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Denosumab: A New Therapy for Osteoporosis by Candice Gehret, Pharm.D.

Introduction: Osteoporosis is defined as the structural deterioration of bone due to an imbalance in bone removal (resorption) and replacement.¹ Increases in bone resorption lead to low bone mass, increased bone fragility, and ultimately fractures of the hip, spine, and wrist. Currently, 10 million people in the United States have osteoporosis and an additional 34 million have osteopenia (low bone mass).¹ Of the 10 million people with osteoporosis, 80% are females and 20% are males. Osteoporosis is usually seen in elderly people; however, it may occur at any age. People of all ethnic backgrounds have a significant risk of acquiring osteoporosis; however, the risk for Hispanic women is increasing most rapidly. In 2005, 19 billion dollars were spent on osteoporosis-related fractures and an estimated 25.3 billion dollars are to be spent in 2025.

Bone Remodeling: Bone is made of collagen, calcium and phosphate salts, and bone cells (e.g., osteoclasts and osteoblasts).^{2,3} Collagen is the flexible framework for bony structures. Calcium and phosphate salts, particularly hydroxyapatite, deposit into the collagen matrix and mineralize bone. These minerals are responsible for the strength of bone, as well as regulation of calcium and phosphorous blood levels. Osteoclasts and osteoblasts are responsible for bone remodeling.

Osteoclasts are responsible for bone resorption.^{2,4} They attach to bone and degrade the area through acidification and proteolytic digestion. Osteoblasts are responsible for bone formation. They follow osteoclasts and lay down new bone at the site. Osteoclasts and osteoblasts are regulated by Receptor Activator for Nuclear Factor κ B (RANK) and its ligand, RANKL. RANK is located on the surface of osteoclasts and is responsible for osteoclast proliferation and subsequent bone destruction. RANKL is expressed on osteoblasts, T cells, and tumor cells and is responsible for osteoclast formation, function, and survival. When RANKL binds to RANK, osteoclasts are activated and bone resorption occurs. Osteoprotegerin, a member of the tumor necrosis family, competes with RANKL for binding to RANK and subsequently prevents bone destruction.

Bone Loss in Osteoporosis: Bone loss associated with osteoporosis is generally due to an increase in osteoclastic action.³ Most people possess 85 to 90% of their adult bone mass by the age of 18 years in females and 20 years in males.¹ Once adult bone mass is obtained, it is maintained with minimal bone loss for a period of time. However, once this plateau is reached, bone loss accelerates, causing osteoporosis.

Women have less bone mass than men and lose it much more rapidly once they reach menopause. After menopause, women become estrogen deficient. Estrogen inhibits multiple cytokines that are responsible for osteoclast formation. Therefore, postmenopausal women do not have estrogen stores available to combat the excessive osteoclast formation and are more prone to developing osteoporosis.

Osteoporosis Diagnosis: Osteoporosis is diagnosed by bone mineral density (BMD), the amount of mineralized tissue in a scanned area (usually the hip or spine).⁵ The measurement is used to determine an individual’s risk for fracture development. Dual-energy x-ray absorptiometry (DXA) is used to determine BMD. Two scores are reported with DXA, a Z score and a T score. The Z score is the comparison of an individual’s BMD to the expected BMD for that individual’s age and gender. The T score is the comparison of an individual’s BMD to the “young normal” BMD for the same gender. The Z and T scores are reported in standard deviations, and the T score is used for diagnosis of osteoporosis. Dual-energy x-ray absorptiometry should not be performed in patients in whom treatment will not be initiated or changed, regardless of the results. Table 1 lists the World Health Organization (WHO) T score ranges for normal, low bone mass, and osteoporosis.

Fracture Risk Assessment: The WHO has developed a tool for evaluating fracture risk, known as the Fracture Risk Assessment Tool (FRAX™).⁶ This tool is available online and is to be used in postmenopausal women and men greater than 50 years from the United States. The FRAX reports the 10-year risk of fracture. Risk factors included in the analysis are in Table 2. Bone mineral density T scores and the FRAX can be used for determination of treatment.

Table 1: WHO T Score Ranges⁵

Normal	≥ -1.0
Low bone mass (osteopenia)	-1.0 to -2.5
Osteoporosis	≤ -2.5

Table 2: FRAX™ Risk Factors⁶

Age	Current smoking
Gender	Glucocorticoids
Weight	Rheumatoid arthritis
Height	Secondary osteoporosis
Previous fracture	Alcohol intake
Parent fractured hip	Femoral neck T score

Treatment Recommendations: The National Osteoporosis Foundation (NOF) recommends postmenopausal women be considered for treatment if they have one of the following: hip or vertebral fracture, T score less than or equal to -2.5 at the femoral neck or spine after ruling out secondary causes, and a low bone mass with a 10-year probability of a hip fracture ≥3%, or a 10-year probability for any major osteoporosis-associated fracture ≥20%, based upon the United States-adapted FRAX.³ There are multiple treatment options for postmenopausal osteoporosis and selection should depend upon the benefits versus risks for each patient. The NOF does not have specific recommendations on which medication to use, and it does not recommend the use of medications not approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis.

A Brief Review of FDA-Approved Medications for the Treatment of Osteoporosis

Bisphosphonates: Select bisphosphonates are FDA-approved for the *treatment* of osteoporosis in postmenopausal women [alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), and zoledronic acid (Reclast®)].⁷⁻¹³ Refer to Table 3 (located on pages 8 and 9) for FDA-approved dosing of these agents. Other FDA-approved indications for bisphosphonates include *prevention* of osteoporosis in postmenopausal women (alendronate, risedronate, ibandronate, and zoledronic acid), treatment of osteoporosis in men (alendronate, risedronate, and zoledronic acid), Paget’s disease (alendronate, risedronate, zoledronic acid, and pamidronate), treatment of glucocorticoid-induced osteoporosis (alendronate, risedronate, and zoledronic acid), prevention of glucocorticoid-induced osteoporosis (risedronate and zoledronic acid), treatment of hypercalcemia of malignancy (zoledronic acid and pamidronate), treatment of multiple myeloma (zoledronic acid and pamidronate), and treatment of bone metastases in solid tumors (zoledronic acid and pamidronate).⁷⁻¹⁵

Bisphosphonates are used for osteoporosis due to their effects on bone resorption.¹⁶⁻¹⁸ They bind and inhibit hydroxyapatite dissolution in bone. Bisphosphonates accumulate at sites of active bone remodeling and are incorporated into the bone matrix. They reside in the matrix until the bone is remodeled and are released into the acidic environment created by the bone resorption process. Bone resorption is decreased as a result of their effects on osteoclasts.

Commercially available bisphosphonates contain nitrogen within their structure and subsequently inhibit farnesyl pyrophosphate synthase (FPPS), an enzyme involved in the cholesterol synthesis pathway, and important for the production of proteins used by osteoclasts. Bisphosphonates inhibit osteoclast recruitment to and activity on the bone surface, reduce osteoclast lifespan, and decrease the rate of bone dissolution.

Oral bisphosphonates are rapidly absorbed and reach maximal concentrations within 30 to 60 minutes, however, the bioavailability for these agents is poor (<2%).¹⁶ Absorption is best when these agents are taken on an empty stomach. Bisphosphonates are rapidly distributed almost exclusively to the bone (50 to 60%) and kidneys following absorption.^{16,19,20} They have a high affinity for bone surfaces undergoing remodeling and are deposited into resting and resorbing surfaces and released once osteoclasts resorb that region of the bone.²⁰ Bisphosphonates do not undergo metabolism.⁷⁻¹⁵ The terminal half-life of bisphosphonates is variable and have been reported to be 7 days up to 10 years. This is due to the sequestration of bisphosphonates into bone and release during bone resorption.^{17,19,21} Bisphosphonates are only active once released from the bone. Bisphosphonates are renally eliminated as unchanged drug. Elimination is decreased with poor renal function. The use in patients with severe renal dysfunction (defined as a creatinine clearance < 30-35 mL/min) is not recommended.⁷⁻¹⁶

Common adverse effects seen with oral bisphosphonates are esophagitis, dysphagia, and gastric ulcers. These effects may occur a result of the tablet formulation.^{7-11,22} It is recommended that these agents are taken first thing in the morning after an overnight fast with six to eight ounces of water and at least 30 to 60 minutes prior to consuming any food or beverages (other than water). An acute phase reaction is commonly seen with injectable aminobisphosphonates (e.g., ibandronate, pamidronate, and zoledronic acid).¹²⁻¹⁵ Patients may experience myalgias, arthralgias, fevers, and headaches within the first 3 days after therapy. It generally resolves within 3 to 4 days, but may persist for up to 14 days. Acetaminophen may be given prior to the infusion and for 72 hours following the infusion to prevent the occurrence of the reaction. Serious adverse events, such as osteonecrosis of the jaw (ONJ), bone pain, atrial fibrillation, esophageal cancer, and atypical fractures have been reported, however, the incidence is rare.^{7-15,23,24} There are few drug interactions associated with bisphosphonates.⁷⁻¹⁵ Oral antacids and minerals, such as some calcium, iron, and magnesium salts, may decrease the absorption of oral bisphosphonates.⁷⁻⁹ Administration of oral antacids and minerals should be separated by at least 30 to 60 minutes. Bisphosphonate use is contraindicated in patients with esophageal abnormalities, such as stricture or achalasia, which may delay esophageal emptying.⁷⁻¹⁵ Patients with hypocalcemia or hypersensitivity to bisphosphonates should not use these agents. Hypocalcemia must be corrected prior to administration. Patients unable to stand or sit upright for 30 to 60 minutes should not use the oral bisphosphonate formulations.⁷⁻¹¹ The oral solution formulation should not be used in patients at risk for aspiration.⁷

Calcitonin: Salmon calcitonin has been used for the treatment of osteoporosis since the 1980s.²⁵ It is a peptide similar to human calcitonin and is obtained from the thyroid-like gland of salmon with much higher intrinsic potency than human calcitonin. Calcitonin is FDA-approved for the treatment of osteoporosis in women who are greater than 5 years postmenopausal.^{26,27} It is also approved for the treatment of Paget's disease and as an adjunctive treatment for hypercalcemia. Calcitonin is destroyed by gastric acid and must be administered parenterally or intranasally, however, unique oral formulations are being investigated.²⁹ Refer to Table 3 for FDA-approved dosing of calcitonin (Miacalcin[®], Fortical[®]).

Calcitonin is used in osteoporosis due to its effect on osteoclast activity.²⁵⁻²⁸ Calcitonin binds membrane receptors located on osteoclasts and inhibits bone resorption. It may also decrease the number of osteoclasts and their secretory action. Calcitonin increases renal calcium excretion and subsequently reduces blood calcium levels.

Absorption from the nasal administration of calcitonin is rapid.^{26,28} Peak concentrations are seen 31 to 39 minutes after administration of the intranasal formulation and 16 to 25 minutes after the injectable formulation.²⁶⁻²⁸ The bioavailability of the intranasal formulation is reported to be 3% (range, 0.3% to 30.6%) of the injectable formulation. Calcitonin is rapidly metabolized by the kidneys, blood, and peripheral tissues to inactive metabolites. The elimination half-life of calcitonin is 43 minutes. Some inactive metabolites and unchanged drug are excreted in the urine.

Adverse effects associated with calcitonin products are specific to the formulation. Common adverse effects observed with injectable calcitonin include flushing and transient nausea and vomiting.^{25,27,29} Since calcitonin is a protein, the injectable formulation may cause systemic hypersensitivity reactions. The most common adverse effect associated with the intranasal formulation is transient rhinitis.^{26,28} Tachyphylaxis can occur within 48 hours of calcitonin administration.³⁰

No drug interactions have been identified with the use of calcitonin.²⁶⁻²⁸ Patients with a hypersensitivity to salmon-derived products should not use these agents.²⁶⁻²⁸

Teriparatide: Teriparatide (Forteo[®]) is a human recombinant peptide of the N-terminal fragment of human parathyroid hormone (PTH).³¹ Teriparatide is FDA-approved for the treatment of osteoporosis in postmenopausal women.³² It is also approved for the treatment of primary or hypogonadal osteoporosis in men and glucocorticoid-induced osteoporosis in women and men. It is FDA-approved for a maximum duration of use of 2 years due to lack of safety and efficacy data beyond 2 years. Refer to Table 3 for FDA-approved dosing of teriparatide.

Teriparatide is a peptide fragment of human PTH with the same anabolic activity as PTH.^{31,33} Endogenous PTH and teriparatide exert their actions on high-affinity receptors located on osteoblasts and renal tubular cells. Teriparatide stimulates bone formation through its activation of osteoblasts. Levels of bone formation increase earlier than those of bone resorption. This period of bone formation before resorption is called the “anabolic window.” Endogenously, the parathyroid gland secretes PTH in response to low serum calcium levels and PTH subsequently stimulates osteoclasts to release calcium and phosphorus into the bone. Renal excretion of calcium is decreased and phosphorous is increased. PTH also stimulates intestinal absorption of dietary calcium and phosphorus. Similar effects are seen with teriparatide.

Absorption of subcutaneous teriparatide is rapid, and the absolute bioavailability of teriparatide is 95%.^{31,32} Peak serum concentrations are reached 30 minutes after administration. The half-life of subcutaneous teriparatide is 1 hour. Levels decrease to non-detectable within 3 hours. Accumulation in the bone has not been shown. Metabolism is unknown for teriparatide, however, endogenous PTH is metabolized by the liver. Teriparatide is excreted in the urine.

The most common adverse effect reported with teriparatide is transient hypercalcemia.^{31,32} Dizziness, nausea, headache, and leg cramps have also been reported. A black box warning exists for teriparatide concerning an increased risk of osteosarcoma. Patients with metabolic bone disease other than osteoporosis should not use this agent. Teriparatide is contraindicated in patients with a hypersensitivity to teriparatide or its formulation.³² Caution is advised with use in patients with hepatic and renal impairment; however, dosage recommendations are not provided. There are no known significant drug interactions, however, caution should be exercised when administering digoxin with teriparatide.^{31,32} Teriparatide can cause hypercalcemia and may predispose a patient to digoxin toxicity.

Raloxifene: Raloxifene (Evista[®]) is a selective estrogen receptor modulator FDA-approved for the treatment of osteoporosis in postmenopausal women.³⁴ It is also FDA-approved for the prevention of osteoporosis and risk reduction of invasive breast cancer in postmenopausal women at high risk for developing invasive breast cancer or with osteoporosis.

Raloxifene has estrogenic and antiestrogenic actions on various tissues in the body.^{35,36} It is used in osteoporosis due to its agonistic effects on estrogen receptors in bone and inhibition of bone resorption. Osteoclast-mediated bone resorption is reduced by raloxifene whereas expression of bone matrix proteins is increased. Other actions of raloxifene include antagonism of estrogen receptors in uterine and breast tissues.

Approximately 60% of raloxifene is absorbed rapidly from the gastrointestinal tract, however, the mean absolute bioavailability is 2%.³⁴⁻³⁶ Raloxifene has extensive distribution and is more than 95% bound to plasma proteins. Peak concentrations are seen 6 hours after administration. Extensive hepatic first-pass metabolism by glucuronidation occurs. Unchanged drug accounts for only 1% of circulating concentrations. The plasma elimination half-life is 27.7 hours. Raloxifene is primarily eliminated by the fecal route within 5 days of administration. Renal excretion of glucuronide metabolites accounts for 5% of the administered dose.

The most common adverse effects seen with raloxifene are hot flashes and leg cramps.^{34,35} Other adverse effects include peripheral edema, breast pain, and vaginal bleeding. Rare venous thromboembolic events have been associated with raloxifene use. Few clinically significant drug interactions have been identified with raloxifene.^{34,35} Bile acid sequestrants can bind raloxifene and decrease its absorption and enterohepatic cycling. Raloxifene may decrease the absorption of levothyroxine. Therefore, caution should be used when these agents are used together. One study showed a 10% decline in prothrombin time following co-administration of raloxifene and warfarin. If a patient is taking raloxifene and warfarin concomitantly, the patient’s international normalized ratio (INR) could decrease. Thus, the INR should be closely monitored in patients on warfarin when raloxifene is initiated or discontinued.

Raloxifene is contraindicated in patients with a history of or who have current venous thromboembolic disorders.³⁴ Caution should be used with raloxifene therapy in patients with cardiovascular disease. Patients who are to be immobilized for prolonged periods of time should discontinue raloxifene 72 hours prior to the event and may be restarted only when fully ambulatory. Safety and efficacy has not been established in males, premenopausal women, or patients with hepatic or renal impairment. Raloxifene should not be used in combination with systemic estrogens as safety has not been established.

Denosumab: A New Therapy for Osteoporosis

Denosumab (Prolia[®]) is a monoclonal antibody recently FDA-approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture.³⁷ It is also being evaluated for prevention of osteoporosis in postmenopausal women as well as for the treatment and prevention of bone loss in patients undergoing hormone ablation therapy for breast and prostate cancer.³⁸

Denosumab is a fully human IgG2 monoclonal antibody that neutralizes RANKL.³⁸⁻⁴⁰ It acts in a similar manner to osteoprotegerin, a cytokine of the tumor necrosis family, that inhibits binding of RANKL to RANK. Denosumab competes with RANKL for RANK binding sites and prevents osteoclast-mediated bone resorption.

Denosumab follows nonlinear, dose-dependent pharmacokinetics.⁴¹ The bioavailability of one subcutaneous denosumab injection is 61% and serum concentrations are detected within 1 hour.^{42,43} Maximal serum concentrations are achieved in 5-21 days and denosumab may be detectable for 9 months or longer.⁴¹ Based upon monoclonal antibody pharmacokinetics, denosumab is most likely cleared by the reticuloendothelial system with minimal renal filtration and excretion.^{44,45} The elimination half-life of denosumab is 32 days, and the terminal half-life is 5-10 days.⁴¹ Denosumab does not incorporate into bone.⁴⁶

The most common adverse effects identified in initial studies of postmenopausal women include arthralgia (25%), nasopharyngitis, back pain, headache, extremity pain, upper respiratory infection, constipation, urinary tract infection, and shoulder pain.^{38,40,47} Sore throat, rash, and asymptomatic hypocalcemia have also been reported. Malignancy has also been a concern with denosumab; however, current studies have not demonstrated a statistically significant increase in these events. There are no reported drug interactions at this time. Denosumab is contraindicated in patients with severe hypocalcemia.³⁷ Caution should be used in patients with impaired renal function as they are at an increased risk of hypocalcemia. There is an increased risk of serious infections, including skin infections, with denosumab. Patients with impaired immune systems or those on concomitant immunosuppressant agents may be at an increased risk and the benefits and risks of starting denosumab should be evaluated. Dermatologic reactions, such as rash, eczema, and dermatitis have been reported with denosumab. Osteonecrosis of the jaw has been observed in patients receiving denosumab, and all patients should receive an oral exam prior to therapy initiation and maintain good oral hygiene during therapy. Bone turnover is significantly suppressed with denosumab, and all patients should be monitored for the consequences of bone suppression, such as ONJ, atypical fractures, and delayed fracture healing.

Denosumab has a Risk Evaluation and Mitigation Strategy (REMS) associated with its use that consists of a patient medication guide and Dear Healthcare Professional Letter (DHCP). All patients are to receive the medication guide at each administration.

For the treatment of osteoporosis, denosumab 60 mg every 6 months is administered as a subcutaneous injection in the upper arm, upper thigh, or abdomen.³⁹ All patients should take 1000 mg of calcium and at least 400 IU of vitamin D daily in conjunction with denosumab. If a dose of denosumab is missed, administer the injection as soon as convenient and then schedule injections every 6 months from the date of the last injection. Prior to administration, denosumab should be removed from the refrigerator and brought to room temperature. The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex). The average wholesale price (AWP) of one single-use prefilled syringe of denosumab is \$990 (or \$1,980 annually). To date, denosumab has not been reviewed for addition to the Cleveland Clinic Health-System Formulary.

Summary: There are many agents available for the treatment of osteoporosis in postmenopausal women. Route and frequency of administration, adverse effects, and drug interactions should be taken into consideration when selecting therapy. Denosumab has recently been FDA-approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture and is being investigated for bone loss associated with hormone ablation therapy in prostate and breast cancer patients.

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Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Tuesday, January 19, 2010, and the following decisions were made:

Additions:

1. **Pralatrexate (Folotynt[®]):** Pralatrexate is FDA-approved for patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). It is a competitive inhibitor of the dihydrofolate reductase and folylpolyglutamyl synthetase enzymes. The most common adverse effects include neutropenia, thrombocytopenia, and mucositis. Vitamin B and folic acid supplementation are recommended with this medication to help reduce the incidence of these adverse effects. The dosing schedule is 30mg/m² IV push once weekly for 6 weeks out of a 7-week cycle. Pralatrexate will be mainly given in the outpatient setting (Taussig).
2. **Ofatumomab (Arzerra[®]):** Ofatumomab is FDA-approved for the treatment of chronic lymphocytic leukemia (CLL). It is a monoclonal antibody that binds specifically to the extracellular loops of the CD20 molecule present on normal B-lymphocytes and leukemia cells. The most common adverse effects include infusion-related reactions, thrombocytopenia, neutropenia, and infection. All patients should be pre-medicated with acetaminophen, an antihistamine, and a corticosteroid. The recommended dosing schedule is listed in the prescribing information. Ofatumomab will be used both in the inpatient and outpatient setting (Taussig).
3. **Lamotrigine Orally Disintegrating Tablets (Lamictal[®] ODT):** This orally disintegrating medication can be used in both adult and pediatric patients. Additionally, for pediatric patients, there will be an automatic therapeutic interchange from Lamictal Chewable Tablets to Lamictal ODT.
4. **Vigabatrin (Sabril[®]) Oral Solution:** Vigabatrin oral solution is FDA-approved for the treatment of infantile spasms in children 1 month to 2 years of age. Its use is *restricted* to Pediatric Neurology and Epilepsy Service physicians that are enrolled in the SHARE (Support Help and Resource for Epilepsy) program. The physician initiating treatment must complete a "Treatment Initiation Form" from the SHARE program. The physician needs to over a Medication Guide with the patient/family/guardian and obtain consent on the "Parent/Legal/Guardian-Physician Agreement for Vigabatrin Use" document. The physician must also complete an "Ophthalmic Assessment Form" at baseline and every 3 months as part of the SHARE program. *Note: According to the SHARE program, as long as the ORIGINAL prescription was written by a SHARE-registered provider, an order for vigabatrin can be continued for an inpatient by any prescriber.*

Changes to Restrictions:

1. **Lacosamide IV (Vimpat[®] IV):** The restriction on lacosamide IV has been expanded to include use in adult patients prescribed by the Departments of Neurology, NeuroSurgery, or Epilepsy for adult patients having acute seizures, suspected or confirmed status epilepticus, or those who are unable to receive oral medications. *Note: Lacosamide IV was also reviewed for use in the management of headaches by the CC Headache Center; however, due to lack of data, lacosamide IV was not approved at CC for this specific use.*
2. **Bivalirudin (Angiomax[®]):** The restriction on bivalirudin has been expanded to include use by Vascular Surgery in patients with heparin-induced thrombocytopenia (HIT). Standard dosing for bivalirudin for use by Vascular Surgery will be developed to minimize dosing errors and decrease the risk for adverse effects (this information will be included in the Adult IV Guideline for bivalirudin).

Declined to Add: These are true non-formulary medications, and they will not be ordered, stocked, or dispensed by the pharmacy: clevidipine (Cleviprex[®]), tolvaptan (Samsca[®]), and intravenous ibuprofen (Caldolor[®]).

Combination Narcotic and Acetaminophen Containing Products for Children (Children's Hospital only): Due to the concern for a pediatric patient receiving too much acetaminophen, the Children's Hospital will not dispense combination narcotic and acetaminophen containing products to children (e.g., Percocet[®] would be dispensed as oxycodone and acetaminophen, separately). The details of this are still being finalized. More information will follow as well as an implementation date.

Table 3. Current Therapies for the Treatment of Osteoporosis

Medication	Brand Name	Route	Treatment Dosing	Key Adverse Effects	Key Drug Interactions
Bisphosphonates					
Alendronate	Fosamax ^{®7}	Oral	10 mg daily, or 70 mg weekly	Common: Oral Formulation: Esophagitis Dysphagia Gastric ulcers Injectable Formulation: Myalgia Arthralgia Fever Headache Rare (All Formulations): Osteonecrosis of the jaw Bone pain Atrial fibrillation Esophageal cancer Atypical fractures	Oral formulation: Antacids Minerals
Alendronate and cholecalciferol	Fosamax [®] Plus D ⁸	Oral	Alendronate 70 mg and cholecalciferol 2800 IU or 5600 IU weekly		
Risedronate	Actonel ^{®9}	Oral	5 mg daily, or 35 mg weekly, or 150 mg monthly		
Risedronate and calcium	Actonel [®] and Calcium ¹⁰	Oral	Risedronate 35 mg once weekly on day 1, then calcium carbonate 1250 mg daily on days 2 - 7		
Ibandronate	Boniva ^{®11,12}	Oral	2.5 mg daily, or 150 mg monthly		
		IV	3 mg every 3 months		
Zoledronic acid	Reclast ^{®13}	IV	5 mg once yearly		
Calcitonin					
	Miacalcin ^{®27}	IM, SC	100 units/every other day	Common: Injectable Formulation: Transient nausea/vomiting Injection site reaction Flushing Inhaled Formulation: Rhinitis Stinging/tingling of nasal passages Sneezing Nasal mucosa erythema Minor bleeding Rare (All Formulations): Severe allergic reaction Influenza-like reaction Hypertension Angina pectoris	No known drug interactions
	Miacalcin ^{®26}	Nasal	200 units in one nostril daily using alternate nostrils each day		
	Fortical ^{®28}	Nasal	200 units in one nostril daily using alternate nostrils Each day		

Table 3. Current Therapies for the Treatment of Osteoporosis (continued)

Medication	Brand name	Route	Treatment Dosing	Key Adverse Effects	Key Drug Interactions
Parathyroid Hormone					
Teriparatide	Forteo ^{®32}	SC	20 mcg daily	Common: Transient hypercalcemia Nausea Dizziness Headache Leg cramps Rare: Osteosarcoma	Hypercalcemia from teriparatide may predispose a patient to digoxin toxicity
Selective Estrogen Receptor Modulator (SERM)					
Raloxifene	Evista ^{®34}	Oral	60 mg daily	Common: Hot flashes Leg cramps Peripheral edema Rare: Venous thromboembolic events	Bile acid sequestrants Levothyroxine Highly protein-bound medications Warfarin
Receptor Activator of Nuclear Factor-κB Ligand (RANKL) Inhibitor					
Denosumab	Prolia ^{®37}	IV	60 mg every 6 months	Common: Arthralgias Nasopharyngitis Upper respiratory infection Urinary tract infection Back/extremity pain Headache Rare: Serious infections Sore throat Rash Asymptomatic hypocalcemia	No known drug interactions