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Drug Class Update with New Drug Evaluation: Bone Metabolism Agents for Osteoporosis or Paget Disease

Date of Review: November 2017
Date of Last Review: July 2016
Generic Name: Abaloparatide

End Date of Literature Search: July 7, 2017
Brand Name (Manufacturer): Tymlos™ (Radius Health)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for a new parathyroid hormone analog (abaloparatide) recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women at high risk for fracture. In addition, new comparative evidence for existing bone metabolism agents for management of osteoporosis and Paget disease will be reviewed.

Research Questions:
- Is there new comparative evidence that bone metabolism agents differ in efficacy or effectiveness for osteoporosis or Paget Disease?
- Is there any new comparative evidence the bone metabolism agents differ in harms?
- Are there specific subpopulations (gender, fracture risk) for which one agent is better tolerated or more effective than other available agents?

Conclusions:
- Two new systematic reviews and two updated clinical guidelines were identified for this class update.[1-4]
- There is no new comparative evidence to evaluate the comparative safety and efficacy or effectiveness of the bone metabolism agents.
- One systematic review evaluated the use of bisphosphonates in men and provides moderate quality evidence that bisphosphonates reduce fracture risk for men with osteoporosis. Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[3]
- The Institute for Clinical and Economic Review (ICER) evaluated the effectiveness of anabolic therapies for osteoporosis in postmenopausal women. Currently, there are no head-to-head trials that compare abaloparatide to teriparatide so there is insufficient evidence to assess the comparative clinical effectiveness of the two anabolic therapies on reduction of fractures in patients with osteoporosis. Teraparatide and abaloparatide are both administered via subcutaneous injection once daily and have similar adverse effect profiles.[1]

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- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) and American College of Physicians (ACP) continue to recommend alendronate, risedronate, zoledronic acid, or denosumab as first-line treatment options for postmenopausal osteoporosis in their clinical practice guideline due to these agent's evidence for reducing risk of fractures (spine, hip, and nonvertebral fracture risk).[2]
- In one randomized, placebo-controlled trial, abaloparatide significantly reduced the risk of new vertebral fractures in postmenopausal women compared to placebo over 18 months (relative risk (RR) 0.14, 95% confidence interval (CI) 0.05 to 0.39, p<0.001, absolute risk reduction (ARR) 3.6%, number-needed-to-treat (NNT) 28).[5] The risk of nonvertebral fractures, a secondary endpoint for this trial, was also reduced when abaloparatide was compared to placebo over 18 months (hazard ratio (HR) 0.57; 95% CI 0.32 to 1.00, p<0.049, ARR 2%, NNT 50).[5]
- Rates of serious treatment-emergent adverse events between abaloparatide, open-label teriparatide, and placebo were similar in the same trial (9.7%, 10.0%, and 11% respectively).[5] The most common adverse effects that led to treatment discontinuation with abaloparatide included nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%).[5]
- The duration of therapy for abaloparatide is limited to 2 years due to the risk of osteosarcoma noted in rats with systemic exposure 4 to 28 times the exposure in humans receiving recommended doses.[6] Teriparatide also has a risk of osteosarcoma, and duration of therapy is limited to 2 years.[7] Abaloparatide also carries risks of orthostatic hypotension (17.1%), hypercalcemia (3.4 %), and hypercalciuria (11.3%) as described in the phase 3 randomized controlled trial.[5]
- There was no new evidence for the use of bone metabolism agents in managing Paget disease.
- Xgeva® (denosumab) received an expanded indication to include prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.[8] This indication is only for the Xgeva® branded formulation of denosumab, not the other branded formulation of denosumab known as Prolia®.
- The warnings and precautions section of the denosumab labeling was revised to include the risk of embryo-fetal toxicity based on data from animal studies.[8]

Recommendations:
- Maintain abaloparatide as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical PA criteria for bone metabolism agents to include abaloparatide.
- Evaluate costs in executive session.

Previous Conclusions:
Efficacy
- The Endocrine Society recommends IV zoledronic acid 5 mg in a single dose for most patients with active Paget disease who are at risk for complications unless contraindications exist.
- One systematic review and meta-analysis found no statistically significant and consistent difference in vertebral and nonvertebral fracture risk reduction between bisphosphonates, denosumab, or teriparatide.
- Denosumab had lower rates of nonvertebral fracture compared to other bisphosphonates or placebo in one systematic review and meta-analysis.[3] On the contrary, two systematic reviews and meta-analyses found that denosumab had an increased risk for infections.
- A systematic review and meta-analysis found no benefit in terms of vertebral or nonvertebral fracture risk with bisphosphonate use at 12 months in patients with cystic fibrosis, though a significant increase in percent change in bone mineral density (BMD) of the lumbar spine, hip and femur.

- In patients with osteogenesis imperfecta, oral alendronate and IV pamidronate showed no difference in fracture incidence. A significant increase was seen in Z score BMD between patients dosed 0.2 mg/kg versus 2 mg/kg of IV risedronate.[5] No difference was seen in patients treated with zoledronic acid versus pamidronate in change in number of fractures.
- Bisphosphonate-treated patients with inflammatory bowel disease had improvements in BMD at the lumbar spine and total hip and lower rates of vertebral and nonvertebral fractures when compared to active controls.
- Early breast cancer patients scheduled to receive aromatase inhibitors had a greater increase in BMD in the lumbar spine in terms of percent change and absolute change in bisphosphonate treated groups compared to groups treated with oral calcium, oral vitamin D or cholecalciferol with or without placebo.[7]
- Patients with Parkinson disease and previous stroke had reduced rates of hip fractures when treated with bisphosphonates compared to controls.[8]

Safety
- Raloxifene was not found to prevent nonvertebral fractures and is associated with a significant rate of severe side effects including thromboembolic events, pulmonary embolism, and fatal strokes.
- Cases of osteonecrosis of the jaw have been reported with bisphosphonate use but are associate much more significantly with IV bisphosphonates versus oral formulations and in patients being treated for malignant conditions.

Previous Recommendations:
- Consider inclusion of zoledronic acid due to the Endocrine Society's recommendation for use as first-line for Paget's disease.
- Consider inclusion of bazedoxifene on preferred list due to superiority over other bisphosphonates in patients at high risk for fractures (FRAX score ≥20%).
- Consider inclusion of denosumab, zoledronic acid, risedronate, alendronate in various routes and dosing schedules for osteoporosis treatment based upon cost.
- Include at least one nitrogen-containing bisphosphonate for Paget disease (zoledronic acid, pamidronate, risedronate, alendronate or ibandronate).
- Make calcitonin, raloxifene and teriparatide non-preferred due to limited evidence to reduce nonvertebral and hip fracture risk in post-menopausal women. Calcitonin has limited evidence for Paget disease.
- Make tiludronate non-preferred as it is only indicated for Paget disease, is not a nitrogen containing bisphosphonate and it has insufficient evidence for osteoporosis treatment.

Background:
Osteoporosis is characterized by low bone mass, deterioration of bone tissue, compromised bone strength, and increased risk of fracture.[9] Osteoporosis occurs as part of the aging process or secondary to nutritional deficiency, metabolic disorders, or utilization of certain medications.[9] Long-term intake of anticoagulants, antiepileptics, aromatase inhibitors, gonadotropin releasing-hormones, glucocorticoids, lithium, thiazolidinediones, or proton pump inhibitors are also associated with increased risk for osteoporosis.[9] Lifestyle factors that adversely impact the risk for osteoporosis include low calcium intake, vitamin D deficiency, excess vitamin A intake, inadequate physical activity, smoking and alcohol abuse.[9] Other patients at high risk for osteoporosis include those with low body weight (<57.6 kg), rheumatic disease, hyperparathyroidism, multiple myeloma, malabsorption, diabetes, or inflammatory bowel disease.[10] Throughout life, older bone is resorbed by osteoclasts and replaced with new bone made by osteoblasts.[11] This process is known as remodeling and is orchestrated and targeted to a particular site that is in need for repair by osteocytes.[11] When this system is out of balance, bone loss occurs. In the past decade, the master signals that regulate this process have been defined. The receptor activator of nuclear factor kappa-B ligand (RANKL) is a key signal that increases bone loss and has become a target for the treatment of osteoporosis with the monoclonal antibody denosumab.

The estimated prevalence of osteoporosis in the US is 10.3%, or approximately 10.2 million older adults using 2010 population estimates.[12] One study estimated that 7.7 million non-Hispanic White, 0.5 million non-Hispanic Black, and 0.6 million Mexican American adults had osteoporosis and another 33.8, 2.9, and 2.0 million had low bone mass, respectively.[12] Although most of the individuals with osteoporosis or low bone mass were non-Hispanic white women, a substantial number of men and women from other racial/ethnic groups also had osteoporosis or low bone mass.[12]

Bone mineral density (BMD) assessed with dual x-ray absorptiometry (DXA) is a surrogate marker used to diagnose osteoporosis. A patient is considered to have osteoporosis with a BMD T-score of less than 2.5 standard deviations below the average of a young adult.[9] BMD can be used in conjunction with the World Health Organization fracture-risk assessment tool (FRAX) to estimate an individual's 10-year risk of sustaining a hip fracture or major osteoporotic fractures.[13] The life-time fracture risk of a patient with osteoporosis can be as high as 40% and fractures of the hip, spine or wrist are the most common locations.[9] The primary goal of osteoporosis management is to reduce fracture risk. Fractures are associated with decreased quality of life, reduced independence, and increased morbidity and mortality.[14] The US Preventative Services Task Force (USPSTF) recommends screening average-risk women with a bone density measurement at age 65 years and screening younger women whose fracture risk is equal to or greater than that of a 65-year old white woman with no additional risk factors.[15] The USPSTF concluded that there is insufficient evidence to assess the balance of benefits and harms for screening for osteoporosis in men.[15]

Drugs to treat osteoporosis fall into two groups: the anti-resorptive drugs, which slow down bone resorption, and anabolic drugs, which stimulate bone formation. The anti-resorptive drugs include bisphosphonates, raloxifene, calcitonin, and denusomab, which suppresses the RANKL pathway. Teriparatide and abaloparatide are recombinant forms of parathyroid hormone which stimulate osteoblasts to form new bone. Teriparatide is approved for use up to 2 years in the US due to concerns that prolonged use may cause osteosarcoma based on data from rat studies. All drugs require adequate serum levels of calcium and vitamin D for optimum effect. Bisphosphonates are considered first line therapy, but short-term tolerability and potential long-term risk of atypical femur fracture, osteonecrosis of the jaw and esophageal cancer may limit their utilization. Dosing recommendations of the bone metabolism agents for osteoporosis and Paget disease are presented in **Table 1.**

Paget disease is a disorder of bone metabolism that includes an accelerated rate of bone remodeling, resulting in overgrowth of bone at selected sites and impaired integrity of affected bone.[16] It is a finding in aging bone, with estimates ranging from 2.3 to 9% in patients older than 55 years.[16] Many patients with Paget disease are asymptomatic but others exhibit joint pain and deformities. Most frequently affected areas are the pelvis, femur, lumbar spine, skull, and tibia.[16] Paget disease that affects the skull may result in hearing loss. Fractures, bone tumors, neurologic disease, cardiac disease, and abnormalities in calcium and phosphate balance can also occur.[16] Diagnosis of Paget disease is confirmed by x-ray or bone scintigraphy in addition to an elevated serum total alkaline phosphatase (ALP) level that is not due to hepatic dysfunction. The goals of treatment are to reduce pain, normalize bone remodeling and slow disease progression.[17] The nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, and alendronate) are first-line agents for the treatment of Paget disease.[16,17] Bisphosphonate therapy may resolve bone pain, reduce ALP levels, and slow bone turnover; however, there is insufficient evidence to demonstrate improved clinical outcomes or reduced complications with bisphosphonate therapy.[16] Analgesics, nonsteroidal anti-inflammatory drugs, or antineuropathic agents may control pain that does not respond to bisphosphonates. In one comparative study, bisphosphonate therapy did not reduce the risk of fracture or need for orthopedic surgery more than analgesics or anti-inflammatory agents.[18]

Fee-for-service (FFS) utilization of bone metabolism drugs in the third quarter of 2017 (July 1, 2017 through September 30, 2017) included a total of 63 paid claims for preferred bisphosphonates. Eighty-eight percent were for alendronate, 6% were for risedronate, and 5% were for ibandronate. One paid claim was received for the nonpreferred agent teriparatide. There was no utilization of calcitonin or raloxifene during this quarter.

Table 1. Bone Metabolism Agent Dosing in Osteoporosis and Paget Disease[19]

Anti-Resorptive Agents				
		Osteoporosis Dosing		
Generic Name (Brand Name)	**Drug Class**	**Prevention**	**Treatment**	**Paget Disease Dosing**
Alendronate (Fosamax)	Bisphosphonate	5 mg orally once daily 35 mg orally once a week	10 mg orally once daily 70 mg orally once a week	40 mg orally once daily for 6 months
Risedronate (Actonel, Atelvia)	Bisphosphonate	5 mg orally once daily 35 mg orally once a week 150 mg orally once a month	5 mg orally once daily 35 mg orally once a week 150 mg orally once a month	30 mg orally once daily for 2 months
Ibandronate (Boniva)	Bisphosphonate	2.5 mg orally once daily 150 mg orally once a month	2.5 mg orally once daily 150 mg orally once a month 3 mg IV once every 3 months	-
Pamidronate (Aredia)	Bisphosphonate	-	-	30-60 mg IV once daily for 3 consecutive days
Zoledronic Acid (Reclast)	Bisphosphonate	5 mg IV every 2 years	5 mg IV once a year	5 mg IV as a single dose
Denosumab (Prolia)	RANKL inhibitor	-	60 mg SC every 6 months	-
Raloxifene (Evista)	Selective estrogen receptor modulator (SERM)	60 mg orally once daily	60 mg orally once daily	-
Calcitonin (Miacalcin)	Hormone	-	100 units IM or SC once daily 200 units intranasal in one nostril once daily	100 units IM or SC once daily
Anabolic Agents				
Teriparatide (Forteo)	Parathyroid hormone analog	-	20 mcg SC once daily	-
Abaloparatide (Tymlos)	Parathyroid hormone analog	-	80 mcg SC once daily	-

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

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of this review is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Anabolic Therapy in Osteoporosis
The Institute for Clinical and Economic Review (ICER) evaluated the effectiveness of anabolic therapies for osteoporosis in postmenopausal women.[1] Two placebo controlled trials evaluated the effectiveness of teraparatide or abaloparatide in reducing vertebral fractures.[5,20] Both drugs were significantly better than placebo in reducing the proportion of women with vertebral fractures. No head to head randomized controlled trials that compare the efficacy of teraparatide to abaloparatide have been published. Both drugs are administered via a once daily subcutaneous injection. The adverse effects of both drugs are similar as they are both associated with injection site reactions and hypercalcemia. Duration of therapy with both drugs is limited to two years due to evidence that rats developed osteosarcoma after being treated with teriparatide or abaloparatide. This adverse effect has not been observed in humans. In summary, although teraparatide and abaloparatide appear similar in efficacy, dosing and adverse effects, there is insufficient evidence to assess the comparative clinical effectiveness of the two anabolic therapies to manage osteoporosis.

Osteoporosis in Men
A systematic review and meta-analysis published in 2017 evaluated the efficacy of treatment options to reduce osteoporotic fracture risk in men.[21] FDA approved osteoporosis treatments for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab. A total of 3802 studies published between 1998 and 2013 were reviewed. Twenty-two studies (including 4,868 male participants) met inclusion criteria. Very few studies had active comparators and most agents were compared to placebo. Most of the studies were supported by pharmaceutical company funding. The quality of the evidence was rated by the reviewers as low to moderate due to unclear bias in selection, performance, detection, attrition, and reporting domains. Separate meta-analysis were completed to assess the outcome of vertebral fractures for alendronate, calcitonin, denosumab and risedronate; nonvertebral fractures for alendronate; and clinical fractures with zoledronic acid. The bisphosphonates were also analyzed as treatment category to evaluate outcomes of vertebral, nonvertebral and clinical fractures. Fixed-effects meta-analyses demonstrated significantly lower risk of vertebral fractures with alendronate (relative risk (RR) = 0.328, 95% CI = 0.155–0.692) and risedronate (RR = 0.428, 95% CI = 0.245–0.746) but not with calcitonin (RR = 0.272, 95% CI = 0.046–1.608) or denosumab (RR = 0.256, 95% CI = 0.029–2.238) than in controls.[21] The meta-analysis findings for individual treatment options did not demonstrate significantly lower risk of nonvertebral fractures with alendronate (RR = 0.751, 95% CI = 0.352–1.602) or clinical fractures with zoledronic acid (RR = 0.742, 95% CI = 0.436–1.263) than in controls.[21] For bisphosphonates as a treatment category, meta-analyses demonstrated significantly lower risk of vertebral fractures (RR = 0.368, 95% CI = 0.252–0.537) and nonvertebral fractures (RR = 0.604, 95% CI = 0.404–0.904) than in controls.[21] In conclusion, this systematic review supports the use of bisphosphonates to reduce

fracture risk for men with osteoporosis. Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[21]

New Guidelines:

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2016 the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) updated clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis.[2] The panel of subject matter experts evaluated available literature and graded the evidence using AACE protocols which are based on the Grades of Recommendation, Development and Evaluation (GRADE) approach developed by Guyatt et al.[22,23] Randomized controlled trials (RCTs) and meta-analysis of RCTs are considered strong evidence while case series and case reports are rated as weak evidence. Only evidence graded as "A" (benefit far outweighs risk) with best level evidence "1" (strong) is reported below.

- Pharmacologic therapy is recommended for the following patients:
  - Osteopenia or low bone mass and a history of fragility fracture of the hip or spine [2]
  - T-score of -2.5 or lower in the spine, femoral neck, total hip, or 33% radius.[2]
- First-line of treatment of postmenopausal osteoporosis include alendronate, risedronate, zoledronic acid, and denosumab due to their evidence for reducing risk of fractures (spine, hip, and nonvertebral fractures).[2]
- Injectable agents such as teriparatide, denosumab, and zoledronic acid are recommended first-line for treatment of patients with high fracture risk (e.g., older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores), upper gastrointestinal (GI) problems, lower GI problems or poor compliance to oral medications.[2]
- Ibandronate and raloxifene are considered appropriate treatment for patients at high risk for spine fracture but not at risk for hip or nonvertebral fractures. Raloxifene also reduces the risk for breast cancer.[2]
- Denosumab is the treatment of choice for patients with renal insufficiency but is not recommended for patients on dialysis or those with stage 5 kidney disease due to the risk of hypocalcemia.[2]
- Treatment with teriparatide should be limited to 2 years.[2]
- Treatment with teriparatide should always be followed by anti-resorptive agents to prevent bone density decline and loss of fracture efficacy.[2]

American College of Physicians

Updated guidelines from the American College of Physicians (ACP) for the treatment of low bone density or osteoporosis to prevent fractures in men and women were published in 2017.[4] The evidence review was conducted by the Agency for Healthcare Research and Quality (AHRQ) Southern California Evidence-Based Practice Center. The recommendations were graded by the quality of evidence using the GRADE methodology.[23] Only 2 of the 6 recommendations are based on moderate to high quality evidence. Both ACP and AACE/ACE agree the choice of first-line agents to manage osteoporosis should include alendronate, risedronate, zoledronic acid, or denosumab. The ACP guidelines do not address the use of anabolic agents such as teriparatide or abaloparatide. Although AACE/ACE recommends raloxifene as appropriate treatment for patients at high risk for spinal fracture, ACP does not recommend using estrogen or raloxifene for the treatment of osteoporosis in postmenopausal women due to increased risk of adverse events with these drugs. Also, ibandronate is not recommended in the ACP guidelines due to insufficient data regarding its effects on reducing the risk for hip fracture. The recommendations are as follows:

- Clinicians should offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)

- ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)[21]
- Clinicians should offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)[21]
- ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence).[22]
- ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)[22]
- Estrogen therapy, estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in post-menopausal women is not recommended due to the increased risk of cerebrovascular accidents and venous thromboembolism with these therapies. (Grade: strong recommendation; moderate-quality evidence)[21]

New Formulations or Indications:
Xgeva (denosumab) (January 2018). The FDA approved indications for denosumab were expanded to include prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.[8] The expanded indication only applies to the Xgeva® branded formulation of denosumab 120 mg injection. Prolia®, the 60mg formulation of denosumab is only indicated for treatment of postmenopausal men or women with osteoporosis at high risk for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, or to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[24]

New FDA Safety Alerts:
Xgeva (denosumab) (January 2018). The warnings and precautions section of the denosumab labeling was revised to include the risk of embryo-fetal toxicity based on data from animal studies.[8] In animal reproduction studies, administration of denosumab to cynomolgus monkeys throughout pregnancy at a dose 25-fold higher than the recommended human dose of denusomab based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth.[8] Pregnant women or females of reproductive potential should be advised that exposure to denosumab during pregnancy or within 5 months prior to conception can result in fetal harm.

Randomized Controlled Trials:
A total of 160 citations were manually reviewed from the initial literature search. After further review, 160 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Abaloparatide (Tymlos™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Abaloparatide is a synthetic analog of human parathyroid hormone-related protein (PThrP 1-34) and has binding selectivity to the RG conformation of the parathyroid hormone receptor Type 1 (PTHR1).[6] Abaloparatide was approved by the FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture. It is an anabolic agent that stimulates bone formation similar to teriparatide. However, abaloparatide and teriparatide differ in their conformational binding to PTH1 receptors. Teriparatide binding results in prolonged signaling, while the binding of abaloparatide causes a more transient response.[25] The transient response appears to cause an anabolic effect on bone with fewer bone resorptive effects. Teriparatide initially increases bone formation, but also increases bone resorption over time, which limits its nets anabolic effect. The FDA approved abaloparatide on the results of one phase 2 dose finding trial and one phase 3 randomized controlled trial.[5,26]

Clinical Efficacy:
The Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial randomized 2,463 post-menopausal women to daily subcutaneous injections of abaloparatide 80 mcg, teriparatide 20 mcg, or identical placebo and followed them for 18 months.[5] The teriparatide arm was open label due to proprietary labeling which prevented dispensing teriparatide in other devices besides the prefilled pen. The teriparatide arm was not sufficiently powered to compare efficacy with abaloparatide. The participants were aged 49 to 86 years and had at least one moderate or two mild vertebral fractures or other fragility fractures in the previous 5 years and BMD T-scores between -2.5 and -5.0, or were women at least 65 years of age without a history of a fragility fracture with BMD T-scores between -3.0 and -5.0.[5] At baseline, the mean T-score at the total hip was -1.9 and 63% of subjects had a history of fracture. The primary outcome was the percentage of patients with new vertebral fractures at 18 months. Secondary end points included change in BMD at total hip, femoral neck, and lumbar spine and percentage of patients with nonvertebral fracture. Hypercalcemia was a prespecified safety end point in abaloparatide-treated versus teriparatide participants.

New vertebral fractures occurred in 0.6% (n=4) of women in the abaloparatide group, 0.8% (n=6) of women in the teriparatide group, and 4.2% (n=30) of women in the placebo group over the 18 month trial (abaloparatide RR 0.14, 95% CI 0.05 to 0.39, $p < 0.001$, NNT 28; teriparatide RR 0.20, 95% CI 0.08 to 0.47, $p < 0.001$, NNT 26, both vs. placebo).[5] Nonvertebral fractures event rates estimated using Kaplan-Meier estimates were 2.7% of women in the abaloparatide group, 3.3% of women in the teriparatide group and 4.7% of women in the placebo group (abaloparatide hazard ratio (HR) 0.57, 95% CI 0.32 to 1.00, $p = 0.049$; teriparatide HR 0.72, 95% CI 0.42 to 1.22, $p = 0.22$ both vs. placebo).[5] The HR for abaloparatide versus teriparatide was 0.79 (95% CI 0.43 to 1.45; p=0.44) for nonvertebral fractures.[5] BMD at 18 months was improved with abaloparatide compared to placebo at the hip (4.2% vs. -0.1%), femoral neck (3.6% vs. -0.4%) and lumbar spine (11.2% vs. 0.6%).[5] Incidence of hypercalcemia was lower with abaloparatide (3.4%) versus teriparatide (6.4%) (risk difference [RD], −2.96 [95% CI, −5.12 to −0.87]; $p = 0.006$).[5] In this trial, abaloparatide significantly reduced the risk of new fractures in postmenopausal women compared to placebo.

One limitation of this study is that 63% of participants had a prior fracture. The impact of abaloparatide on reducing fracture in women with lower risk for fracture cannot be determined from this trial. The trial was only conducted over 18 months; therefore, it is not clear how long the reduction in fracture risk with abaloparatide will persist using data from this trial. The trial was not powered to detect differences in efficacy between abaloparatide and teriparatide. The trial was not sufficiently powered to detect the effects of abaloparatide on hip fracture. Finally, the open label arm of teriparatide and lack of blinding may have

resulted in bias because subjects and investigators were aware of the treatment which may have affected adverse reaction reporting or adherence. This trial may have limited applicability to Medicaid patients, who are primarily under the age of 65 years.

Patients in both the abaloparatide and placebo groups of the ACTIVE trial were offered an additional two years of follow-up receiving open-label oral alendronate 70 mg weekly and 92% (n=1139) of eligible patients agreed to participate.[27] The 6-month follow-up results reported lower rates of vertebral fractures (HR 0.13, 95% CI 0.04-0.41) and nonvertebral fractures (HR 0.48, 95% CI 0.26-0.89) for abaloparatide followed by alendronate compared to placebo followed by alendronate when analyzed from the beginning of the ACTIVE trial.[27] However, the number of new fractures in the extension trial was low in both the abaloparatide/alendronate and placebo/alendronate groups (vertebral 0 vs. 7; nonvertebral 3 vs. 7, respectively).[27] These data suggests that alendronate therapy can preserve the fracture reduction benefits of abaloparatide.

Clinical Safety:
During the ACTIVE trial, discontinuation of the study drug due to adverse events was higher in the abaloparatide group (9.9% vs. teriparatide 6.8% and placebo 6.1%).[5] However, rates of serious treatment-emergent adverse events were similar when abaloparatide, teriparatide, and placebo were evaluated in this trial (9.7%, 10.0%, and 11% respectively).[5] Most common adverse effects that led to treatment discontinuation with abaloparatide included nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%).[5] Hypercalcemia was more common in the parathyroid hormone analog groups than placebo (3.4% abaloparatide, 6.4% teriparatide, 0.4% placebo).[5] Other significant adverse effects of abaloparatide in the ACTIVE trial were orthostatic hypotension (17.1%) and hypercalciuria (11.3%).[5] The safety profile of abaloparatide compared to placebo as described in the ACTIVE trial is presented in **Table 2**.[5]

Abaloparatide labeling contains a black box warning about the possible risk of osteosarcoma is based on an increased incidence in rats with systemic exposure 4-28 times the exposure in humans receiving recommended doses.[6] It is unknown if abaloparatide causes osteosarcoma in humans. Teriparatide contains a similar warning.[7] Use of abaloparatide greater than 2 years during a patient's lifetime is not recommended per the manufacturer's prescribing information.[6]

Table 2. Safety Profile of abaloparatide compared to placebo from the ACTIVE trial[5]

Common Adverse Events	**Abaloparatide N = 822**	**Placebo N = 820**
Hypercalciuria	11.3%	9%
Dizziness	10%	6.1%
Arthralgia	8.6%	9.8%
Headache	8%	6%
Nausea	8.3%	3%
Upper Respiratory Tract Infection	8.3%	7.7%
Serious Adverse Events	**Abaloparatide**	**Placebo**

Orthostatic Hypotension	17.1%	16.4%
Hypercalcemia	3.4%	0.4%
Tachycardia	2%	1%

Look-alike / Sound-alike Error Risk Potential: No other drugs identified

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Human parathyroid hormone related peptide (PTHrP1-34) analog which results in an anabolic effect on bone
Bioavailability	Bioavailability of an 80 mcg subcutaneous dose was 36%
Distribution and Protein Binding	Volume of distribution is 50 liters. Protein binding is 70%
Elimination	Peptide fragments are primarily eliminated through renal elimination
Half-Life	Mean half-life is 1.7 hours
Metabolism	No specific metabolism or excretion studies have been performed with abaloparatide

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:

1) Percentage of patients with new vertebral fractures
2) Percentage of patients with new non-vertebral fractures
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage of patients with new vertebral fractures over 18 months

Table 4. Comparative Evidence Table.

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/NNT**	**Safety Outcomes**	**ARR/NNH**	**Risk of Bias/ Applicability**
1. Miller et al[5] RCT, DB, PC, MC, Phase 3	1. Abaloparatide 80 mcg SC once daily 2. Placebo SC daily 3.Teriparatide 20 mcg once daily (open label due to	Demographics: -Mean age: 69 years -Mean femoral neck T score = -2.1 -White = 80% -Asian = 16% -Black = 3%	ITT: 1.824 2.821 3.818 mITT	Primary Endpoint: New vertebral fractures: ABL: 0.58% PBO: 4.2% RR 0.14 (95% CI, 0.05 to 0.39; P < 0.001)	3.6/28	Hypercalcemia (corrected Ca >10.7 mg/dL): ABL 3.4% TPTD 6.4% RD -2.96 (95% CI,	2.96/33	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW - Randomized 1:1:1 using permuted-blocks design with a block size of 6. Patients were sequentially assigned a treatment number and allocated to each group using a centralized IVRS system. The IVRS system recorded site number, subject number, and kit/randomization number and

	proprietary packaging of teriparatide) 18 months	-History of prior fracture: 63% -No prior fracture: 37% <u>Key Inclusion Criteria</u>: -Women who were postmenopausal for at least 5 years -Age 49-86 years -BMD T score ≤ -2.5 and > -5.0 at the lumbar spine or femoral neck AND radiologic evidence ≥ 2 mild or ≥ 1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years -Women aged 65 years with T score ≤ -2.0 and > 5.0 or with fracture criteria OR T score ≤ -3.0 and > -5.0 without fracture criteria <u>Key Exclusion Criteria</u>: -> 4 mild, moderate or severe vertebral fractures -< 2 evaluable lumbar vertebrae -unevaluable hip BMD	1.711 2.690 3.717 <u>Attrition</u>: 1.26% 2.22% 3.20%	TPTD: 0.84% PBO: 4.2% RR 0.20 (95% CI 0.08 to 0.47; p < 0.001) <u>Secondary Endpoints</u>: Nonvertebral fractures: ABL 2.7% PBO 4.7% HR 0.57 (95% CI, 0.32 to 1.00; p < 0.049) TPTD: 3.3% PBO 4.7% HR 0.72 (95% CI, 0.42 to 1.22; P = 0.22)	3.38/26	-5.12 to - 0.87; p= 0.006) All TEAE: ABL: 89.4% PBO: 87.6% TPTD: 88.9% Serious TEAE: ABL: 9.7% PBO: 11% TPTD: 10%		details were blinded to investigators. Baseline characteristics similar among treatment groups. <u>Performance Bias</u>: HIGH- Double blinded arms for abaloparatide and placebo (participant, provider, investigator, radiologists). Teriparatide arm was blinded until after randomization, then open label to participant, provider and investigator. Primary endpoint compared to placebo for both drugs. <u>Detection Bias</u>: LOW – All radiologists assessing radiographs were blinded to treatment. A second radiologist reviewed radiographs to confirm reading of incident fracture. <u>Attrition Bias</u>: HIGH - Attrition similar between groups. Data from 2118 subjects was analyzed using mITT analysis for all patients who had pre-treatment and end of treatment evaluable spine x-rays. Missing data was imputed using a logistic regression model that used 5 data sets combined with the final results. <u>Reporting Bias</u>: LOW – Detailed study protocol is available in supplemental publication. All endpoints reported as stated a priori. Funded by manufacturer. Study design and statistical analysis completed by manufacturer. **Applicability**: <u>Patient</u>: Mean age of patients in this study was 69 years with a mean T score of -2.1. Sixty-three percent of subjects had prior fracture (vertebral and nonvertebral combined). These demographics may not represent OHP population. <u>Intervention</u>: FDA approved doses were used in the study for both abaloparatide and teriparatide. Patients were taught to self-administer the drug. If they could not self-administer, a trained family member could

		-Evidence of metabolic bone disease -Use of bisphosphonates > 3 months within the past 5 years or denosumab within the past year -history of osteosarcoma -Treatment with anticonvulsants that affect Vitamin D metabolism or with chronic heparin with the 6 months prior to screening period -Daily treatment with corticosteroids within the previous 12 months						assist with administration. Adherence was assessed by patient diaries, cartridge accountability, and site-assessment of remaining drug content of returned cartridges. Comparator: Only powered to detect differences between abaloparatide and placebo in order to establish efficacy of the drug. Not powered to detect a difference between abaloparatide and teriparatide, which would have been a more meaningful comparison. Outcomes: Primary outcome was an appropriate assessment for treatment of osteoporosis. Fracture rate was smaller than anticipated given the incidence predicted in the population of postmenopausal women. Setting: 28 International sites including in 10 countries including US, Denmark, China, and Brazil. Most patients were from Europe (56%) and South America (27%). Only 39 patients (1.6%) were from the US.

Abbreviations [alphabetical order]: ABL = abaloparatide; ALN = alendronate; ARR = absolute risk reduction; BMD = bone mineral density; DB = double blind; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; IVRS = interactive voice response system; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PBO = placebo; PC = Placebo controlled; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SC = subcutaneously; TD = treatment difference; TEAE + treatment-emergent adverse event; TPTD = teriparatide

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Appendix 1: Current Preferred Drug List

Brand	Generic	PDL	Route	Formulation
ACTONEL	RISEDRONATE SODIUM	Y	ORAL	TABLET
ALENDRONATE SODIUM	ALENDRONATE SODIUM	Y	ORAL	TABLET
BONIVA	IBANDRONATE SODIUM	Y	ORAL	TABLET
FOSAMAX	ALENDRONATE SODIUM	Y	ORAL	TABLET
IBANDRONATE SODIUM	IBANDRONATE SODIUM	Y	ORAL	TABLET
RISEDRONATE SODIUM	RISEDRONATE SODIUM	Y	ORAL	TABLET
MIACALCIN	CALCITONIN,SALMON,SYNTHETIC	N	INJECTION	VIAL
BONIVA	IBANDRONATE SODIUM	N	INTRAVEN	SYRINGE
IBANDRONATE SODIUM	IBANDRONATE SODIUM	N	INTRAVEN	SYRINGE
CALCITONIN-SALMON	CALCITONIN,SALMON,SYNTHETIC	N	NASAL	SPRAY/PUMP
ALENDRONATE SODIUM	ALENDRONATE SODIUM	N	ORAL	SOLUTION
ETIDRONATE DISODIUM	ETIDRONATE DISODIUM	N	ORAL	TABLET
FOSAMAX PLUS D	ALENDRONATE SODIUM/VITAMIN D3	N	ORAL	TABLET
RALOXIFENE HCL	RALOXIFENE HCL	N	ORAL	TABLET
ATELVIA	RISEDRONATE SODIUM	N	ORAL	TABLET DR
RISEDRONATE SODIUM DR	RISEDRONATE SODIUM	N	ORAL	TABLET DR
BINOSTO	ALENDRONATE SODIUM	N	ORAL	TABLET EFF
FORTEO	TERIPARATIDE	N	SUB-Q	PEN INJCTR
PROLIA	DENOSUMAB	N	SUB-Q	SYRINGE
RECLAST	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PGGYBK BTL
ZOLEDRONIC ACID	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PGGYBK BTL
ZOMETA	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PGGYBK BTL
ZOLEDRONIC ACID	ZOLEDRONIC AC/MANNITOL/0.9NACL		INTRAVEN	PIGGYBACK
ZOLEDRONIC ACID	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PIGGYBACK
IBANDRONATE SODIUM	IBANDRONATE SODIUM		INTRAVEN	VIAL
PAMIDRONATE DISODIUM	PAMIDRONATE DISODIUM		INTRAVEN	VIAL
ZOLEDRONIC ACID	ZOLEDRONIC ACID		INTRAVEN	VIAL
ZOMETA	ZOLEDRONIC ACID		INTRAVEN	VIAL
XGEVA	DENOSUMAB		SUB-Q	VIAL

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 4 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 03, 2017

1.	Paget Disease, Extramammary/ or pagets disease.mp.	3262
2.	Osteoporosis, Postmenopausal/ or Osteoporosis/ or osteoporosis.mp.	57969
3.	Risedronate Sodium/	1056
4.	Alendronate/	3183
5.	ibandronate.mp.	922
6.	Etidronic Acid/	1672
7.	calcitonin/	6175
8.	Raloxifene Hydrochloride/	2390
9.	Teriparatide/	1144
10.	Denosumab/	982
11.	zoledronic acid.mp.	3872
12.	pamidronate.mp.	2395
13.	1 or 2	60780
14.	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	20054
15.	abaloparatide.mp.	33
16.	14 or 15	20082
17.	13 and 16	6638
18.	limit 17 to (english language and humans and yr="2016 -Current")	160

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYMLOS safely and effectively. See full prescribing information for TYMLOS.

TYMLOS™ (abaloparatide) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: RISK OF OSTEOSARCOMA
See full prescribing information for complete boxed warning.

- **Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma, a malignant bone tumor, in male and female rats. It is unknown whether TYMLOS will cause osteosarcoma in humans. (5.1, 13.1)**
- **Use of TYMLOS is not recommended in patients at increased risk for osteosarcoma. (5.1)**
- **Cumulative use of TYMLOS and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. (5.1)**

----------INDICATIONS AND USAGE----------
TYMLOS is a human parathyroid hormone related peptide [PTHrP(1-34)] analog indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose is 80 mcg subcutaneously once daily; patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. (2.1)
- Administer as a subcutaneous injection into periumbilical region of abdomen. (2.2)
- Administer initially where the patient can sit or lie down in case symptoms of orthostatic hypotension occur. (2.2, 5.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 3120 mcg/1.56 mL (2000 mcg/mL) in a single-patient-use prefilled pen. The prefilled pen delivers 30 daily doses of 80 mcg abaloparatide in 40 mcL of sterile, clear, colorless solution. (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Orthostatic Hypotension: Instruct patients to sit or lie down if symptoms develop after dose administration. (5.2)
- Hypercalcemia: Avoid use in patients with pre-existing hypercalcemia and those known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism. (5.3)
- Hypercalciuria and Urolithiasis: Monitor urine calcium if preexisting hypercalciuria or active urolithiasis are suspected. (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥2%) are hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain and vertigo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Radius Health, Inc. at 1-855-672-3487 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2017

Bone Resorption Inhibitors and Related Agents

Goal(s):

To ensure appropriate drug use and safety of bone resorption suppression agents by authorizing utilization in specified patient populations.

Length of Authorization:

- 12 to 24 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Note: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Is the request for raloxifene?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Is the patient pregnant and/or at increased risk for thromboembolism or stroke?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: inform prescriber of pregnancy category X and boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months
6. Is the request for teriparatide or abaloparatide and is the patient at high risk for fractures? Examples include: • Postmenopausal women with osteoporosis and T-score ≤ 2.5 or history of fracture • Men with primary or hypogonadal osteoporosis • Osteoporosis associated with sustained glucocorticoid therapy	**Yes:** Go to #7	**No:** Pass to RPh. Go to #8
7. Does the patient meet one of the following conditions: • Concomitant bisphosphonate; or • Pediatric or young adult with open epiphyses; or • History of osteosarcoma or skeletal malignancies; or • Metabolic bone disease; or • Underlying hypercalcemic disorders; or • Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 24 months (depending on when therapy was initiated. These two agents are only FDA approved for a total duration of therapy of 2 years.)
8. RPh only: All other indications need to be evaluated as to whether they are funded by the OHP or not.	If funded and clinic provides supporting literature, approve for up to 12 months	If non-funded, deny; not funded by the OHP

P&T Review: *3/18 (DM); 7/16; 9/10*
Implementation: *8/16, 1/1/11*