Therapeutic Class Overview
Bone Density Regulators

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) estimates that 10.2 million Americans have 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*).
- 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), Didronel (etidronate), and Zometa (zoledronic acid), which will not be discussed in this review (*Micromedex 2.0 2018*).
- Other agents used to treat postmenopausal osteoporosis include calcitonin (Miacalcin), an estrogen agonist/antagonist (Evista), the parathyroid hormone analogs (Forteo and Tymlos), and receptor activator of nuclear factor K-B ligand inhibitor (Prolia). 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.
- Other agents in the estrogen agonist/antagonist class include Clomid or Serophene (clomiphene), tamoxifen, Fareston (toremifene), and Osphena (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 2.0 2018*). These agents are not approved for treatment of osteoporosis and will not be discussed in this review.
- Another agent in the receptor activator of nuclear factor K-B ligand inhibitor class is Xgeva (denosumab). It 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 2.0 2018*). 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)	✔
Fosamax* (alendronate)	✔
Fosamax Plus D (alendronate/cholecalciferol)	-
Reclast (zoledronic acid)	✔
Calcitonin	
Miacalcin† (calcitonin salmon synthetic)	✔ (nasal spray only)
Estrogen Agonist-Antagonist	
Evista (raloxifene)	✔
Parathyroid Hormone Analogs	
Forteo (teriparatide)	-
Tymlos (abaloparatide)	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors	
Prolia (denosumab)	-

* Brand Fosamax oral solution is not currently marketed; however, a generic is available.
† Brand Miacalcin nasal spray is not currently marketed; however, a generic is available. Miacalcin injection is only available as a branded product.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	alendronate* (Binosto, Fosamax, Fosamax Plus D)	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)	✔
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)	✔

* Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of Actonel, Reclast and Boniva for the treatment of osteoporosis are based on clinical data of 3 years duration. The safety and effectiveness of Atelvia 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 2015, Atelvia 2015, Binosto 2016, Boniva injection 2016, Boniva tablets 2016, Fosamax 2016, Fosamax Plus D 2016, Reclast 2017)

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

Indication	Evista (raloxifene)	Forteo (teriparatide)	Miacalcin (calcitonin)	Prolia (denosumab)	Tymlos (abaloparatide)
Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause			✔		
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	✔				
Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture		✔			
Treatment of Paget's disease			✔ (injection only)		
Treatment of hypercalcemia			✔ (injection only)		
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture		✔			
Treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer				✔	
Treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer				✔	
Treatment to increase bone mass in men with osteoporosis at high risk for fracture				✔	

(*Prescribing Information: Evista 2016, Forteo 2016, Miacalcin nasal spray 2017, Miacalcin injection 2017, Prolia 2017, Tymlos 2017*)

- 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 one bisphosphonate agent to another.

- Data from trials 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, Lyles et al 2007, Ringe et al 2009, Sawka et al 2005*). 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*). 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, 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*).

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 (*Kanis 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). 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 different 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).

- 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 ACTIVExtend 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*).

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 (odds ratio [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).
- 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*).

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.

- 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 & Greenspan 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]*).

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 2016], Adler et al 2016, Buckley et al 2017, Camacho et al 2016, Cosman et al 2014, 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, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*).
  - Bisphosphonates are generally considered first-line therapy. Clinical trials have not consistently shown one agent to be more effective than another.
  - While some national guidelines recommend denosumab as an alternative to bisphosphonates (*ACOG 2012*), the American Association of Clinical Endocrinologists (AACE) 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, Watts et al 2012*). Osteoporosis guidelines have yet to be updated to include abaloparatide, the most recently approved parathyroid hormone analog.
  - 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.

SAFETY SUMMARY

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

- **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)
  - 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

○ Parathyroid Hormone Analogs
- **Boxed warning:** Teriparatide and abaloparatide 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 parathyroid hormone analogs (abaloparatide and/or teriparatide) > 2 years not recommended
- Orthostatic hypotension
- Caution should be used in patients with active or recent urolithiasis
- Hypercalcemia

○ Calcitonin
- Potential increased risk of malignancies
- Circulating antibodies and abnormal urine sediment
- 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

• **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.

○ 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, and cystitis. Pancreatitis has also been reported in clinical trials.

• **Drug Interactions**

○ Bisphosphonates
- 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

○ Raloxifene

- Cholestyramine, warfarin, and highly protein-bound drugs
- Teriparatide
  - 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 Web site 2018*).
    - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe denosumab.

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.
- Denosumab
  - Denosumab should be administered by a healthcare professional in the upper arm, upper thigh, or abdomen.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Bisphosphonates			
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)
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			

Drug	Available Formulations	Route	Usual Recommended Frequency
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 (teriparatide)	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

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

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, Cosman et al 2014, 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 is 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*).
- Teriparatide is generally reserved for patients at high risk for fractures or those unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Watts et al 2012*). Abaloparatide is the most recently approved parathyroid hormone analog and is not included in current osteoporosis guidelines. 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.
- 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.
- Calcitonin lacks sufficient evidence for fracture reduction in the treatment of osteoporosis.
- For the treatment of Paget's disease, risedronate, alendronate, calcitonin injection, and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, teriparatide, alendronate, and zoledronic acid are all FDA-approved. Selection of an agent should be based on the patient's preference of administration. Teriparatide should be reserved for higher doses of steroids and longer lengths of treatment per the national guidelines (*Buckley et al 2017*).

REFERENCES

- Actonel prescribing information. Warner Chilcott. Rockaway, NJ. April 2015.
- Adler RA, Fuleihan GE, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a task force of the American society for bone and mineral research. *J Bone & Miner Res*. 2016;31(1):16-35.
- American College of Obstetricians and Gynecologists (ACOG). Practice bulletin 129: Osteoporosis. *Obstetrics & Gynecology*. 2012;120(3):718-734.
- Anastaskilakis AD, Toulis KA, Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. *Horm Metab Res*. 2009;41:721-729.
- Atelvia prescribing information. Warner Chilcott. Rockaway, NJ. April 2015.
- Bachmann G, Kriegman A, Goncalves J, et al. Effect of zoledronic acid compared to raloxifene on bone turnover markers in postmenopausal women with low bone density. *Menopause*. 2011;18(8):851-856.
- Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355(2):125-137.
- Binosto prescribing information. Mission Pharmacal Company. San Antonio, TX. December 2016.
- Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535-41.
- Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2002 Oct;87(10):4528-35.
- Bone HG, Chapuriat R, Brandi ML, et al. The effect of 3 or 6 years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. *J Clin Endocrin Metab*. 2013;98(11):4483-4492.
- Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;5(7):513-523.
- Boniva injection prescribing information. Genentech USA, Inc. South San Francisco, CA. December 2016.
- Boniva tablets prescribing information. Genentech USA, Inc. South San Francisco, CA. December 2016.
- Bonnick S, Saag KG, Kiel DP, et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate vs risedronate over two years. *J Clin Endocrinol Metab*. 2006;91:2631-2637.
- Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009;24:153-161.
- Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol*. 2017;69(8):1521-1537.
- Cadarette SM, Katz JN, Brookhart A, et al. Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann Intern Med*. 2008;148:637-646.
- California Technology Assessment Forum (CTAF). Anabolic therapies for osteoporosis in postmenopausal women: effectiveness and value (evidence report). 2017. https://icer-review.org/wp-content/uploads/2016/11/CTAF_Osteoporosis_Evidence_Report_061617.pdf. Accessed February 14, 2018.
- Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016. *Endocr Pract*. 2016;22(Suppl 4):1-42.
- Chen LX, Zhou ZR, Li YL, et al. Comparison of Bone Mineral Density in Lumbar Spine and Fracture Rate among Eight Drugs in Treatments of Osteoporosis in Men: A Network Meta-Analysis. *PLoS ONE*. 2015;10(5):e0128032.
- Chestnut CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med*. 2000;109(4):267-276.
- Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014; 25(10): 2359–2381.
- Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26(3):503-511.
- Cosman F, Miller PD, Williams GC, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. *Mayo Clin Proc*. 2017;92(2):200-210.
- Cosman R, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresportive agent. *J Clin Endrocinol Metab*. 2009;94:3772-3780.
- Crandall CJ, Newberry SJ, Gellad WG, et al. Treatment to prevent fractures in men and women with low bone density or osteoporosis: update of a 2007 report. Comparative Effectiveness Review No. 53. (Prepared by Southern California Evidence-based Practice Center under Contract No. HHSA-290-2007-10062-I.) Rockville, MD: Agency for Healthcare Research and Quality; March 2012. Surveillance report: August 2016. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/osteoporosis-bone-fracture_surveillance.pdf. Accessed February 14, 2018.
- Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev*. 2002[a];23(4):524-528.
- Cranney A, Tugwell P, Zytaruk N, et al; Osteoporosis Methodology Group and Osteoporosis Research Advisory Group. Meta-analysis of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. *Endoc Rev*. 2002[b];23(4):540-551.
- Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA*. 1999;281(23):2189-2197.
- Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.
- Downs RW JR, Bell NH, Ettinger MP, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. *J Clin Endocrinol Metab*. 2000;85(5):1783-1788.
- Drugs@FDA. FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 14, 2018.
- Eastell R, Nickelsen T, Marin F, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled, European Study of Forteo (EUROFORS). *J Bone Miner Res*. 2009;24:726-736.

- Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromastase inhibitors for nonmetastatic breast cancer. *J Clin Oncol*. 2008;26(30):4875-4882.
- Ensrud K, Genazzani AR, Geiger MJ, et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol*. 2006;97:520-527.
- Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a three-year randomized clinical trial. *JAMA*. 1999;282(7):637-624.
- Evista prescribing information. Lilly USA, LLC. Indianapolis, IN. December 2016.
- Finkelstein JS, Hayes A, Hunzelman JL, et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med*. 2003;349(13):1216-1226.
- Finkelstein JS, Leder BZ, Burnett SM, et al. Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. *J Clin Endocrinol Metab*. 2006;91(8):2882-287.
- Fontalis A, Kenanidis E, Prousali E, Potoupnis M, Tsiridis E. Safety and efficacy of denosumab in osteoporotic patients previously treated with other medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2018 Jan 25:1-16. doi: 10.1080/14740338.2018.1430764. [Epub ahead of print].
- Food and Drug Administration (FDA). Approved Risk Evaluation and Mitigation Strategies (REMS). Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed February 14, 2018.
- Forteo prescribing information. Lilly USA, LLC. Indianapolis, IN. October 2016.
- Fosamax PLUS D prescribing information. Merck and Co., Inc. Whitehouse Stations, NJ. March 2016.
- Fosamax prescribing information. Merck and Co., Inc. Whitehouse Station, NJ. March 2016.
- Gluer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. *J Bone Miner Res*. 2013;28(6):1355-1368.
- Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2015 Aug 1;386(9992):433-43. doi: 10.1016/S0140-6736(15)60995-3.
- Guanabens N, Monegal A, Cerda D, et al. Randomized Trial Comparing Monthly Ibandronate and Weekly Alendronate for Osteoporosis in Patients With Primary Biliary Cirrhosis. *Hepatology*. 2013;58(6):2070-208.
- Harris ST, Reginster JY, Harley C, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the evaluation of ibandronate efficacy (VIBE) database fracture study. *Bone*. 2009;44:758-765.
- Hwang JS, Tu ST, Yang TS, et al. Teriparatide vs calcitonin in the treatment of Asian postmenopausal women with established osteoporosis. *Osteoporos Int.* 2006;17:373-378.
- Johnston Jr CC, Bjarnason NH, Cohen FJ, et al. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women. *Arch Intern Med*. 2000;160:3444-3450.
- Kanis JA, Barton IP, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. *Osteoporos Int.* 2005;16:475-482.
- Kanis JA, Horn DB, Scott RDM, Strong JA. Treatment of Paget's disease of bone with synthetic salmon calcitonin. *Br Med J*. 1974;3:727-731.
- Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int.* 2005;16:510-516.
- Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicenter, double-blind, double-dummy, randomized controlled trial. *Lancet*. 2017 Nov 9. pii: S0140-6736(17)32137-2. doi: 10.1016/S0140-6736(17)32137-2. [Epub ahead of print].
- Kung AWC, Chao HT, Huang KE, et al. Efficacy and safety of raloxifene 60 mg/day in postmenopausal Asian women. *J Clin Endocrinol Metab*. 2003;88:3130-136.
- Langdahl BL, Marin F, Shane E, et al. Teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. *Osteoporos Int.* 2009;20(12):2095-2104.
- Langdahl BL, Teglbjaerg CS, Ho P, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. *J Clin Endocrinol Metab*. 2015;100:1335–1342.
- Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA extension study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014;99:1694-1700.
- Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res*. 2007;22:1832-1841.
- Lin T, Wang C, Cai XZ, et al. Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. *Int J Clin Pract*. 2012;66(4):399-408.
- Lindsay R, Scheele WH, Neer R, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med*. 2004;164:2024-2030.
- Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007;357:1799-1809.
- Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst*. 2004;96(23):1751-1761.
- McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*. 2007;41:122-128.
- McClung MR, Lewiecki M, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354:821-831.
- McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. *Arch Intern Med*. 2005;165:1762-1768.
- Miacalcin injection prescribing information. Mylan Institutional LLC. Rockford, IL. September 2017.
- Miacalcin nasal spray prescribing information. Mylan Institutional LLC. Rockford, IL. September 2017.

- Micromedex 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2018. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed February 14, 2018.
- Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008[b];43:222-229.
- Miller PD, Epstein S, Sedarati F, Reginster JY. Once-monthly oral ibandronate compared to weekly oral alendronate in postmenopausal osteoporosis: results from the heat-to-head MOTION study. *Curr Med Res Opin*. 2008[a];24(1):207-213.
- Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316(7):722-33.
- Minne H, Audrah M, Simones ME, et al. Bone density after teriparatide in patients with or without antiresportive treatment: one-year results from the EUROFORS study. *Curr Med Res Opin*. 2008;24(11):3117-3128.
- Mok CC, Tong KH, To CH, et al. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. *Osteoporos Int.* 2008;19:357-364.
- Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2017 Mar;65(3):490-495.
- Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434-1441.
- North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause*. 2010;17(1):25-54.
- Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresportive treatment. *J Bone Miner Res*. 2008;23(10):1591-1600
- Okada Y, Nawata M, Nakayamada S, et al. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. *J Rheumatol*. 2008;35:2249-2254.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2018. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 14, 2018.
- Orwoll ES, Miller PD, Adachi JD, et al. Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg vs a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. *J Bone Miner Res*. 2010;25(10):2239-2350.
- Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis (abstract). *J Bone Miner Res*. 2003;18(1):9-17.
- Prolia prescribing information. Amgen, Inc. Thousand Oaks, CA. May 2017.
- Qaseem A, Forciea MA, McLean RM, et al. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(11):818-839.
- Recker RR, Kendler D, Recknor CP, et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone*. 2007;40:843-851.
- Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol.* 2013;121(6):1291-1299.
- Reclast prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. July 2017.
- Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicenter, double-blind, double-dummy, randomized controlled trial. *Lancet*. 2009;373:1253-1263.
- Reid DM, Hosking D, Kendler D, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-international. *Int J Clin Pract*. 2008;62(4):575-584.
- Reid DM, Hosking D, Kendler D, et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: results of FACTS-International. *Clin Drug Invest.* 2006;26(2):63-74.
- Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med*. 2005;353(9):898-908.
- Ringe JD, Farahman P, Faber H, Dorst A. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. *Rheumatol Int.* 2009;29:311-315.
- Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007;357(20):2028-2039.
- Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis. Thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum.* 2009;60(11):3346-3355.
- Sarioglu M, Tuzum C, Unlu Z, et al. Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers in postmenopausal osteoporosis. *Rheumatol Int.* 2006;26:195-200.
- Sawka AM, Papaioannou A, Adachi JD, et al. Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. *BMC Musculoskelet Disord*. 2005;6:39.
- Silverman SL, Watts NB, Delmas PD, et al. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. *Osteoporos Int.* 2007;18:25-34.
- Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after eight years: results from the continuing outcomes relevant to Evista (CORE) study. *J Bone Miner Res*. 2005;20(9):1514-1524.
- Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379:39-46.
- Tadrous M, Wong L, Mamdani MM, et al. Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis. *Osteoporos Int.* 2014;25:1225-1235.
- Tanaka M, Itoh K, Matsushita K, et al. Effects of raloxifene on bone mineral metabolism in postmenopausal Japanese women on hemodialysis. *Ther Apher Dial*. 2011 Jun;15(Suppl 1):S62-S6.

- Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet*. 2013;382: 50–56.
- Tymlos prescribing information. Radius Health, Inc. Waltham, MA. April 2017.
- Vogel VG, Constantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295(23):2727-2741.
- Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer. *Cancer Prev Res (Phila).* 2010;3(6):696-706.
- Wang G, Sui L, Gai P, et al. The efficacy and safety of vertebral fracture prevention therapies in postmenopausal osteoporosis treatment: Which therapies work best? A network meta-analysis. *Bone Joint Res*. 2017[b];6(7):452-463.
- Wang YK, Qin SQ, Ma T, et al. Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2017[a];96(21):e6970.
- Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: An endocrine society clinical practice guideline. *J Clin Endocrin Metab*. 2012; 97(6):1802–1822.
- Woodhouse NJY, Chalmers AH, Wells IP, et al. Paget's disease. Radiological changes occurring in untreated patients and those on therapy with salmon calcitonin during two years' observation. *Br J Radiol*. 1977;50(598):699-705.
- World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. Geneva, World Health Organization, 1994 (WHO technical report series, No. 843).
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288(3):321-333.
- Yang XC, Deng ZH, Wen T, et al. Network meta-analysis of pharmacological agents for osteoporosis treatment and fracture prevention. *Cell Physiol Biochem*. 2016;40(3-4):781-795.

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