Bone Resorption Suppression and Related Agents

Therapeutic Class Review (TCR)

February 14, 2014

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Road, Suite 201
Cincinnati, Ohio 45242

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
BISPHOSPHONATES		
alendronate (Binosto®)[1]	Mission	Treatment and prevention of osteoporosis in postmenopausal women. Treatment to increase bone mass in men with osteoporosis.
alendronate (Fosamax®)[2]	generic, Merck	Treatment and prevention of osteoporosis in postmenopausal women. Treatment to increase bone mass in men with osteoporosis. Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone and who have low bone mineral density. Treatment of Paget's disease of bone in men and women.
alendronate/ vitamin D (Fosamax Plus D™)[3]	Merck	Treatment of osteoporosis in postmenopausal women. Treatment to increase bone mass in men with osteoporosis.
etidronate (Didronel®)[4]	generic	Treatment of Paget's disease of bone. Prevention and treatment of heterotopic ossification following total hip. replacement or spinal cord injury.
ibandronate (Boniva®)[5]	generic, Roche	Treatment and prevention of osteoporosis in postmenopausal women.
risedronate (Actonel®)[6]	Warner-Chilcott	Treatment and prevention of osteoporosis in postmenopausal women. Treatment to increase bone mass in men with osteoporosis. Prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone for chronic diseases. Treatment of Paget's disease of bone in men and women.
risedronate delayed-release (Atelvia™)[7]	Warner-Chilcott	Treatment of osteoporosis in postmenopausal women.
CALCITONINS		
calcitonin-salmon (Miacalcin®)[8]	generic	Treatment of postmenopausal osteoporosis in females greater than five years postmenopause with low bone mass. It should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated.
calcitonin-salmon (Fortical®)[9]	Upsher-Smith	Treatment of postmenopausal osteoporosis in females greater than five years postmenopause with low bone mass.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
OTHERS		
denosumab (Prolia™)[10]	Amgen*	Treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or in patients who have failed or are intolerant to other available osteoporosis therapy. Treatment of bone loss in men with prostate cancer on androgen deprivation therapy. Treatment of bone loss in women undergoing breast cancer therapy with adjuvant aromatase therapy. Treatment to increase bone mass in men diagnosed with osteoporosis and a high fracture risk who have failed or are intolerant to other potential therapies.
raloxifene (Evista®)[11]	generic, Lilly	Treatment and prevention of osteoporosis in postmenopausal women. Reduction in risk of invasive breast cancer in postmenopausal women who either have osteoporosis or are at high risk for invasive breast cancer.
teriparatide (Forteo™)[12]	Lilly	Treatment of osteoporosis in postmenopausal women who are at high risk for fractures. Increase of bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fractures. Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

* Amgen is also the manufacturer of denosumab (Xgeva™), indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors and administered as a 120 mg subcutaneous injection every four weeks.[13]

** Manufacturer of Actonel with Calcium® (risedronate/calcium) was discontinued in December 2009.

*** Manufacturer of Fosamax (alendronate) oral solution was discontinued in January 2011.

OVERVIEW

Osteoporosis is characterized by the deterioration of bone tissue and low bone mass. Approximately ten million Americans have the diagnosis of osteoporosis, and an additional 34 million have low bone mass, placing them at increased risk for this disease.[14] As many as one-in-two postmenopausal women and one-in-five older men are at risk for an osteoporosis-related fracture.[15] Approximately one-in-four men in the U.S. over the age of 50 will have an osteoporosis-related fracture in his remaining lifetime.[16] Osteoporosis is common in all racial groups but is most common in white persons.

There are three categories of osteoporosis: postmenopausal, age-related, and secondary osteoporosis. Postmenopausal osteoporosis affects mainly trabecular bone in the decade after menopause as estrogen deficiency increases bone resorption more than bone formation. Age-related osteoporosis results from increased bone resorption that begins shortly after peak bone mass is obtained. Cortical and trabecular bone are both affected. Secondary osteoporosis is caused by medications (glucocorticoids, excess thyroid replacement, some antiepileptic drugs, and long-term heparin use) or diseases (hyperthyroidism, type 1 diabetes). Both types of bone are affected.

The primary goal of osteoporosis management is to reduce fracture risk. This can be done by reducing bone loss, increasing bone mass or improving bone architecture to maintain bone strength, and minimizing or eliminating factors that may contribute to fractures (e.g., reducing the risk of falls).[17] Non-pharmacologic prevention and treatment methods include social habit and dietary changes, as

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

well as exercise and fall prevention. Pharmacologic prevention and treatment focuses on limiting bone resorption. Each of the medication classes has a different mechanism of action and side effect profile. The North American Menopause Society (NAMS), in its 2010 position statement, recommends bisphosphonates as first-line drugs for treating postmenopausal women with osteoporosis (defined as having a T-score below or equal to -2.5). Calcitonin (Fortical, Miacalcin) is not a first-line drug for postmenopausal osteoporosis treatment; however, it is an option for women with osteoporosis who are more than five years beyond menopause.[18] The American Association of Clinical Endocrinologists (AACE) guidelines for the prevention and treatment of postmenopausal osteoporosis (2010 update), recommend alendronate, risedronate, zoledronic acid, or denosumab as first-line agents, ibandronate as a second-line agent, raloxifene as a second-or third-line agent (Grade A), and calcitonin as the last-line agent (Grade C). Teriparatide is recommended for patients with very high fracture risk or those in whom bisphosphonate therapy has been ineffective (Grade A).[19] The 2013 National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis continues to recognize all U.S. FDA-approved medications for the prevention and/or treatment of osteoporosis as possible options. The guide also states that the treatment agent of choice should be based on available clinical information in addition to intervention thresholds. Further, the 2013 guide recommends that the duration of pharmacologic therapy be specific to each individual with the need for continuation of medications reviewed on an annual basis.[20] The United States Preventive Services Task Force (USPSTF) advises that the choice of treatment should take into account the patient's clinical situation and the trade off between benefits and harms.[21]

PHARMACOLOGY[22, 23, 24, 25, 26, 27, 28]

Bisphosphonates adsorb to bone apatite and are permanently incorporated into bone. Osteoclasts are unable to adhere to bone surfaces containing bisphosphonates and, ultimately, are unable to resorb and turnover bone. Bisphosphonates include alendronate (Fosamax), etidronate (Didronel), ibandronate (Boniva), and risedronate (Actonel, Atelvia). The inclusion of vitamin D with alendronate (Fosamax Plus D) promotes calcium absorption.

Calcium is a major substrate for mineralization and has an antiresorptive effect and decreases bone turnover. Vitamin D is required for normal bone formation, and insufficient levels are associated with negative calcium balance, increased parathyroid hormone (PTH) levels, bone loss, and increased risk of skeletal fracture.

The hormone calcitonin is secreted in response to high serum calcium levels. Calcitonin receptors have been found on osteoclasts, osteoblasts, and renal cell membranes. Stimulation of these receptors by calcitonin-salmon (Miacalcin, Fortical) results in a decrease in osteoclast activity and a decrease in renal reabsorption of calcium and sodium. Bone formation may also be augmented by increased osteoblastic activity.

RANK ligand (RANKL) is a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab (Prolia), a RANK ligand inhibitor, binds to RANKL and prevents it from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

The biological actions of raloxifene (Evista) are largely mediated through estrogen receptor binding. Binding results in activation of certain estrogenic pathways that act to decrease resorption of bone and reduce the biological markers of bone turnover. Raloxifene antagonizes estrogenic receptors in the uterine and breast tissue and also decreases total and low density lipoprotein (LDL) cholesterol.

Parathyroid hormone increases bone resorption. Teriparatide (Forteo) contains recombinant human parathyroid hormone and stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. The anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life	Metabolism	Excretion (%)
BISPHOSPHONATES				
alendronate (Binosto)[29]	0.64 women, 0.59 men	>10 yrs	No metabolism	Renal: 50
alendronate (Fosamax)[30]	0.64 women, 0.59 men	>10 yrs	No metabolism	Renal: 50
etidronate (Didronel)[31]	3	1-6 hrs	No metabolism	Renal: 50
ibandronate (Boniva)[32]	0.6	37-157 hrs	No metabolism	Renal and Fecal
risedronate (Actonel)[33]	0.63	20 days	No metabolism	Renal and fecal
risedronate delayed-release (Atelvia)[34]	Varies dependent upon food (see below)	23.4 days	No metabolism	Renal and fecal
vitamin D* (Fosamax Plus D)[35]	0.64 women, 0.59 men		Liver hydroxylation to active form; metabolized to active form by kidneys	Renal and fecal
CALCITONINS				
calcitonin-salmon (Miacalcin, Fortical)[36,37]	3	43 min	nr	nr
OTHERS				
denosumab (Prolia)[38]	nr	25.4 days	nr	nr
raloxifene (Evista)[39]	2	27.7 hrs	Extensively metabolized to three glucuronide conjugates	Fecal
teriparatide (Forteo)[40]	95	1 hr	nr	nr

Alendronate effervescent tablets pharmacokinetics are equivalent to similar doses of the oral tablets.

* Alendronate pharmacokinetics are not altered by the addition of vitamin D.

nr = not reported

Risedronate delayed-release (Atelvia) tablets contain a pH-sensitive enteric coating and a chelating agent (EDTA).[41] The bioavailability of risedronate delayed-release (Atelvia) 35 mg tablet administered after a high-fat breakfast was approximately two- to four-fold greater than the risedronate immediate-release (Actonel) 35 mg tablet administered 30 minutes prior to a high-fat breakfast. Risedronate

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

delayed-release (Atelvia) should be taken immediately following breakfast and not under fasting conditions.

CONTRAINDICATIONS/WARNINGS[42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52]

Chronic, severe musculoskeletal pain has been reported in patients taking bisphosphonates. Patients may experience pain symptoms at any time after treatment initiation with a bisphosphonate. Upon discontinuation of the bisphosphonate, relief of pain symptoms has come in the form of slow or incomplete symptom resolution to complete relief. The FDA continues to investigate this possible association.[53,54]

Teriparatide (Forteo) has a black box warning indicating that osteosarcoma has been seen in both male and female rats. The osteosarcoma was dependent on dose and treatment duration. Teriparatide should not be used in patients who are at increased risk of osteosarcoma, including those with Paget's disease, open epiphyses, previous recipients of radiation of the bone, or those with unexplained elevations of alkaline phosphatase. In addition, patients with a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or underlying hypercalcemic disorder, should not be treated with teriparatide.

Bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Esophageal adverse experiences include esophagitis, esophageal ulcers, and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation. The FDA is investingating the possible risk of esophageal cancer with oral bisphosphonates but the data is conflicting.[55] The FDA believes that the benefits of oral bisphosphonates in reducing the risk of serious fractures in osteoporosis continue to outweigh their potential risks.

Bisphosphonates are generally contraindicated in the following conditions: abnormalities of the esophagus which delay esophageal emptying, such as stricture or achalasia, an inability to stand or sit upright for 30 to 60 minutes after dosing, and hypocalcemia.

Osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection, has been reported in patients taking bisphosphonates; most cases reported in patients treated intravenously, but some reports have occurred in patients treated orally. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and comorbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection). For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ.

Raloxifene (Evista) is contraindicated in lactating and pregnant women, as well as women who may become pregnant and women with active or a history of venous thromboembolism. There are black box warnings for the increased risk of venous thromboembolism and death from stroke.

Denosumab (Prolia, Xgeva) is contraindicated in patients exhibiting systemic hypersensitivity reactions to any component of each medication and in patients with hypocalcemia. Hypersensitivity reactions have been known to include facial swelling and urticaria. Denosumab (Xgeva) has also been reported to cause severe symptomatic hypocalcemia with some fatal cases noted. Pre-existing hypocalcemia must be corrected prior to initiation of therapy. Hypocalcemia may actually worsen in patients with severe renal impairment. Adequate supplementation with calcium and vitamin D is recommended. In addition, denosumab has been associated with serious skin infections that could lead to

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

hospitalizations. Prompt medical attention is suggested upon initial signs and symptoms of skin infection, including cellulites. Infections of the abdomen and urinary tract have also been reported and other dermatologic reactions, as well as osteonecrosis of the jaw, have been reported with the use of denosumab. Patients receiving denosumab (Prolia) should not receive denosumab (Xgeva) therapy, as Xgeva has the same active ingredient as Prolia.

The FDA continues to review information regarding atypical fractures of the femur associated with the long term use of bisphosphonates to treat osteoporosis.[56, 57] Currently, the FDA recommends that healthcare professionals: be aware of the possibility of atypical femur fractures in patients taking bisphosphonates; rule out an incomplete femoral fracture if a patient presents with new thigh or groin pain; discontinue potent anti-resorptive medications, including bisphosphonates, in patients who have evidence of a femoral fracture; periodically re-evaluate whether continued bisphosphonate therapy is needed, especially in patients who have been treated for more than five years; and instruct patients to seek medical attention if they experience new groin or thigh pain. This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer (e.g., Didronel).

DRUG INTERACTIONS[58, 59, 60, 61, 62, 63]

As this agent is highly protein bound, raloxifene (Evista) should be used with caution with other highly protein-bound medications, such as diazepam.

Concomitant use of bisphosphonates with hormone replacement therapy (HRT) in women shows a greater degree of bone turnover suppression than with either HRT or a bisphosphonate alone. Concomitant use of risedronate delayed-release (Atelvia) with estrogens and estrogen agonist/antagonists has not been studied. The safety of concomitant use of raloxifene with systemic estrogens has not been established, and its use is not recommended.

Calcium supplements and antacids, as well as other oral medications, may interfere with the absorption of bisphosphonates. Patients should not take other medications until the 30 to 60 minute period following administration is completed.

The incidence of upper gastrointestinal adverse events is higher in patients taking aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) concomitantly with bisphosphonates. Administration with a proton pump inhibitor (PPI) or H2-blocker may decrease the incidence. However, drugs such as H2-blockers, PPIs, and antacids that raise stomach pH may affect the enteric coating on risedronate delayed-release (Atelvia) tablets and thereby reduce its bioavailability. The effects of concomitant administration of these agents on bioavailability of risedronate delayed-release tablets have not been evaluated.

Cholestyramine, and possibly other bile acid resins, can cause a decrease in the absorption of raloxifene (Evista), thus concomitant use of these agents is not recommended.

Hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, patients receiving digoxin should use teriparatide with caution.

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. Currently, no drug interactions with calcitonin-salmon have been observed.

No drug interaction studies have been conducted with denosumab (Prolia).

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

ADVERSE EFFECTS

Drug	Abd. pain	Nausea	Dyspepsia	Constipation	Diarrhea	Flatulence	Musculoskeletal pain	Headache
BISPHOSPHONATES								
alendronate (Binosto)[64] 70 mg once-weekly	3.7	1.9	2.7	0.8	2.8	0.4	2.9	nr
alendronate (Fosamax)[65] 5-10 mg daily	1.5-6.6	1.1-3.6	1.1-3.6	0-3.1	0.6-3.1	0.2-4.1	0.4-4.1	0.2-2.6
alendronate (Fosamax)[66] 35 mg once-weekly	2.2	1.4	1.7	0.3	0.6	nr	2.2	nr
alendronate (Fosamax)[67] 70 mg once-weekly	3.7	1.9	2.7	0.8	<1	0.4	2.9	<1
etidronate (Didronel)[68]	nr	6.7	nr	nr	6.7	nr	reported	reported
ibandronate (Boniva)[69] 2.5 mg daily	5.3-6	4.8	7.1-11.9	2.5	4.1	nr	3.5	4.1-6.5
ibandronate (Boniva)[70] 150 mg once-monthly	7.8-8.0	5.1	5.6	4.0	5.1	nr	nr	3.3
risedronate (Actonel)[71] 5 mg daily	7.3-12.2	10.5-13.2	6.9-10.8	12.9	4.7-10.8	nr	11.5-24.7	7.3-9.9
risedronate (Actonel)[72] 35 mg once-weekly	7.6	7.3	7.6	nr	4.9	nr	13.9-14.2	nr
risedronate (Actonel)[73] 75 mg two days/month	nr	nr	nr	nr	reported	nr	nr	nr
risedronate (Actonel)[74] 150 mg once/month	nr	nr	nr	nr	8.2	nr	nr	nr
risedronate delayed-release (Atelvia) 35 mg weekly[75]	2.9	3.6	3.9	4.9	8.8	nr	2	2.6

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

Adverse Effects (continued)

Drug	Abd. pain	Nausea	Dyspepsia	Constipation	Diarrhea	Flatulence	Musculoskeletal pain	Headache
OTHERS								
denosumab (Prolia)[76]	3.3 (2.9)	nr	nr	reported	nr	2.2 (1.4)	7.6 (7.5)	nr
raloxifene (Evista)[77] 60 mg daily	6.6	8.3-8.8	5.9	nr	7.2	1.6-3.1	10.7-15.5	9.2
teriparatide (Forteo)[78]	nr	8.5 (6.7)	5.2 (4.1)	5.4 (4.5)	5.1 (4.6)	nr	10.1 (8.4)	7.5 (7.4)
CALCITONINS								
calcitonin-salmon (Miacalcin)[79]	1-3	1-3	1-3	1-3	1-3	<1	3.8 (5.3)	3.2 (4.6)
calcitonin-salmon (Fortical)[80]	1-3	1-3	1-3	1-3	1-3	<1	3.8 (5.3)	3.2 (4.6)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all-inclusive. nr = not reported. Numbers in parentheses are reported placebo adverse effect rates.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

Although there has been no study of adverse events with Fosamax Plus D, in one study with 682 women and 35 men, a combination of alendronate and vitamin D over 15 weeks had a safety profile similar to alendronate 70 mg once weekly.[81]

Other bisphosphonates have had reports of bone, joint, and muscle pain, as well as osteonecrosis of the jaw.[82, 83, 84]

Other common adverse events reported with raloxifene (Evista) include leg cramps, hot flashes, varicose veins, peripheral edema, and vaginal hemorrhage.[85]

Calcitonin-salmon (Miacalcin, Fortical) causes rhinitis (12 percent), epistaxis (3.5 percent), and other bothersome effects of the nose. Periodic nasal examinations are recommended during nasal calcitonin-salmon therapy.[86, 87]

Adverse effects reported with teriparatide (Forteo) included hypertension (7.1 percent), angina pectoris (2.5 percent), syncope (2.6 percent), rhinitis (9.6 percent), dizziness (eight percent), depression (4.1 percent), insomnia (4.3 percent), and sweating (2.2 percent). Transition elevation of serum calcium has been seen in both women and men.[88]

The most common treatment-emergent adverse effects associated with denosumab (Prolia) for patients on active therapy include back pain (34.7 percent versus 34.6 for placebo), extremity pain (11.7 percent versus 11.1 for placebo), musculoskeletal pain (7.6 percent versus 7.5 for placebo), hypercholesterolemia (7.2 percent versus 6.1 for placebo), and cystitis (5.9 percent versus 5.8 for placebo).

There have been reports of atypical femoral fractures occurring in patients receiving denosumab (Prolia). While a causality has not been established, as these type of fractures are also seen in patients who have not been administered anti-resorptive agents, many reports indicate these patients also received glucocorticoid therapy at the time of the fracture. Atypical femoral fractures commonly occur with minimal or no trauma to the area. They may be bilateral and are often accompanied by prodromal pain in the area for some time prior to the resultant fracture.[89,90]

SPECIAL POPULATIONS

Pediatrics

These products are not FDA-approved for use in the pediatric population. There are limited data available studying the use of alendronate or risedronate in pediatric disorders such as osteogenesis imperfecta, but large, properly-designed studies have not been conducted. The safety and effectiveness of denosumab (Prolia) for pediatric patients have not been established.

Pregnancy

The majority of products in this class are Pregnancy Category C, with the exception of denosumab (Prolia) and raloxifene (Evista), which are Pregnancy Category X.[91,92] It should be noted that denosumab (Xgeva) is Pregnancy Category D.[93]

Hepatic Impairment

Raloxifene (Evista) should be used with caution in patients with hepatic impairment.[94]

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

Renal Impairment

The use of bisphosphonates is not recommended in patients with severe renal dysfunction. Raloxifene (Evista) should be used with caution in patients with moderate or severe renal impairment. No dosage adjustment of denosumab (Prolia) is required for patients with renal impairment; however, patients with severe renal impairment or receiving dialysis may be at greater risk of developing hypocalcemia.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

DOSAGES

Drug	Treatment of osteoporosis in postmenopausal women	Prevention of osteoporosis in postmenopausal women	Treatment to increase bone mass in men with osteoporosis	Treatment of glucocorticoid-induced osteoporosis	Paget's disease	Availability
BISPHOSPHONATES						
alendronate (Binosto)[95]	70 mg once per week	-	70 mg once per week	-	-	70 mg effervescent tablets
alendronate (Fosamax)[96]	10 mg per day or 70 mg once per week	5 mg per day or 35 mg once per week	10 mg per day or 70 mg once per week	5 mg per day, For post-menopausal women not receiving estrogen: 10 mg once daily	40 mg per day for 6 months May retreat if relapse occurs following a 6-month post-treatment evaluation	5, 10, 35, 40, 70 mg tablets; 70 mg/75 mL oral solution
alendronate/vitamin D (Fosamax Plus D)[97]	70 mg/2,800 IU or 70 mg/5,600 IU weekly	--	70 mg/2,800 IU or 70 mg/5,600 IU weekly	--	--	70 mg/ 2,800 IU, 70 mg/ 5,600 IU tablets
etidronate (Didronel)[98]	--	--	--	--	5-10 mg/kg/day up to 6 months or 11-20 mg/kg/day up to 3 months May retreat if relapse occurs following a 90 day post-treatment evaluation	200, 400 mg tablets
ibandronate (Boniva)[99]	2.5 mg per day or 150 mg per month	2.5 mg per day or 150 mg per month	--	--	--	2.5 mg tablets (brand only), 150 mg tablets (brand and generic)
risedronate (Actonel)[100]	5 mg per day or 35 mg once per week or 75 mg for 2 consecutive days every month or 150 mg once a month	5 mg per day or 35 mg once per week or 75 mg for 2 consecutive days every month or 150 mg once a month	35 mg once per week	5 mg per day	30 mg per day for 2 months May retreat if relapse occurs, after a 2-month post-treatment observation.	5, 30, 35, 75, 150 mg tablets

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

Dosages (continued)

Drug	Treatment of osteoporosis in postmenopausal women	Prevention of osteoporosis in postmenopausal women	Treatment to increase bone mass in men with osteoporosis	Treatment of glucocorticoid-induced osteoporosis	Paget's disease	Availability
BISPHOSPHONATES						
risedronate delayed-release (Atelvia)[101]	35 mg once weekly	--	--	--	--	35 mg delayed-release tablets
CALCITONINS						
calcitonin-salmon (Miacalcin)[102]	200 IU intranasally per day, alternating nostrils daily	--	--	--	--	7 mL (30 dose) bottles
calcitonin-salmon (Fortical)[103]	200 IU intranasally per day, alternating nostrils daily	--	--	--	--	3.7 mL (30 dose) bottle
OTHERS						
denosumab (Prolia)[104]	60 mg SC every 6 months; administered by a healthcare professional	--	60 mg SC every 6 months; administered by a healthcare professional	--	--	60 mg/ 1 mL single use pre-filled syringe; 60 mg/ 1 mL single use vial
raloxifene (Evista)[105]	60 mg per day	60 mg per day	--	--	--	60 mg tablets
teriparatide (Forteo)[106]	20 mcg SC per day	--	20 mcg SC per day	20 mcg SC per day	--	750 mcg/3 mL prefilled pen

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

Dosages (continued)

Etidronate (Didronel) for Heterotrophic Ossification - for spinal cord injury: 20 mg/kg/day for two weeks then 10 mg/kg/day for ten weeks; for hip replacement: 20 mg/kg/day for one month prior to surgery followed by 20 mg/kg/day for three months postoperatively.

Raloxifene (Evista) dosing is 60 mg daily for the reduction in risk of invasive breast cancer in postmenopausal women.

Etidronate (Didronel) requires a dose reduction in patients with renal insufficiency. Bisphosphonates and raloxifene are not recommended in patients with severe renal impairment.

Alendronate and risedronate (Actonel) must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Patients should not lie down for at least 30 minutes after taking the medication. Ibandronate must be taken at least one hour before the first food, beverage, or medication of the day with plain water, and patients should not lie down for at least 60 minutes after taking the medication. Raloxifene may be administered any time of day without regard to meals. All regimens should include an adequate intake of calcium and vitamin D.

When compared with risedronate immediate-release (Actonel), treatment with risedronate delayed-release (Atelvia) resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions. Risedronate delayed-release (Atelvia) should be taken immediately following breakfast and not under fasting conditions.

The safety, efficacy and benefit of teriparatide (Forteo) have not been evaluated beyond two years of treatment. Therefore, use for more than two years during a patient's lifetime is not recommended.

Patients receiving denosumab (Prolia) should also maintain a regimen of calcium 1,000 mg daily and at least 400 IU of vitamin D daily. Denosumab should be refrigerated until use. Prior to administration, the container may be brought to room temperature by removing it from the refrigerator to stand for 15 to 30 minutes.

Alendronate is available generically in 5 mg, 10 mg, 35 mg, and 40 mg tablet strengths and a 70 mg/75 mL solution; however, Fosamax is currently only available as a 70 mg strength tablet.

Optimal duration of use for bisphosphonates has not been determined. For patients at low-risk for fracture, consider discontinuation after three to five years of use.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Binosto: alendronate effervescent tablets 70 mg (Binosto) was approved based on the evidence demonstrated in clinical data of alendronate sodium 10 mg daily and alendronate sodium 70 mg weekly for fracture reduction efficacy and bone mineral density changes.[107] The same clinical trial results have been attributed to Binosto and are based on the demonstrated bioequivalence of alendronate effervescent tablets 70 mg to oral alendronate sodium tablet 70 mg.

alendronate (Fosamax) versus placebo

Two double-blind, multicenter studies were conducted enrolling postmenopausal women who were 45 to 80 years of age with osteoporosis [bone mineral density (BMD) at least 2.5 standard deviations below the mean value in premenopausal white women].[108] The women were randomized to receive placebo or 5, 10, or 20 mg of alendronate per day for two years. During the third year, women continued with open-label therapy with the 20 mg per day group changing to 5 mg per day. All women also received 500 mg of calcium daily. A total of 909 women completed at least one year of the study. There were significant increases in the BMD of the spine, femoral neck, trochanter, and total body at 36 months in all three alendronate groups. The 10 mg dose was significantly more effective than the 5 mg dose and, at two years, was as effective as the 20 mg dose. During the study, 6.2 percent of the placebo group had at least one new vertebral fracture compared with 3.2 percent of the alendronate-treated females (p=0.03).

In the Fracture Intervention Trial (FIT), 4,432 women with a femoral neck BMD of 0.68 g/cm^2 or less were randomized in a double-blind manner to receive alendronate 5 mg per day for two years followed by 10 mg per day for two years or placebo.[109] Alendronate increased BMD at all sites studied and reduced clinical fractures from 312 in the placebo group to 272 in the intervention group. However, the clinical fracture reduction was not significant.

A randomized, double-blind trial enrolled 1,099 postmenopausal women who had received alendronate treatment in the FIT trial for a mean of five years. These patients were again randomized to alendronate 5 or 10 mg daily or placebo for an additional five years. The primary outcome measure

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

was total hip BMD; secondary measures were BMD at other sites and biochemical markers of bone remodeling. Patients who switched to placebo for five years had a decline in BMD at the total hip (-2.4 percent; p<0.001) and spine (-3.7 percent; p<0.001), but mean levels remained at or above pretreatment levels 10 years earlier. After five years, the cumulative risk of nonvertebral fractures was not significantly different between those continuing and discontinuing alendronate (RR, 1.00; 95% CI, 0.76-1.32). Among those who continued, there was a significantly lower risk of clinically recognized vertebral fractures (RR, 0.45; 95% CI, 0.24-0.85) but no significant reduction in morphometric vertebral fractures.

In a one-year, double-blind study, 1,258 osteoporotic women were randomized to receive alendronate 10 mg daily, 35 mg twice weekly, or 70 mg once weekly.[110] The percent increases for BMD of the lumbar spine at month 12 were 5.4 percent, 5.2 percent, and 5.1 percent for the three dosing regimens, respectively. Upper gastrointestinal adverse experiences occurred in 23.5 percent, 23.8 percent, and 22.4 percent of patients in the daily, twice-weekly, and once-weekly treatment groups, respectively.

In a one-year, double-blind, multicenter study of postmenopausal women aged 40 to 70 years, 362 patients were randomized to alendronate 35 mg once weekly, and 361 patients received alendronate 5 mg once daily.[111] Lumbar spine BMD at 12 months increased to the same degree in both groups. Both treatments were well tolerated.

A multicenter, international, randomized, blinded, 12-month study was conducted to assess the effect of alendronate on BMD in women who had recently discontinued HRT.[112] One hundred forty-four postmenopausal women were randomized to receive either a daily dose of 10 mg alendronate or matching placebo. A high rate of bone loss was observed in the first 12 to 15 months after discontinuation of HRT. Alendronate increased or maintained both spine and hip BMD and prevented the increase in bone resorption seen with withdrawal of HRT in this population. Bone turnover decreased significantly with alendronate but increased in the placebo group. Alendronate was well tolerated, with no increase in adverse events compared with placebo.

alendronate (Fosamax) versus raloxifene (Evista)

A randomized, double-masked, double-dummy multicenter international study was done to compare the efficacy and tolerability of alendronate to raloxifene in postmenopausal women with low-bone density.[113] A total of 487 postmenopausal women with low bone density, based on BMD of the lumbar spine or hip (T-score < -2.0), received either alendronate 70 mg once weekly and daily placebo identical to raloxifene or raloxifene 60 mg daily and weekly placebo identical to alendronate for 12 months. Alendronate demonstrated substantially greater increases in BMD than raloxifene at both lumbar spine and hip sites at 12 months. Lumbar spine BMD increased 4.8 percent with alendronate compared to 2.2 percent with raloxifene (p<0.001). The increase in total hip BMD was 2.3 percent with alendronate and 0.8 percent with raloxifene (p<0.001). The proportion of patients reporting vasomotor events was significantly higher with raloxifene (9.5 percent) than with alendronate (3.7 percent, p=0.010). Reductions in bone turnover were significantly larger with alendronate than raloxifene. The proportion of patients reporting gastrointestinal events was similar between groups.

To compare the efficacy and tolerability of once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis, a 12-month, randomized, double-blind study enrolled 456 patients.[114] Over 12 months, alendronate produced a significantly greater increase in

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

lumbar spine BMD than raloxifene (4.4 versus 1.9 percent; p<0.001). The percentage of women with an increase in lumbar spine BMD (94 versus 75 percent; p<0.001) and at least a three percent increase (66 versus 38 percent; p<0.001) was significantly greater with alendronate than raloxifene. Total hip and trochanter BMD increases were also significantly greater (p<0.001) with alendronate. No significant differences in the incidence of upper gastrointestinal or vasomotor adverse experiences were seen.

alendronate (Fosamax) versus risedronate immediate-release (Actonel)

A total of 515 postmenopausal women received risedronate 5 mg or alendronate 10 mg daily for two weeks.[115] At baseline and days eight and 15, subjects underwent endoscopy and evaluator-blinded assessment of the esophageal, gastric, and duodenal mucosa. Gastric ulcers were seen in 4.1 percent of risedronate-treated patients and in 13.2 percent of the alendronate group (p<0.001). Esophageal ulcers were noted in three subjects in the alendronate group compared to none in the risedronate group. Duodenal ulcers were found in one patient in the alendronate-treated group and in two patients in the risedronate group.

In a similarly conducted study, 318 subjects received risedronate 5 mg and 317 received alendronate 10 mg daily for 14 days.[116] Overall, gastric ulcers greater than 3 mm were observed in 18 (six percent) of 300 evaluated subjects in the risedronate group and 36 (12.1 percent) of 297 in the alendronate group during treatment (p=0.013). Mean gastric endoscopy scores at days eight and 15 were significantly lower in the risedronate group than in the alendronate group (p<0.001). Mean esophageal and duodenal endoscopy scores were similar in the two groups at days eight and 15. Upper GI adverse events were reported by 18 (5.7 percent) subjects in the risedronate group (19 events) and 28 (8.8 percent) subjects in the alendronate group (32 events).

In a multicenter, double-blind trial, 235 men and postmenopausal women were randomized to receive 28 days of alendronate 40 mg per day, risedronate 30 mg per day, placebo, or placebo with aspirin 650 mg four times a day for the last seven days.[117] Endoscopy showed alendronate- and risedronate-treated patients with comparable mean gastric and duodenal erosion scores that were significantly lower than those of the aspirin group. Gastric ulcers and/or large numbers of gastric erosions occurred in approximately three percent of alendronate and risedronate patients versus 60 percent with aspirin.

In FACT, a total of 1,053 patients were randomized in a double-blind study to alendronate 70 mg once weekly (n=520) or risedronate 35 mg once weekly (n=533) taken in the morning after fasting.[118] Greater increases in hip trochanter BMD were seen with alendronate (3.4 percent) than risedronate (2.1 percent) at 12 months (p<0.001), as well as six months (p<0.001). Significant gains in BMD were greater with alendronate at all BMD sites measured (12-month difference: total hip, one percent; femoral neck, 0.7 percent; lumbar spine, 1.2 percent). No significant differences were seen between treatment groups in the incidence of upper gastrointestinal adverse events or those causing discontinuation.

A randomized, double-blind, one-year extension of FACT compared changes in BMD, bone turnover, and upper gastrointestinal tolerability over two years of treatment.[119] Of the 1,053 women who completed one year of treatment, 833 postmenopausal women with low BMD entered the extension, continuing their same treatment allocation. Alendronate produced greater increases from baseline in BMD at 24 months than did risedronate at the trochanter (alendronate 4.6 percent; risedronate 2.5 percent, p<0.001), as well as at all other BMD sites. Fewer alendronate patients had measured decreases of three percent or more at all BMD sites. Significantly greater reductions in all biochemical

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

markers of bone turnover occurred with alendronate, compared with risedronate. No differences were seen in occurrence or discontinuations due to upper gastrointestinal adverse effects. The manufacturer of alendronate supported the study.

A three-month, randomized, double-blind, placebo-controlled study with a double-blind extension to 12 months enrolled 549 postmenopausal women who were 60 years of age or older.[120] Patients received alendronate 70 mg once weekly or risedronate 5 mg daily. Over three months, alendronate produced a significantly greater mean reduction in biochemical markers of bone turnover than did risedronate, which was maintained at 12 months. Alendronate produced a significantly greater mean BMD increase than did risedronate at six months, and it was maintained at 12 months at the lumbar spine (4.8 versus 2.8 percent, $p<0.001$) and total hip (2.7 versus 0.9 percent, $p<0.001$), as well as at the trochanter and femoral neck. Tolerability was generally similar among alendronate, risedronate, and placebo, and the incidence of adverse events was similar in both active treatment groups.

alendronate with vitamin D (Fosamax Plus D) versus alendronate (Fosamax)

In a 15-week study, 717 men and postmenopausal women with osteoporosis were randomized to receive weekly alendronate/vitamin D 70 mg/2,800 IU tablets or weekly alendronate 70 mg.[121] Patients who were vitamin D deficient at baseline were excluded. Treatment with alendronate/vitamin D resulted in a smaller reduction in serum calcium levels (-0.9 versus -1.4 percent, respectively) as well as a significantly smaller increase in parathyroid hormone levels when compared to alendronate alone (14 versus 24 percent, respectively).

calcitonin salmon (Miacalcin) versus placebo

For five years, 1,255 randomized, postmenopausal women with osteoporosis received salmon calcitonin nasal (100, 200, or 400 IU) or placebo daily in a double-blind manner.[122] The 200 IU dose of salmon calcitonin nasal spray significantly reduced the risk of new vertebral fractures by 33 percent compared with placebo ($p=0.03$). The reductions in vertebral fractures in the 100 and 400 IU groups were not significantly different from placebo. Lumbar spine BMD increased significantly from baseline (one percent to 1.5 percent, $p<0.01$) in all active treatment groups.

denosumab (Prolia) versus placebo

Women between the ages of 60 and 90 years (n=7,868) who had a bone mineral density T score of less than -2.5 but not less than -4 at the lumbar spine or total hip were randomly assigned to receive either denosumab 60 mg or placebo subcutaneously every six months for 36 months.[123] The primary endpoint was new vertebral fracture. Secondary endpoints included nonvertebral and hip fractures. Denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3 percent in the denosumab group versus 7.2 percent in the placebo group (hazard ratio, 0.32; 95% CI, 0.26 to 0.41; $p<0.001$). Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7 percent in the denosumab group versus 1.2 percent in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; $p=0.04$). Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5 percent in the denosumab group versus 8 percent in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; $p=0.01$). There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to injection for denosumab.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

ADAMO was a phase 3 randomized, double-blind, placebo-controlled, multicenter trial in 242 men with lowBMD.[124] At one year, compared with placebo, SC denosumab 60 mg every six months resulted in BMD increases at the primary endpoint of lumbar spine (5.7 versus 0.9 percent), and for the secondary endpoints of total hip (2.4 versus 0.3 percent) and femoral neck (2.1 versus zero percent), (adjusted p≤0.0144 for BMD percent differences at all sites compared with placebo). Effects of Prolia on BMD at the lumbar spine were independent of baseline testosterone levels, age, BMD status, and estimated fracture risk. Treatment with denosumab significantly reduced the bone resorption marker serum type 1 C-telopeptide (CTX) levels at day 15 (adjusted p<0.0001). The incidence of adverse events was similar between groups.

ibandronate (Boniva) versus placebo

In total, 653 women (mean BMD T-score > -2.5 at the lumbar spine) who had been postmenopausal for at least one year were enrolled in a multicenter, double-blind, randomized, placebo-controlled, Phase II/III study to receive calcium (500 mg daily) plus either placebo (n=162) or ibandronate 0.5 mg (n=162), 1 mg (n=166), or 2.5 mg (n=163) as daily treatment for two years.[125] After two years, daily ibandronate produced a dose-related and sustained maintenance or increase in BMD at the lumbar spine and hip (total hip, femoral neck, trochanter), together with a dose-related reduction in the rate of bone turnover. The greatest increases in spinal and hip BMD were observed with the 2.5 mg dose, which produced statistically significant BMD gains compared with placebo at six months and all subsequent time-points (3.1 and 1.8 percent increase in lumbar spine and total hip BMD, respectively, versus placebo; p<0.0001 after 24 months). Ibandronate was well tolerated with an incidence of upper gastrointestinal adverse events similar to placebo.

A randomized, double-blind, placebo-controlled, parallel-group, Phase III study enrolled 2,946 postmenopausal women with a BMD T score ≤ - 2.0 at the lumbar spine in at least one vertebra and one to four prevalent vertebral fractures.[126] Patients received placebo or ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every three months. After three years, ibandronate significantly reduced the risk of new vertebral fractures by 62 percent (p=0.0001) for the daily group and 50 percent (p=0.0006) for the intermittent group, versus placebo. Significant and progressive increases in lumbar spine and hip BMD, normalization of bone turnover, and significantly less height loss than in the placebo group were also observed for both ibandronate regimens. Ibandronate did not reduce the incidence of nonvertebral fractures, which was a secondary efficacy measure. The percentages of nonvertebral fractures over three years were similar for ibandronate 2.5 mg (9.1 percent; 95% CI, 7.1-11.1%), 20 mg group (8.9 percent), and placebo groups (8.2 percent; 95% CI, 6.3-10.2%). Ibandronate was well tolerated.

MOBILE study: A total of 1,609 women with postmenopausal osteoporosis were assigned to one of four oral ibandronate regimens, 2.5 mg daily, 50 mg/50 mg monthly (single doses, consecutive days), 100 mg monthly, or 150 mg monthly, in a two-year, randomized, double-blind, Phase III, non-inferiority trial.[127] After one year, lumbar spine BMD increased by 3.9, 4.3, 4.1, and 4.9 percent in the 2.5, 50/50, 100, and 150 mg arms, respectively. All monthly regimens were proven non-inferior to the daily regimen in increasing lumbar BMD, while the 150 mg regimen was superior. All arms of the study produced similar hip BMD gains, and all arms were similarly well tolerated.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

ibandronate (Boniva) versus alendronate (Fosamax)

MOTION study: A 12-month, randomized, multinational, multicenter, double-blind, double-dummy, parallel-group, non-inferiority trial enrolled postmenopausal women with mean lumbar spine (L2-L4) BMD T-score < -2.5 and > -5.0.[128] Patients received either ibandronate 150 mg once monthly or alendronate 70 mg once weekly. The primary efficacy endpoints were 12-month percent change from baseline in mean lumbar spine and total hip BMD, while percent changes from baseline in trochanter and femoral neck BMD were also evaluated. Once-monthly ibandronate was considered non-inferior to weekly alendronate if the lower boundary of the one-sided 97.5% confidence interval (CI) (or two-sided 95% CI) was > -1.41 percent for lumbar spine and > -0.87 percent for total hip. The mean relative 12-month changes were 5.1 percent and 5.8 percent (95% CI, -1.13 to -0.23) in lumbar spine and 2.9 percent and 3.0 percent (95% CI, -0.38 to 0.18) in total hip BMD with once-monthly ibandronate and weekly alendronate, respectively. Therefore, once-monthly ibandronate was shown to be clinically comparable to weekly alendronate at increasing BMD after 12 months in both the lumbar spine and total hip.

raloxifene (Evista) versus placebo

To evaluate the three-year effects of raloxifene treatment on BMD, 1,145 postmenopausal women were enrolled in a randomized, double-blind trial.[129] They received raloxifene 30, 60, or 150 mg or placebo daily. Lumbar spine BMD changed from baseline to 36 months as follows: placebo, -1.32 percent; raloxifene 30 mg, +0.71 percent; raloxifene 60 mg, +1.28 percent; and raloxifene 150 mg, +1.2 percent. Comparable BMD changes were observed in the hip and total body. The significant adverse effect of active treatment was hot flashes (25 percent in the raloxifene 60 mg group versus 18 percent in the placebo group).

In a randomized double-blind trial, 7,705 women who had osteoporosis received raloxifene 60 or 120 mg per day or placebo.[130] Women receiving raloxifene had fewer new vertebral fractures. One hundred seventeen women had two or more new vertebral fractures. Compared to placebo, BMD increased after 36 months by 2.1 and 2.6 percent at the femoral neck and spine, respectively, in the 60 mg raloxifene group and by 2.4 and 2.7 percent at the femoral neck and spine, respectively, in the 120 mg raloxifene group (all p<0.001). Thromboembolic events were reported more frequently in the raloxifene groups (one percent for each active treatment group compared to 0.3 percent for the placebo group). In an extension of the study, placebo-treated women continued with placebo (n=1,286), but those previously given raloxifene 60 or 120 mg daily received raloxifene 60 mg daily (n=2,725).[131] As a secondary endpoint, new non-vertebral fractures were analyzed in 4,011 postmenopausal women after eight years. The risk of at least one new non-vertebral fracture was similar in the placebo (22.9 percent) and raloxifene (22.8 percent) groups, and the incidence of at least one new non-vertebral fracture at six major sites (clavicle, humerus, wrist, pelvis, hip, lower leg) was 17.5 percent in both groups. The differences in mean lumbar spine and femoral neck BMD with raloxifene were 1.7 percent (p=0.30) and 2.4 percent (p=0.045), respectively, from placebo. Compared with baseline, raloxifene treatment significantly increased lumbar spine (4.3 percent from baseline, 2.2 percent from placebo) and femoral neck BMD (1.9 percent from baseline, three percent from placebo).

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

risedronate immediate-release (Actonel) versus placebo

A randomized, double-blind, placebo-controlled trial of 2,458 postmenopausal women younger than 85 years with at least one vertebral fracture at baseline were randomly assigned to receive oral treatment for three years with risedronate 2.5 or 5 mg daily or placebo.[132] The risedronate 2.5 mg daily arm was discontinued after one year; the placebo (450 subjects) and risedronate 5 mg daily (489 subjects) arms completed all three years of the trial. Treatment with 5 mg daily of risedronate significantly reduced the cumulative incidence of new vertebral fractures over three years (11.3 versus 16.3 percent) versus placebo (p=0.003). The cumulative incidence of nonvertebral fractures over three years was significantly reduced (5.2 versus 8.4 percent) versus placebo. BMD increased significantly compared with placebo at the lumbar spine (5.4 versus 1.1 percent), femoral neck (1.6 versus -1.2 percent), femoral trochanter (3.3 versus -0.7 percent), and midshaft of the radius (0.2 versus -1.4 percent).

In a two-protocol study, 9,331 women were randomized to evaluate the effects of risedronate 2.5 mg, 5 mg, or matching placebo given daily for three years to prevent hip fractures.[133] All women also received supplemental calcium carbonate. The women were divided into two groups: 70 to 79 years of age with osteoporosis and 80 years of age or older with one or more clinical risk factors for hip fracture. The mean duration of therapy was two years, and 64 percent of patients had complete follow-up data. There was a significant decrease in the risk of hip fracture in all patients who were on risedronate versus placebo treatment (2.8 percent compared to 3.9 percent, p=0.02). Patients in the 80 years of age and older group did not show a significant decrease in risk of hip fracture when treated with risedronate.

In order to determine the effects of five years of risedronate treatment, the authors extended a three-year, placebo-controlled vertebral fracture study in osteoporotic women for an additional two years.[134] Women who entered the extension study continued to receive 5 mg risedronate or placebo according to the original randomization, with maintenance of blinding. The risk of new vertebral fractures was significantly reduced with risedronate treatment in years four and five by 59 percent (p=0.01) compared with a 49 percent reduction in the first three years. Significant decreases in markers of bone turnover observed in the first three years were similarly maintained in the next two years of treatment. Increases in spine and hip BMD that occurred in the risedronate group during the first three years were maintained or increased with a further two years of treatment.

In an 18-month, randomized, double-blind trial, 280 male patients 65 years or older who were post-stroke received a risedronate 2.5 mg daily (n=140) or placebo (n=140).[135] Ten patients sustained hip fractures in the placebo group, and two hip fractures occurred in the risedronate group. The relative risk of a hip fracture was 0.19 (95% CI, 0.04-0.89). Bone mineral density increased by 2.5 percent in the risedronate group and decreased by 3.5 percent in the placebo group (p<0.001).

In a multinational, two-year, double-blind study, male patients (n=284) with osteoporosis were randomized to receive risedronate 35 mg once a week or placebo. All patients also took 1,000 mg elemental calcium and 400-500 IU vitamin D daily.[136] Treatment with risedronate resulted in a significant increase from baseline to endpoint in lumbar spine BMD compared with placebo (p<0.001). Few new vertebral and nonvertebral fractures were reported, with no differences in fracture rates between the two groups. There was a significant (p<0.01) reduction from baseline in bone turnover markers for the risedronate group compared with placebo at all time points. No differences in adverse effects were observed.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

risedronate immediate-release (Actonel) versus etidronate (Didronel)

Patients with Paget's disease of bone received risedronate 30 mg daily for two months (n=62) or etidronate 400 mg daily for six months (n=61) in a prospective, randomized, double-blind study.[137] Serum alkaline phosphatase, serum bone-specific alkaline phosphatase, and urinary deoxypyridinoline concentrations were monitored for 12 to 18 months. Serum alkaline phosphatase concentration normalized by month 12 in 73 percent of risedronate-treated patients, compared with 15 percent of those receiving etidronate ($p<0.001$). Median time to normalization was 91 days for risedronate-treated patients and greater than 360 days for etidronate-treated patients ($p<0.001$); relapse rates were three percent in the risedronate group and 15 percent in the etidronate group ($p<0.05$). At month 18, 53 percent of the risedronate group and 14 percent of the etidronate group remained in biochemical remission. Urinary deoxypyridinoline and serum bone-specific alkaline phosphatase levels normalized in significantly more risedronate patients than etidronate patients, as well. Reductions in pain were statistically significant in the risedronate group but not in the etidronate group. Both drugs were well tolerated.

risedronate delayed-release (Atelvia) versus risedronate immediate-release (Actonel)

A randomized, double-blind, active-control trial of approximately 900 subjects with postmenopausal osteoporosis compared the efficacy of risedronate delayed-release (DR) 35 mg once-a-week and risedronate immediate-release (IR) 5 mg daily.[138] All patients in the study received supplemental calcium (1,000 mg/day) and vitamin D (800 – 1,000 IU/day). The primary efficacy endpoint was percent change in lumbar spine bone mineral density at one year. Risedronate delayed-release 35 mg once-a-week administered after breakfast was shown to be non-inferior to risedronate sodium immediate-release 5 mg daily (3.1 versus 3.3 percent, respectively).

teriparatide (Forteo) versus placebo

A total of 1,637 postmenopausal women with prior vertebral fractures were randomized to receive parathyroid hormone 20 or 40 mcg subcutaneously (SC) or placebo daily for a median duration of 21 months.[139] In the blinded trial, new vertebral fractures occurred in five, four, and 14 percent of the 20 mcg and 40 mcg parathyroid hormone compared to placebo patients, respectively. New nonvertebral fragility fractures occurred in six percent of the women in the placebo group and in three percent of those in each parathyroid hormone group. BMD was increased by nine and 13 more percentage points in the lumbar spine and by three and six more percentage points in the femoral neck for the 20 mcg and 40 mcg parathyroid hormone groups compared to the placebo groups. Occasional nausea and headache occurred in the parathyroid hormone patients. The 40 mcg dose increased BMD more than the 20 mcg dose but had similar effects on the risk of fracture and was more likely to have side effects.

teriparatide (Forteo) versus alendronate (Fosamax)

In a double-blind study of 146 postmenopausal women with osteoporosis, 73 women were randomized to once daily SC injections of teriparatide 40 mcg, and 73 women were randomized to once daily alendronate 10 mg for 14 months.[140] At three months, teriparatide increased lumbar spine BMD by 12.2 percent, and alendronate increased BMD by 5.6 percent ($p<0.001$). Teriparatide also increased femoral neck BMD and total body bone mineral significantly more than did alendronate ($p<0.05$). Additionally, nonvertebral fracture incidence was significantly lower in the teriparatide group

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

(p<0.05). Both treatments were well tolerated despite transient mild asymptomatic hypercalcemia with teriparatide treatment.

A randomized and blinded clinical trial involving 238 postmenopausal women with low hip or spine BMD was carried out at four centers.[141] In the study, the women were given a daily regimen of PTH, alendronate, or a combination of the two. After 12 months, results showed no significant benefit to combining treatments.

In an 18-month, randomized, parallel, double-blind study, 203 postmenopausal women with osteoporosis received teriparatide 20 mcg or alendronate 10 mg.[142] Teriparatide significantly increased markers of bone turnover that peaked at six months (serum procollagen type I N-terminal propeptide, 218 percent and urinary N-telopeptide corrected for creatinine, 58 percent; p<0.001); alendronate significantly decreased the markers at six months (-67 percent and -72 percent, respectively; p<0.001). At 18 months, areal and volumetric spine BMDs were significantly higher with teriparatide than with alendronate (10.3 percent versus 5.5 percent [p<0.001] and 19 percent versus 3.8 percent [p<0.01], respectively). Areal femoral neck BMD was significantly higher than baseline in the teriparatide and alendronate groups (3.9 and 3.5 percent, respectively). There were no significant differences in trabecular femoral neck BMD between the teriparatide and alendronate groups (4.9 and 2.2 percent, respectively). Cortical volumetric femoral neck BMD was significantly different between the teriparatide and alendronate groups (-1.2 and 7.7 percent, respectively; p=0.05).

A 36-month randomized, double-blind, controlled trial in 428 subjects compared teriparatide (20 microg/day) with alendronate (10 mg/day) for treating glucocorticoid-induced osteoporosis.[143] Patients had received ≥ 5 mg/day of prednisone equivalent for at least three months preceding screening. Increases in BMD from baseline were significantly greater in the teriparatide group than in the alendronate group, and at 36 months were 11 percent versus 5.3 percent for lumbar spine, 5.2 percent versus 2.7 percent for total hip, and 6.3 percent versus 3.4 percent for femoral neck (p<0.001 for all). Fewer subjects had vertebral fractures in the teriparatide group than in the alendronate group (1.7 percent versus 7.7 percent; p=0.007), with most occurring during the first 18 months. There was no significant difference between groups in the incidence of nonvertebral fractures (7.5 percent for teriparatide versus 7 percent for alendronate; p=0.843). More subjects in the teriparatide group (21 percent) versus the alendronate group (7 percent) had elevated pre-dose serum calcium concentrations (p<0.001).

teriparatide (Forteo) versus raloxifene (Evista)

A six-month randomized, double-blind trial comparing teriparatide plus raloxifene (n=69) versus teriparatide plus placebo (n=68) was conducted in postmenopausal women with osteoporosis.[144] Bone formation increased similarly in both treatment groups. However, the increase in bone resorption in the combination group was significantly smaller than in the teriparatide-alone group (p=0.015). Lumbar spine BMD significantly increased 5.19 percent from baseline in the teriparatide-alone group, and 6.19 percent in the combination group. Also, femoral neck and total hip BMD significantly increased in the combination group, and the increase in total hip BMD was significantly greater than in the teriparatide-alone group (p=0.04). The safety profile of combination therapy was similar to teriparatide alone.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

Adherence to Treatment Regimen

Daily dosing versus weekly dosing

Claims data for 30 health plans between 1997 and 2002 were used to identify postmenopausal women with osteoporosis who had been newly prescribed a once weekly bisphosphonate (alendronate 35 mg or 70 mg; n=731) or a once daily bisphosphonate (alendronate 5 mg or 10 mg or risedronate 5 mg; n=2,010).[145] Data were examined for 12 months from the date of the initial prescription in an attempt to compare weekly and daily bisphosphonate treatment regimens relative to compliance and persistence. Medication possession ratios (MRPs) were used to measure refill compliance during follow up. Patients treated with a weekly bisphosphonate were found to have significantly higher medication compliance as compared to patients taking daily treatment (69.2 percent versus 57.6 percent MRP, $p \leq 0.0001$). Those patients on weekly treatment were also found to persist with treatment significantly longer than patients on daily treatment ($p<0.0001$) and had higher rates of retention on treatment at 12 months (44.2 percent versus 37.1 percent, respectively). Dosing frequency was the strongest predictor of time to discontinuation ($p<0.0001$).

Weekly dosing versus monthly dosing

A study compared the relative rates of treatment persistence and medication adherence in patients taking either weekly risedronate or monthly ibandronate.[146] Prescription claims data from the IMS longitudinal prescription database were used to identify patients taking either risedronate 35 mg weekly (n=234,862) or ibandronate 150 mg monthly (n=5,139). Two study periods were examined: May through November 2005 and six months after initial market availability of each agent. Prescription refill history was tracked for 180 days from the date the original prescription was filled to evaluate adherence and persistence. Patients being treated with weekly risedronate were found to have significantly higher mean persistence and compliance rates than those patients receiving monthly ibandronate.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

SUMMARY

Clinical trials have shown a decreased risk of fractures with alendronate (Fosamax), calcitonin (Fortical, Miacalcin), ibandronate (Boniva), raloxifene (Evista), risedronate (Actonel, Atelvia), denosumab (Prolia) and teriparatide (Forteo) in women with osteoporosis. The data are less clear in women who are postmenopausal but have not been diagnosed with osteoporosis. Additionally, data in men show an increase in BMD but a less clear picture on fracture reduction.

Teriparatide (Forteo) showed the greatest increase in BMD in clinical trials, ranging from five to more than ten percent. In general, the bisphosphonates increased BMD about two to five percent in patients in randomized, controlled trials. Gains in BMD vary by the bone measured; however, BMD gains are greater in vertebral sites compared to those found in hips. Calcitonin (Miacalcin, Fortical) and raloxifene (Evista) trials showed BMD increases of approximately of one to two percent.

Ibandronate (Boniva) and risedronate immediate-release (Actonel) are both available in a once monthly dosage form. Risedronate immediate-release (Actonel) is also available in a dosing regimen that is taken two consecutive days each month. Alendronate (Fosamax) and risedronate (Actonel, Atelvia) are available for once weekly dosing. Based on currently available studies, it appears that bisphosphonates dosed weekly foster greater medication adherence, as well as longer treatment persistence compared to daily dosing regimens. However, when compared to once-weekly regimens, once monthly dosing regimens do not appear to give rise to greater treatment adherence and persistence. Binosto, a once weekly effervescent alendronate, is the most recent entry in this class. It is considered equivalent in efficacy to oral once weekly alendronate dosage forms and only offers an alternative delivery form.

Risedronate delayed-release (Atelvia) is indicated for the treatment of osteoporosis in postmenopausal women. Significantly higher incidence of abdominal pain has been reported for risedronate delayed-release when administered under fasting conditions compared to risedronate immediate-release (Actonel) tablets. Risedronate delayed-release (Atelvia) should be taken immediately following breakfast and not under fasting conditions, unlike other bisphosphonates which should be given prior to breakfast. Risedronate immediate-release (Actonel) is approved for treatment and prevention of osteoporosis in postmenopausal women, treatment to increase bone mass in men with osteoporosis, prevention and treatment of glucocorticoid-induced osteoporosis in men and women, and treatment of Paget's disease of bone in men and women. Patients should not lie down for at least 30 minutes after taking any oral bisphosphonate.

Teriparatide (Forteo) should be reserved for patients who have failed other therapies and are also at high risk for fractures. Teriparatide (Forteo) does have a black box warning and also can increase calcium levels.

Subcutaneous injectable formulations used in the treatment of osteoporosis include teriparatide (Forteo) and the newest product, denosumab (Prolia). Denosumab is a RANK ligand inhibitor that exerts its effects by inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. While denosumab does require administration by a healthcare professional, it has a dosing frequency of only twice a year.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

REFERENCES

1 Binosto [package insert]. San Antonio, TX; Mission Pharmacal; April 2013
2 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
3 Fosamax Plus D [package insert]. Whitehouse Station, NJ; Merck; April 2013.
4 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
5 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
6 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
7 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; April 2013.
8 Miacalcin nasal spray [package insert]. East Hanover, NJ; Novartis; July 2011.
9 Fortical nasal spray [package insert]. Minneapolis, MN; Upsher-Smith; April 2011.
10 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012
11 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
12 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
13 Xgeva [package insert]. Thousand Oaks, CA; Amgen; February 2013.
14 National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Available at: http://www.nof.org/hcp/practice/practice-and-clinical-guidelines/clinicians-guide. Accessed February 12, 2014.
15 USPSTF. Screening for Osteoporosis Clinical Summary of U.S. Preventive Services Task Force Recommendation. 2011. Available at: http://www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteosum.pdf. Accessed February 13, 2014.
16 NIH osteoporosis and related bone diseases national resource center, osteoporosis in men. Available at: http://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/men.asp. Accessed February 13, 2014.
17 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.
18 North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause. Vol. 17, No. 1, pp. 25/54.
19 Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2010. Endocr Pract. 2010; 16(3):1-37.
20 National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. http://www.nof.org/hcp/practice/practice-and-clinical-guidelines/clinicians-guide. Accessed February 12, 2014.
21 USPSTF. Screening for Osteoporosis Clinical Summary of U.S. Preventive Services Task Force Recommendation. 2011. Available at: http://www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteosum.pdf. Accessed February 13, 2014.
22 Fosamax [package insert]. Whitehouse Station, NJ; Merck; June 2012.
23 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
24 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
25 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
26 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
27 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
28 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
29 Binosto [package insert]. San Antonio, TX; Mission Pharmacal; April 2013
30 Fosamax [package insert]. Whitehouse Station, NJ; Merck; June 2012.
31 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
32 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
33 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
34 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; October 2011.
35 Fosamax Plus D [package insert]. Whitehouse Station, NJ; Merck; April 2013.
36 Miacalcin nasal spray [package insert]. East Hanover, NJ; Novartis; July 2011.
37 Fortical nasal spray [package insert]. Minneapolis, MN; Upsher-Smith; April 2011.
38 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
39 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
40 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
41 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; April 2013.
42 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
43 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
44 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
45 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
46 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; April 2013.
47 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
48 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
49 Available at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Bisphosphonates. Accessed February 13, 2014.
50 Available at: http://www.nof.org/hcp/practice/practice-and-clinical-guidelines/clinicians-guide. Accessed February 12, 2014.
51 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
52 Xgeva [package insert]. Thousand Oaks, CA; Amgen; February 2013.
53 Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124165.htm. Accessed February 13, 2014.
54 Available at: http://www.nof.org/hcp/practice/practice-and-clinical-guidelines/clinicians-guide. Accessed February 12, 2014.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

55 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm263320.htm. Accessed February 13, 2014.
56 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm. Accessed February 13, 2014.
57 Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=106#1. Accessed February 13, 2014.
58 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
59 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
60 Boniva [package insert]. Nutley, NJ; Roche; April 2011.
61 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
62 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
63 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; April 2013.
64 Binosto [package insert]. San Antonio, TX; Mission Pharmacal; April 2013
65 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
66 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
67 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
68 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
69 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
70 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
71 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
72 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013
73 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
74 Actonel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
75 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; April 2013.
76 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
77 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
78 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
79 Miacalcin nasal spray [package insert]. East Hanover, NJ; Novartis; July 2011.
80 Fortical nasal spray [package insert]. Minneapolis, MN; Upsher-Smith; April 2011.
81 Fosamax Plus D [package insert]. Whitehouse Station, NJ; Merck; April 20123
82 Actonel [package insert]. Cincinnati, OH; Procter and Gamble; April 2013.
83 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
84 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
85 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
86 Miacalcin nasal spray [package insert]. East Hanover, NJ; Novartis; July 2011.
87 Fortical nasal spray [package insert]. Minneapolis, MN; Upsher-Smith; April 2011.
88 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
89 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
90 Xgeva [package insert]. Thousand Oaks, CA; Amgen; February 2013.
91 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
92 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
93 Xgeva [package insert]. Thousand Oaks, CA; Amgen; February 2013.
94 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
95 Binosto [package insert]. San Antonio, TX; Mission Pharmacal; April 2013
96 Fosamax [package insert]. Whitehouse Station, NJ; Merck; April 2013.
97 Fosamax Plus D [package insert]. Whitehouse Station, NJ; Merck; April 2013.
98 Didronel [package insert]. Rockaway, NJ; Warner Chilcott; April 2013.
99 Boniva [package insert]. Nutley, NJ; Roche; April 2013.
100 Actonel [package insert]. Cincinnati, OH; Procter and Gamble; April 2013.
101 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; April 2013.
102 Miacalcin nasal spray [package insert]. East Hanover, NJ; Novartis; July 2011.
103 Fortical nasal spray [package insert]. Minneapolis, MN; Upsher-Smith; April 2011.
104 Prolia [package insert]. Thousand Oaks, CA; Amgen; September 2012.
105 Evista [package insert]. Indianapolis, IN; Lilly; January 2011.
106 Forteo [package insert]. Indianapolis, IN; Lilly; March 2012.
107 Binosto [package insert]. San Antonio, TX; Mission Pharmacal; April 2013
108 Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med. 1995; 333:1437-1443.
109 Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. JAMA. 1998; 280:2077-2082.
110 Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging Clin Exp Res. 2000; 12:1-12.
111 Luckey MM, Gilchrist N, Bone HG, et al. Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. Obstet Gynecol. 2003; 101(4):711-721.
112 Ascott-Evans BH, Guanabens N, Kivinen S, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med. 2003; 163(7):789-94.
113 Sambrook PN, Geusens P, Ribot C, et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. J Intern Med. 2004; 255(4):503-511.

© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.

114 Luckey M, Kagan R, Greenspan S, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause. 2004; 11(4):405-415.
115 Lanza FL, Hunt RH, Thomson AB, et al. Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. Gastroenterology. 2000; 199:631-638.
116 Thomson ABR, Marshall JK, Hunt RH, et al. 14 day endoscopy study comparing risedronate and alendronate in postmenopausal women stratified by Helicobacter pylori status. J Rheumatol. 2002; 29:1965-1974.
117 Lanza F, Schwartz H, Sahba B, et al. An endoscopic comparison of the effects of alendronate and risedronate on upper gastrointestinal mucosa. Am J Gastroenterol. 2000; 95:3112-3117.
118 Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment With Once-Weekly Alendronate 70 mg Compared With Once-Weekly Risedronate 35 mg in Women With Postmenopausal Osteoporosis: A Randomized Double-Blind Study. J Bone Miner Res. 2005; 20(1):141-151.
119 Bonnick S, Saag KG, Kiel DP, et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab. 2006; 91(7):2631-2637.
120 Hosking D, Adami S, Felsenberg D, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomized, placebo-controlled study. Curr Med Res Opin. 2003; 19(5):383-394.
121 Fosamax Plus D [package insert]. Whitehouse Station, NJ; Merck; March 2011.
122 Chesnut CH 3rd, 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. PROOF Study Group. Am J Med. 2000; 109:267-276.
123 Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009; 361(8):756-765.
124 Orwoll E, Teglbaerg CS, Langdahl BL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab. 2012; 97(9):3161-9. doi: 10.1210/jc.2012-1569.
125 McClung MR, Wasnich RD, Recker R, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. J Bone Miner Res. 2004; 19(1):11-18.
126 Chesnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004; 19(8):1241-1249.
127 Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res. 2005; 20(8):1315-1322.
128 Miller PD, Epstein S, Sedarati F, et al. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. Curr Med Res Opin. 2008; 24(1):207-13.
129 Johnston 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: Three-year study from 2 double-blind, randomized, placebo-controlled trials. Arch Intern Med. 2000; 160:3444-3450.
130 Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. JAMA. 1999; 282:637-645.
131 Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005; 20(9):1514-1524.
132 Harris ST, Watts NB, Genant HK et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999; 282(14):1344-52.
133 McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med. 2001; 344:333-340.
134 Sorensen OH, Crawford GM, Mulder H, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003; 32(2):120-6.
135 Sato Y, Iwamoto J, Kanoko T, et al. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med. 2005; 165(15):1743-1748.
136 Boonen S, Orwoll ES, et al. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res. 2009; 24(4):719-25.
137 Miller PD, Brown JP, Siris ES, et al. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Paget's Risedronate/Etidronate Study Group. Am J Med. 1999; 106(5):513-520.
138 Atelvia [package insert]. Rockaway, NJ; Warner-Chilcott; October 2010.
139 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.
140 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; 87(10):4528-4535.
141 Black D, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003; 349(13):1207-1215.
142 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(15):1762-1768.
143 Saag KG, Zanchetta JR, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009; 60(11):3346-55.
144 Deal C, Omizo M, Schwartz EN, et al. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. J Bone Miner Res. 2005; 20(11):1905-1911.
145 Cramer JA, Amonkar MM, Hebbor A, et al. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin. 2005; 21(9):1453-60.
146 Gold DT, Safi W, Trinh H. Patient preference and adherence: comparative US studies between two bisphosphonates, weekly risedronate and monthly ibandronate. Curr Med Res Opin. 2006; 22(12):2383-2391.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2014, Provider Synergies, LLC, an affiliate of Magellan Medicaid Administration, Inc. All Rights Reserved.