconstituted parathyroid hormone should be stored in the Q-Cliq pen device in the refrigerator for no more than 14 days.
- Denosumab
 - Denosumab should be administered by a healthcare professional in the upper arm, upper thigh, or abdomen.
- Romosozumab
 - Romosozumab should be administered by a healthcare professional as 2 separate injections, one after the other in the upper arm, thigh, or abdomen.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Bisphosphonates			

Drug	Available Formulations	Route	Usual Recommended Frequency
Actonel (risedronate)	Tablets	Oral	Once daily Once weekly Once monthly
Atelvia (risedronate)	Delayed release tablets	Oral	Once weekly
Binosto (alendronate)	Effervescent tablets	Oral	Once weekly
Boniva (ibandronate)	Tablets Injection	Oral IV	Once monthly (oral) Every 3 months (IV)
Didronel (etidronate)	Tablets	Oral	Once daily (for osteoporosis and Paget's disease)
Fosamax (alendronate)	Tablets Solution	Oral	Once daily Once weekly
Fosamax Plus D (alendronate/ cholecalciferol)	Tablets	Oral	Once weekly
Reclast (zoledronic acid)	Injection	IV	Once a year (treatment) Once every 2 years (prevention)
Calcitonin			
Miacalcin (calcitonin-salmon synthetic)	Nasal solution Injection	Intranasal SQ, IM	Once daily (for osteoporosis and Paget's disease)
Estrogen Agonist-Antagonist			
Evista (raloxifene)	Tablets	Oral	Once daily
Parathyroid Hormone Analogs			
Forteo, Bonsity (teriparatide)	Injection	SQ	Once daily
Natpara (recombinant parathyroid hormone)	Injection	SQ	Once daily
Tymlos (abaloparatide)	Injection	SQ	Once daily
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors			
Prolia (denosumab)	Injection	SQ	Every 6 months
Sclerostin Inhibitor			
Evenity (romosozumab)	Injection	SQ	Once monthly

Abbreviations: IM = intramuscular; IV = intravenous; SQ = subcutaneous

See the current prescribing information for full details

CONCLUSION

- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (Adler et al 2016, Camacho et al 2016, Conley et al 2020, Cosman et al 2014, Eastell et al 2019, Ketteler et al, 2018, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012). Bisphosphonates are generally considered first-line therapy, and clinical trials have not consistently shown one agent to be more effective than another.
- Data for hip, vertebral, and nonvertebral fractures are most robust for alendronate, risedronate, and zoledronic acid. Ibandronate has data to support reduced vertebral fractures (Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]).
- Patient preference and ease of administration should be considered in the selection of a bisphosphonate, as adherence may be a barrier to the treatment and prevention of osteoporosis. Atelvia (risedronate delayed release) and alendronate can be administered once weekly, while Actonel (risedronate) and ibandronate can be administered once a month. Additionally, zoledronic acid is an intravenous infusion given once a year for treatment or every other year for prevention. Atelvia (risedronate delayed release) can be taken immediately after eating or drinking while other oral bisphosphonates must be administered 30 to 60 minutes before the first food or drink of the day.

- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab, has data for hip, vertebral, and nonvertebral fractures. It is a subcutaneous injection given every six months. Monitoring for infection is required with this agent. The AACE recommends denosumab as an optional first-line treatment for postmenopausal osteoporosis (*Camacho et al 2016*) or **as an option for patients who cannot take oral bisphosphonates** (*Conley et al 2020*)
- Teriparatide and abaloparatide are generally reserved for patients at high risk for fractures (*Conley et al 2020*) or those unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Eastell et al 2019, Watts et al 2012*). Both teriparatide and abaloparatide are administered via daily subcutaneous injection, and lifetime cumulative treatment duration should not exceed 2 years. The parathyroid hormone analogs have a boxed warning for osteosarcoma.
- Romosozumab is the newest agent approved for the treatment of osteoporosis in postmenopausal women at high risk of fracture and in patients who have failed or are intolerant to other therapies, and it has not yet been incorporated into treatment guidelines. It is administered as a monthly subcutaneous injection for no more than 12 months.
- Raloxifene has data for vertebral fracture reduction and is only approved for women. It may be an appropriate initial therapy for patients requiring drugs with spine-specific efficacy who are unable to tolerate bisphosphonates (*Camacho et al 2016*). Raloxifene is also used for breast cancer risk reduction, which is recommended for asymptomatic women ≥ 35 years of age who are at risk for breast cancer. There is an increased risk of thromboembolism and stroke with raloxifene.
- **The ASBMR 2020 guideline mentions anabolic therapy such as romosozumab as an option in patients at high risk of secondary fracture; particularly those with a previous vertebral fracture** (*Conley et al 2020*).
- Calcitonin lacks sufficient evidence for fracture reduction in the treatment of osteoporosis.
- For the treatment of Paget's disease, risedronate, alendronate, etidronate, calcitonin injection, and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, teriparatide, alendronate, **denosumab**, and zoledronic acid are all FDA-approved. Selection of an agent should be based on the patient's preference of administration. **Oral bisphosphonates are preferred. If these cannot be used, the agents recommended in order of preference are IV bisphosphonates, teriparatide, and then denosumab** (*Buckley et al 2017*).

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