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 (Watts et al, 2010). 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 1,200 mg of calcium and 800 to 1,000 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).
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- 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®, 2017).
- 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, 2017). 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, 2017). 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 five 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, 2002). However, the study also reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis during five years of treatment

(Writing Group, 2002). It is now recommended to use estrogen/hormone therapy in the lowest doses for the shortest duration. 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	Manufacturer	FDA Approval Date	Generic Availability
Bisphosphonates			
ACTONEL® (risedronate)	Warner Chilcott	03/27/1998	✔
ATELVIA® (risedronate, delayed release tablet)	Warner Chilcott	10/08/2010	✔
BINOSTO™ (alendronate, effervescent tablet)	Mission	03/12/2012	-
BONIVA® (ibandronate)	Genentech (Roche)	Tablet: 05/24/2005 Injectable: 01/06/2006	✔
FOSAMAX®* (alendronate)	Merck	Tablets: 09/29/1995 Oral Soln: 09/17/2003*	✔
FOSAMAX PLUS D® (alendronate/ cholecalciferol)	Merck	04/07/2005	-
RECLAST® (zoledronic acid)	Novartis	04/16/2007	✔
Calcitonin			
MIACALCIN (calcitonin salmon synthetic)	Novartis	Nasal Spray: 08/17/1995† Injectable: 03/29/1991	✔ -
Estrogen Agonist-Antagonist			
EVISTA (raloxifene)	Eli Lilly	12/09/1997	✔
Parathyroid Hormone Analogs			
FORTEO (teriparatide)	Eli Lilly	06/25/2008	-
TYMLOS (abaloparatide)	Radius Health	04/28/2017	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors			
PROLIA (denosumab)	Amgen	06/01/2010	-

*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.
(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	ACTONEL* (risedronate)	ATELVIA* (risedronate)	BINOSTO* (alendronate)	BONIVA* (ibandronate)	FOSAMAX* (alendronate) FOSAMAX PLUS D (alendronate/ cholecalciferol)	RECLAST* (zoledronic acid)
Treatment of postmenopausal osteoporosis	✔	✔	✔	✔	✔	✔
Prevention of postmenopausal osteoporosis	✔			✔ (tablets only)	✔ (FOSAMAX only)	✔
Treatment to increase bone mass in men with osteoporosis	✔		✔		✔	✔
Treatment of glucocorticoid-induced osteoporosis	✔				✔ (FOSAMAX only)	✔
Prevention of glucocorticoid-induced osteoporosis	✔					✔
Treatment of Paget's disease	✔				✔ (FOSAMAX only)	✔

*Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of ACTONEL, BINOSTO, RECLAST and BONIVA for the treatment of osteoporosis are based on clinical data of three years duration. The safety and effectiveness of ATELVIA for the treatment of osteoporosis are based on clinical data of one year duration. The safety and effectiveness of 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 three to five 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, 2016; FOSAMAX, 2015; 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 Inhibitors

Indication	MIACALCIN (calcitonin salmon synthetic)	EVISTA (raloxifene)	FORTEO (teriparatide)	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		✔			

Indication	MIACALCIN (calcitonin salmon synthetic)	EVISTA (raloxifene)	FORTEO (teriparatide)	PROLIA (denosumab)	TYMLOS (abaloparatide)
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, 2011; FORTEO, 2016; MIACALCIN nasal spray, 2014; MIACALCIN injection, 2016; PROLIA, 2017; TYMLOS, 2017)

Information on indications, mechanism of action, pharmacokinetics, 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 one bisphosphonate agent to another in regard to efficacy. Data from trials specifically examining fractures indicate that bisphosphonates are efficacious and significantly lower the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo (Black et al, 1996; Kanis et al, 2005; Lyles et al, 2007; Ringe et al, 2009; Sawka et al, 2005). 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). Trials also support that risedronate results in a greater reduction in the risk of non-vertebral and hip fractures when compared to alendronate (Silverman et al, 2007). Additionally, there are data to support alendronate and risedronate having similar efficacy (Sarioglu et al, 2006). Zoledronic acid and alendronate 70 mg weekly had comparable increases in lumbar BMD over one year in one study with postmenopausal women with osteoporosis and over two years in a study of men with osteoporosis (McClung et al, 2007; Orwoll et al, 2010). Ibandronate has also been shown to reduce vertebral fractures more than alendronate and risedronate in one trial; while two other trials showed ibandronate to be similar in efficacy to alendronate (Guanabens et al, 2013; Harris et al, 2009; Miller et al, 2008[a]). The included data also show that alendronate, risedronate, and zoledronic acid are effective 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, one meta-analysis measuring bisphosphonate gastrointestinal (GI) adverse events concluded that zoledronic acid had a higher probability of any GI adverse event and nausea. However, risedronate had more serious GI adverse events, and alendronate had more upper GI and esophageal adverse events. Ibandronate was not included in the analysis (Tadrous et al, 2014).

- BINOSTO effervescent 70 mg tablets have been shown to be bioequivalent to alendronate 70 mg tablets. Therefore, clinical efficacy for this product is taken from clinical trials conducted for alendronate 10 mg per day and 70 mg per week.

Calcitonin

- There is a lack of substantial clinical trial data for calcitonin, as trials are typically small in size and observational in design (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 MIACALCIN (calcitonin-salmon) has demonstrated beneficial effects in the treatment of Paget's disease. Treatment produced bone and symptom relief, increased mobility, and decreased alkaline phosphate and other BTMs. In addition, injectable MIACALCIN (calcitonin-salmon) has been shown to cause disease regression in some patients (Kanis et al, 1974; Woodhouse et al, 1977).
- Nasal calcitonin-salmon achieved significant increases in BMD at the lumbar spine compared to placebo after six months of therapy, which was maintained for up to two 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 calcitonins 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 non-vertebral 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; Kung et al, 2003; Johnston et al, 2000; 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 non-vertebral fractures (Kung et al, 2003). There was also no difference in non-vertebral fracture rate during a seven 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 two clinical trials, and neither trial demonstrated a reduction in the risk in non-vertebral 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 four additional years of raloxifene treatment on the incidence of invasive breast cancer, and over a total of eight 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. Furthermore, the incidence of noninvasive breast cancer in women receiving raloxifene was similar to that in women receiving placebo (Martino et al, 2004). The placebo-controlled RUTH trial supports the findings of the MORE trial in that 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 two treatments (Vogel et al, 2006). However, in a follow-up trial of 6.75 median 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 still 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; Kung et al, 2003; Johnston et al, 2000; 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 two year, placebo-controlled trial (N=437) evaluating FORTEO (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 FORTEO (teriparatide). After a median duration of 11 months, FORTEO (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 FORTEO (teriparatide) were observed (Kaufman et

al, 2005). FORTEO (teriparatide) has also 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 FORTEO (teriparatide) and alendronate, FORTEO (teriparatide) significantly increased BMD at the posteroanterior spine, lateral spine, and femoral neck (Finkelstein et al, 2003).

- FORTEO (teriparatide) also significantly increased BMD at the lumbar spine and total hip compared to alendronate in patients with glucocorticoid-induced osteoporosis. In addition, after 36 months, significantly fewer patients receiving FORTEO (teriparatide) had a vertebral fracture (Langdahl et al, 2009; Saag et al, 2007; Saag et al, 2009). FORTEO (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).
- FORTEO (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; Lindsay et al, 2004; McClung et al, 2005; Minne et al, 2008; Neer et al, 2001; Obermayer-Pietsch et al, 2008). The EUROFORS trial was a prospective, two year trial in which all patients received FORTEO (teriparatide) for the first year of treatment. After 12 months, patients were divided into two different substudies. In Substudy 1, for the second year of treatment, patients were randomized to FORTEO (teriparatide), the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on FORTEO (teriparatide) for the second year of treatment. After the first year of treatment, FORTEO (teriparatide) significantly increased BMD at the lumbar spine, total hip, and femoral neck. The benefits of FORTEO (teriparatide) appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued FORTEO (teriparatide) for a total of two 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 FORTEO (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 FORTEO (teriparatide) significantly reduces the risk of vertebral and non-vertebral fractures (Body et al, 2002; Lindsay et al, 2004; Neer et al, 2001). Data also suggest that FORTEO (teriparatide) in combination with a bisphosphonate may result in significant increases in BMD compared to monotherapy with either FORTEO (teriparatide) or a bisphosphonate (Cosman et al, 2009; Cosman et al, 2011). In another study of 12 months duration, combination teriparatide and denosumab were compared to either treatment alone. Combined teriparatide and denosumab increased BMD at the posterior-anterior (PA) spine, femoral neck, and hip significantly more than either drug alone (Leder et al, 2014; Tsai et al, 2013).
- In terms of safety data, no clinically significant concerns related to FORTEO (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 TYMLOS (abaloparatide) was compared with FORTEO (teriparatide) and placebo in the 18-month randomized controlled ACTIVE trial in 2,463 postmenopausal women with osteoporosis. Treatment with TYMLOS (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 vs 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 TYMLOS (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 PROLIA (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 two year, double-blind, placebo-controlled, randomized trial enrolling 252 women (Ellis et al, 2008). Patients were randomized to denosumab SC every six months (n=127) or placebo (n=125) for a total of four 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% compared to placebo (P<0.0001 at both time points). BMD at the lumbar spine bone was significantly higher with PROLIA (denosumab) compared to placebo after 12 months (4.8% vs -0.7%; treatment difference, 5.5%; 95%

confidence interval [CI], 4.8 to 6.3; P<0.0001). Furthermore, after two years, PROLIA (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 3,420 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 six months or placebo. The time to first fracture, the primary outcome measure, 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 adverse events was similar in both treatment groups.
- When compared to placebo, PROLIA (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 two treatments. In this trial, BMD evaluations were not performed; however, it was noted that biochemical markers of bone turnover significantly decreased with PROLIA (denosumab) compared to placebo (P<0.001 for all). Of note, the FDA-approved dosing was not evaluated in this trial; PROLIA (denosumab) was administered once monthly (Smith et al, 2012). The ADAMO trial showed that denosumab therapy administered every six 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 PROLIA (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 PROLIA (denosumab). In this trial, after 36 months, there were significant reductions with PROLIA (denosumab) compared to placebo in the incidence of new vertebral (2.3% vs 7.2%; relative risk, 0.32; 95% CI, 0.26 to 0.41; P<0.001), non-vertebral (6.5% vs 8%; relative risk, 0.80; 95% CI, 0.67 to 0.95; P=0.01), and hip fractures (0.7% vs 1.29%; relative risk, 0.6; 95% CI, 0.31 to 0.97; P=0.04)(Cummings et al, 2009). A three-year extension trial maintained the denosumab patients on active treatment for a total of six years and crossed-over the placebo patients to denosumab treatment for a total of three years. For patients on denosumab for six 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: rapid and marked reduction in BTMs, large increases in BMD, low fracture rates, and a favorable benefit/risk profile (Bone et al, 2013).
- A meta-analysis/systematic review of clinical trials of PROLIA (denosumab) in osteopenic and osteoporotic postmenopausal women with low bone mass sought to evaluate the effect of PROLIA (denosumab) on BTMs and BMD. In this analysis, adverse events, 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 PROLIA (denosumab) based on change in baseline BMD. Despite this, it was observed that treatment with PROLIA (denosumab) was associated with increased BMD at the lumbar spine and hip, as well as decreased BTMs. Regarding secondary outcomes, it was revealed that PROLIA (denosumab) was not associated with a significant reduction in fracture risk (odds ratio, 0.74; 95% CI, 0.33 to 0.64; P=0.45) (Anastaskilakis et al, 2009).
- The efficacy of PROLIA (denosumab) at increasing BMD is also supported by three 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 three dose-ranging trials followed patients for a total of 48 months. In the final trial, it was demonstrated that after 48 months PROLIA (denosumab) 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 PROLIA (denosumab), it was observed that subsequent decreases in BMD at measured skeletal sites occurred. When compared to alendronate, changes in BMD at the total hip were also significantly greater with PROLIA (denosumab) at 12 months (3.5% vs 2.6%; P<0.0001) (Brown et al, 2009). In a second meta-analysis comparing PROLIA (denosumab) to weekly alendronate, no difference in fracture risk was demonstrated (odds ratio, 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 six months (Lin et al, 2012). In a 12-month trial comparing denosumab to monthly ibandronate therapy, denosumab treatment resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate therapy (Recknor et al, 2013).
- In terms of safety data, no clinically significant concerns related to PROLIA (denosumab) were observed; the safety profile of PROLIA (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 BINOSTO (alendronate effervescent tablet), alendronate, risedronate, ibandronate, zoledronic acid, PROLIA (denosumab), FORTEO (teriparatide), and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
    - There is a high level of evidence from RCTs that BINOSTO (alendronate effervescent tablet), alendronate, risedronate, zoledronic acid and PROLIA (denosumab) reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis; there is moderate evidence that FORTEO (teriparatide) reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
    - There is a high level of evidence from RCTs that BINOSTO (alendronate effervescent tablet), alendronate, risedronate, zoledronic acid, and PROLIA (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 combinations of osteoporosis therapies 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 one 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 flushing (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 gastrointestinal 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 PROLIA (denosumab).
- There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments. In two 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 that each drug would be the most preferable for various outcomes (Yang et al, 2016). Among products included in this review, the most preferred agents for various outcomes were FORTEO (teriparatide) in non-vertebral fractures; PROLIA (denosumab), zoledronic acid, and alendronate in hip fractures; FORTEO (teriparatide) in wrist fractures; and raloxifene, alendronate, and PROLIA (denosumab) for adverse events.
- A systematic review and meta-analysis demonstrated FORTEO (teriparatide) to be superior vs alendronate for increasing lumbar spine BMD in patients with postmenopausal osteoporosis. The results of the meta-analysis showed no significant difference in the percentage change in femoral neck BMD or incidence of vertebral and/or nonvertebral fractures between the two therapies (Wang et al, 2017).
- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) evidence report included a network meta-analysis of three 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 significantly lower risk of vertebral fractures and possible nonvertebral fractures vs controls (Nayak & Greenspan, 2017).

SAFETY SUMMARY

- Contraindications
  - Bisphosphonates
    - Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
    - Inability to stand or sit upright for at least 30 minutes (at least 60 minutes for BONIVA)
    - Hypocalcemia
  - FOSAMAX oral solution should not be administered to patients at increased risk of aspiration
  - EVISTA
    - Active or past history of venous thromboembolism
    - Pregnancy or nursing mothers
  - PROLIA
    - Hypocalcemia
    - Pregnancy or nursing mothers
- Warnings/precautions
  - Bisphosphonates
    - Caution should be used in patients with active gastrointestinal problems (except RECLAST).
    - Reports of severe and occasionally incapacitating bone, joint, and/or muscle pain
    - Osteonecrosis of the jaw; can occur spontaneously. Risk factors include dental procedures, cancer diagnosis, poor oral hygiene, medications such as chemotherapy agents, corticosteroids, and angiogenesis inhibitors, or certain co-morbidities (dental disease, anemia, coagulopathy, and infection).
    - Caution should be used in aspirin sensitive patients (RECLAST).
    - Caution should be used in patients who must restrict sodium intake (BINOSTO).
  - EVISTA
    - **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.
    - Treatment with EVISTA should be discontinued 72 hours prior to and during prolonged immobilization.
    - Death due to stroke: increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. No increased risk of stroke was seen in this trial. Risk-benefit balance should be considered in women at risk for stroke.
    - Cardiovascular disease: EVISTA should not be used for the primary or secondary prevention of cardiovascular disease.
    - Treatment with EVISTA is not recommended in premenopausal women
    - Caution should be used in patients with hepatic impairment.
    - Concomitant use with systemic estrogens is not recommended.
    - Hypertriglyceridemia: If previous treatment with estrogen resulted in hypertriglyceridemia, serum triglycerides should be monitored.
  - FORTEO and TYMLOS
    - **Boxed warning:** FORTEO 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).
    - **Boxed warning**: TYMLOS should not be used in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton. Cumulative use of TYMLOS and parathyroid hormone analogs (eg, teriparatide) > 2 years during a patient's lifetime is not recommended.

        - Orthostatic hypotension: Patients should be instructed to sit or lie down if symptoms develop after dose administration with TYMLOS; transient orthostatic hypotension may occur with initial doses of FORTEO.
        - Caution should be used in patients with active or recent urolithiasis; urinary calcium should be monitored.
        - TYMLOS should not be used in patients with hypercalcemia or hypercalcemic disorders; FORTEO may increase serum calcium, urinary calcium, and serum uric acid.
        - FORTEO should not be used > 2 years during a patient's lifetime.
    - MIACALCIN
        - Potential increased risk of malignancies in calcitonin-salmon-treated patients. The benefits for the individual patient should be carefully considered against possible risks.
        - Circulating antibodies and abnormal urine sediment have been reported with MIACALCIN.
        - Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended at beginning of treatment, periodically during the course of therapy, and at any time nasal symptoms occur (MIACALCIN nasal spray only).
    - PROLIA
        - Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported.
        - Osteonecrosis of the jaw; can occur spontaneously. Risk factors consist of dental procedures, cancer diagnosis, poor oral hygiene, medications such as chemotherapy agents, corticosteroids, and angiogenesis inhibitors, or certain co-morbidities (dental disease, anemia, coagulopathy, and infection). A dental examination is recommended prior to the initiation of PROLIA.
        - Severe musculoskeletal pain has been reported with PROLIA.
        - An increased risk for multiple vertebral fractures has been reported following discontinuation of PROLIA therapy.
        - Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections with PROLIA. The benefit-risk profile should be considered in such patients.
- Adverse events
    - Bisphosphonates
        - The most common adverse effects are headache and gastrointestinal effects such as abdominal pain, diarrhea, constipation, nausea, and dyspepsia.
    - EVISTA
        - The most common adverse events (> 2%) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, sweating.
    - FORTEO
        - The most common adverse events (> 10%) include nausea, arthralgia, and pain.
    - MIACALCIN
        - The most common adverse events (≥ 3%) with MIACALCIN nasal spray include rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache.
        - The most common adverse events with MIACALCIN injection include nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2 to 5%).
    - PROLIA
        - The most common adverse events (> 5%) include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has also been reported in clinical trials.
    - TYMLOS
        - The most common adverse events (≥ 2%) include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.
- Drug Interactions
    - Bisphosphonates
        - Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of oral bisphosphonates and should not be taken together.
        - Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral bisphosphonates all cause gastrointestinal irritation; caution should be used when administered together.
    - EVISTA
        - Cholestyramine, warfarin, and highly protein-bound drugs all interact with EVISTA.
    - FORTEO
        - Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use teriparatide with caution

- MIACALCIN
  - Concomitant use of MIACALCIN and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium; the dose of lithium may require adjustment.

- Risk Evaluation and Mitigation Strategy (REMS)
  - PROLIA 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.
    - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe PROLIA.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Bisphosphonates				
ACTONEL (risedronate)	Tablet: 5 mg, 30 mg, 35 mg, 150 mg	• Prevention/ treatment of postmenopausal osteoporosis: 5 mg once daily; 35 mg once a week; or 150 mg once a month • Osteoporosis in men: 35 mg once a week • Prevention/ treatment of glucocorticoid-induced osteoporosis: 5 mg once daily • Paget's disease: 30 mg once daily for 2 months. May repeat times one if failure	Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 30 minutes before the first food or drink of the day other than water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Patients should not lie down for 30 minutes after taking the medication.
ATELVIA (risedronate)	Tablet, delayed release: 35 mg	• 35 mg once weekly	Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of ATELVIA and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Tablet should be taken immediately after breakfast. • Swallow while in an upright position with 4 oz of water. • Patients should not lie down for 30 minutes after taking the medication. • Tablet should not be chewed, cut or crushed.
BINOSTO (alendronate)	Tablet, effervescent: 70 mg	• Treatment of postmenopausal osteoporosis: 70 mg once weekly • Osteoporosis in men: 70 mg once weekly	Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of BINOSTO and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 30 minutes before the first food, drink or medication of the day other than water. • Dissolve the effervescent tablet in 4 oz room temperature plain water only • Patients should not lie down for 30 minutes after taking the medication and until after their first food of the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
BONIVA (ibandronate)	Tablet: 150 mg Injectable syringe: 3 mg/3mL	• 150 mg once monthly on the same date each month • 3 mg IV every 3 months	Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration. Injectable should be given IV over 15 to 30 seconds. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of BONIVA and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 60 minutes before the first food, drink or medication of the day other than water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Patients should not lie down for 60 minutes after taking the medication.
FOSAMAX (alendronate)	Tablet: 5 mg, 10 mg, 35 mg, 40 mg, 70 mg Oral solution: 70 mg/75 mL	• Treatment of postmenopausal osteoporosis: 70 mg once weekly or 10 mg once daily • Prevention of postmenopausal osteoporosis: 35 mg once weekly or 5 mg once daily • Osteoporosis in men: 70 mg once weekly or 10 mg once daily • Treatment of glucocorticoid-induced osteoporosis: 5 mg once daily; postmenopausal women not on estrogen: 10 mg once daily • Paget's disease: 40 mg once daily for 6 months. Retreatment may be considered if not effective.	Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of FOSAMAX and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 30 minutes before the first food, drink or medication of the day other than plain water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Oral solution should be followed by at least 2 oz of water. • Patients should not lie down for 30 minutes after taking the medication and until after their first food of the day.
FOSAMAX PLUS D (alendronate/ cholecalciferol)	Tablet: 70 mg/2,800 IU, 70 mg/5,600 IU	• Treatment of postmenopausal osteoporosis: 70 mg alendronate/2800 IU vitamin D3 or one 70 mg alendronate/5600 IU vitamin D3 tablet once weekly. • Osteoporosis in men: 70 mg alendronate/2800 IU vitamin D3 or one 70 mg alendronate/5600 IU vitamin D3 tablet once weekly.	Supplemental calcium should be given if dietary intake is inadequate. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of FOSAMAX PLUS D and should be taken at a different time of the day.	• Take at least 30 minutes before the first food, drink or medication of the day other than plain water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Patients should not lie down for 30 minutes after taking the medication and until after their first food of the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
RECLAST (zoledronic acid)	Injection: 5 mg/100 mL	• Treatment of postmenopausal osteoporosis: 5 mg IV once yearly. • Prevention of postmenopausal osteoporosis: 5 mg IV once every two years. • Osteoporosis in men: 5 mg IV once yearly. • Prevention/ treatment of glucocorticoid-induced osteoporosis: 5 mg IV once yearly. • Paget's disease: 5 mg IV once. May retreat if relapse.	Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Patient should be appropriately hydrated. • Give 10 mL normal saline flush after injection. • Acetaminophen may be given after administration to decrease acute phase reactions. • Infusion should be given over no less than 15 minutes. • Allow refrigerated solution to come to room temperature prior to injection.
Calcitonin				
MIACALCIN (calcitonin-salmon synthetic)	Nasal solution: 3.7 mL (30 day supply) Injection: 200 IU/mL in 2 mL vials	• Treatment of postmenopausal osteoporosis: one spray (200 IU) intranasally once daily, alternating nostrils daily. Or 100 IU SQ or IM once daily. • Paget's Disease: 100 IU (0.5 mL) SQ or IM once daily • Hypercalcemia: 4 IU/kg SQ or IM* every 12 hours. If no response after 1 to 2 days, can increase to 8 IU/kg every 12 hours. If no response after 2 days, increase to 8 IU/kg every 6 hours.	Store unopened bottle in refrigerator. Once opened, store at room temperature. Discard opened bottle after 35 days. If the volume of the injection exceeds 2 mL, IM injection is preferable and multiple sites of injection should be used. Store injection in refrigerator.	Nasal spray: • Before the first dose, allow bottle to reach room temperature. • Before the first dose, the bottle must be primed. • Depress the side arms toward the bottle 5 times to prime it. • Nasal spray does not need to be primed before each daily dose.
Estrogen Agonist-Antagonist				
EVISTA (raloxifene)	Tablet: 60 mg	• All indications: 60 mg once daily	Adequate calcium and vitamin D intake should be assured in patients with osteoporosis.	• Can take with or without meals.
Parathyroid Hormone Analogs				
FORTEO (teriparatide)	Injection: 28 doses of 20 mcg in a prefilled injectable pen	• All indications: 20 mcg SQ once daily	The injection pen should be refrigerated at all times.	• Inject into the thigh or abdominal wall. • Patients should be able to sit or lie down if orthostatic hypotension occurs.
TYMLOS (abaloparatide)	Injection: 28 doses of 80 mcg in a	• 80 mcg SQ once daily	The injection pen should be refrigerated before first use, and can be stored at room	• Inject into the periumbilical region of the abdomen at

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	prefilled injectable pen		temperature after first use up to 30 days.	approximately the same time every day. • The first several doses should be administered where the patient can sit or lie down if necessary, in case symptoms of orthostatic hypotension occur.
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors				
PROLIA (denosumab)	Injection: 1 mL of 60 mg/mL prefilled syringe;	• All indications: 60 mg SQ every 6 months	Administered by a healthcare professional. Hypocalcemia must be corrected prior to the administration of PROLIA. All patients should receive calcium 1,000 mg daily and at least 400 IU vitamin D daily. Store in the refrigerator. Discard 14 days after removal from refrigerator.	• Administer in the upper arm, the upper thigh, or the abdomen. • People sensitive to latex should not handle the grey needle cap. • Warm to room temperature prior to injecting.

IU=international units; IV=intravenously; SQ=subcutaneously; IM=intramuscularly; oz=ounces

CONCLUSION

- 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 (Adler et al, 2016; Buckley et al, 2017; Camacho et al, 2016; Committee on Practice Bulletins – Gynecology, 2012; Cosman et al, 2014; Florence et al, 2013; 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.
    - Other antiresorptive drugs approved for osteoporosis include calcitonin, raloxifene and denosumab. These are not considered first-line therapies due to adverse events, less evidence of efficacy, and route of administration.
- 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]).
- Because medication adherence may pose challenges for osteoporosis prevention and treatment, choice of a bisphosphonate should be based on ease of administration for the patient. For instance, ATELVIA (risedronate delayed release) and FOSAMAX (alendronate) are 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. An observational study found 2-year persistence and compliance were higher in women initiating osteoporosis with injectable therapies compared to oral therapies (Durden et al, 2017).
- The receptor activator of nuclear factor K-B ligand inhibitor, PROLIA (denosumab), has data for hip, vertebral, and nonvertebral fractures. It is a subcutaneous injection given every six months. National guidelines recommend it as an alternative to the bisphosphonates (Committee on Practice Bulletins – Gynecology, 2012; Florence et al, 2013). However, the American Association of Clinical Endocrinologists (AACE) recommends PROLIA as an optional first-line treatment in post-menopausal women (Camacho et al, 2016). Monitoring for infection is required with this agent.
- FORTEO (teriparatide) is generally reserved for patients at high risk for fractures, or unable to tolerate or manage therapy with oral bisphosphonates (Camacho et al, 2016; Committee on Practice Bulletins – Gynecology, 2012; Watts

et al, 2012). TYMLOS (abaloparatide) is the most recent parathyroid hormone analog approved by the FDA, and is not included in current osteoporosis guidelines. Both FORTEO (teriparatide) and TYMLOS (abaloparatide) are administered via daily subcutaneous injection, and treatment duration should not exceed two years. Osteosarcoma is a risk and there are insufficient data to demonstrate reduction in hip fractures with these agents.

- 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 a breast cancer risk-reduction agent, which is recommended for asymptomatic women ≥35 years of age who are at risk for breast cancer. Depending on individual patient characteristics, raloxifene may be a preferred option (Moyer et al, 2013). There is an increased risk of thromboembolism and stroke with this agent.
- MIACALCIN (calcitonin-salmon) lacks efficacy data for fracture reduction in osteoporosis treatment.
- For the treatment of Paget's disease, risedronate, alendronate, MIACALCIN (calcitonin-salmon injectable), and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, FORTEO (teriparatide), alendronate, and zoledronic acid are all indicated. Selection of an agent should be based on patients' preference of administration. FORTEO (teriparatide) should be reserved for higher doses of steroids and longer lengths of treatment per the national guidelines (Buckley et al, 2017).
- The various other indications for the agents in this class have clinical trial data supporting their use.

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