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Abbreviated Class Update
Bone Metabolism Agents for Osteoporosis or Paget's Disease

Month/Year of Review: August 2012 **Search End Date:** May 2012 (Week 5)

Current Status of PDL Class:

- Preferred Agents: ALENDRONATE, ALENDRONATE /VITAMIN D3, IBANDRONATE TABLET
- Non Preferred: CALCITONIN INH, CALCITONIN SQ/IM, ETIDRONATE, IBANDRONATE (IV), RISEDRONATE, RISDRONATE DR, TERIPARATIDE SQ, RALOXIFENE, DENOSUMAB (PENDING REVIEW), ZOLEDRONIC ACID IV (PENDING REVIEW), TILUDRONATE (PENDING REVIEW)

Research Questions:

- Does any of the new information change previous conclusions regarding effectiveness and safety of bone metabolism agents?
- Are denosumab (2010), zoledronic acid (2001) or tiludronate (1997) more effective or safer for the treatment of osteoporosis or Paget's Disease than currently available agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- The comparative efficacy and safety of treatments has not been assessed for men with osteoporosis.
- There is high strength evidence that specific bisphosphonates (zoledronic acid, risedronate, alendronate) and denosumab reduce the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. No other drugs reduce all three fracture risks.
- There is insufficient or no data to distinguish superiority of any bisphosphonate, or bisphosphonates superior to other drugs for reduction in vertebral fracture risk in postmenopausal women. Evidence for etidronate, ibandronate, pamidronate have not been shown to reduce non-vertebral fractures in post-menopausal women. There is insufficient evidence for tilundronate for osteoporosis treatment.
- There was high strength evidence that the incidence of osteonecrosis of the jaw in patients taking bisphosphonates was low (<1-28 cases in 100,000 person years). Low strength evidence associated bisphosphonate use with atypical femur fractures and insufficient evidence associated bisphosphonate use to esophageal cancer and atrial fibrillation.
- There is high strength evidence of increased risk of infection with denosumab compared to placebo.
- There is high strength evidence that raloxifene increases the odds of pulmonary embolism, thromboembolic events and cerebrovascular accidents compared to placebo.
- Nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate are ibandronate) are considered first-line therapy for Paget's Disease treatment. There is insufficient evidence to distinguish superiority of any nitrogen-containing bisphosphonate.

Recommendations:

- 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's Disease **(**zoledronic acid, pamidronate, risedronate, alendronate or ibandronate).
- Make calcitonin, raloxefene and teriparatide non-preferred due to limited evidence to reduce non-vertebral and hip fracture risk in post-menopausal women. Calcitonin has limited evidence for Paget's Disease.
- Make tiludronate non-preferred as it is only indicated for Paget's, is not a nitrogen containing bisphosphonate and it has insufficient evidence for osteoporosis treatment.
- Consider a RetroDUR intervention of bisphosponates to notify clinicians to re-evaluate patient FRAX score after 5 years of therapy.

Reason for Review:

In May 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the drugs used for osteoporosis. A Provider Synergies Review from January 2010 was the evidence source.[1] The previous review was limited to self-administered drugs with a Food and Drug Administration (FDA) indication for osteoporosis. This review expands to physician administered drugs with indications for osteoporosis or Paget's Disease. It excludes drugs only indicated for oncology related indications (e.g. gallium nitrate & pamidronate).

Previous HRC Conclusions (May 2010):

- Evidence does not support a difference in efficacy/effectiveness but calcitonin is not considered first line treatment.
- Evidence does not support a difference in harms/adverse events but teriparatide (Black box warning) is not considered first line treatment.
- Recommend inclusion of at least one member of the bisphosphonates as primary therapy with accommodation for different dosage regimens to improve compliance.
- Consider prior authorization requirements for calcitonin, raloxifene, and teriparatide.

Background:

Osteoporosis is a skeletal disease of decreasing bone mass resulting in diminished bone strength and increased risk of fractures.[2] Multiple mechanisms are responsible including old age, sex steroid deficiency, lipid oxidation, decreased physical activity and use of glucocorticoids. Throughout life, older bone is resorbed by osteoclasts and replaced with new bone made by osteoblasts.[2] This process is known as remodeling and is orchestrated and targeted to a particular site that is in need for repair by osteocytes.[2] When this system is out of balance, bone loss occurs.[3] 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 prime target for the treatment of osteoporosis.[4]

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.[4] 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 other osteoporotic fractures.[4] The life-time fracture risk of a patient with osteoporosis is as high as 40% and fractures of the hip, spine or wrist the most common locations.[4] The National Osteoporosis Foundation estimates more than 10 million people have osteoporosis with 50% of Caucasian women with a lifetime risk of fracture and 20% of men.[3] The primary goal of osteoporosis management is to reduce fracture risk.

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 the new IgG2 monoclonal antibody, denusomab, which suppresses the RANKL pathway. Parathyroid hormone increases bone formation and is the only anabolic drug. All drugs require adequate serum levels of calcium and vitamin D for optimum effect. Bisphosphonates are considered first line[5] therapy but short-term tolerability and potential long-term risk of atypical femur fracture, osteonecrosis of the jaw and esophageal cancer have left patients and clinicians looking for other options.[6]

Paget's 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.[7] It is a fairly common finding in aging bone, with estimates ranging from 2.3 - 9% in older patients within affected populations.[8] Many patients with Paget's Disease are asymptomatic but others exhibit pain and deformities.[7] Fractures, bone tumors, neurologic disease, cardiac disease, and abnormalities in calcium and phosphate balance can also occur.[7] The goals of treatment are to reduce pain, normalize bone remodeling and slow disease progression.[7] The newer nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate and ibandronate) are first-line for the initial treatment of Paget disease.

Methods:

A Medline literature search ending May 2012 Week 5 for meta-analyses or randomized active-controlled trials (RCT's) comparing bisphosphonates to each other or to other osteoporosis drugs for the treatment of osteoporosis or Paget's Disease was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches the following were reviewed: three systematic reviews of osteoporosis treatments;[9 10 11] one systematic review of Paget treatment;[7] two systematic reviews of denosumab; [12] two denosumab monographs; [13 14] one clinical treatment guideline;[15] and FDA safety warnings.[6]

Systematic Reviews:

<u>ARHQ</u>

The AHRQ[9] updated the comparative effectiveness review of treatments to prevent fractures in men and women with osteoporosis in January 2012 with a search end date of March 2011. It compared the effectiveness and safety of bisphosphonates, raloxefene, hormone replacement therapy, teriparatide, calcium, vitamin D, exercise and denosumab for the prevention or treatment of osteoporosis. The population was limited to adults with low bone density or osteoporosis (excluding those with Paget's disease, cancer, other diseases of bone metabolism, or those on drugs causing

osteoporosis). The outcomes of interest were vertebral, hip and/or total fractures unless the study specifically noted lack of power or reported fractures only as an adverse event. Study duration was a minimum of 6 months. Only RCTs were included and were assessed for quality.

The comparative efficacy of treatments has not been assessed among men with osteoporosis.

There was high strength evidence that bisphosphonates and denosumab reduce the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. There was high strength evidence that teriparatide and raloxifene reduce the risk of vertebral fractures in post-menopausal women. Raloxifene was shown to be not effective in reducing the risk of hip or nonvertebral fractures in post-menopausal women. There was moderate evidence that hormone replacement does not prevent fractures in post-menopausal women with established osteoporosis. There was low to moderate evidence that the effect of calcium alone and vitamin D alone on fracture risk is uncertain. Data were insufficient to distinguish superiority of any bisphosphonate. There was insufficient evidence comparing bisphosphonates to calcium, teriparatide or raloxifene.

There was high strength evidence that the incidence of osteonecrosis of the jaw in patients taking bisphosphonates was low (<1-28 cases in 100,000 person years). Low strength evidence associated bisphosphonate use with atypical femur fractures and insufficient evidence associated bisphosphonate use to esophageal cancer and atrial fibrillation. There is high strength evidence that alendronate users have increased risk of mild upper gastrointestinal events compared to denosumab. There is high strength evidence of increased risk of infection with denosumab. There is high strength evidence that raloxifene increases the odds of pulmonary embolism, thromboembolic events and cerebrovascular accidents compared to placebo.

CADTH

CADTH[10] evaluated the clinical effectiveness and harms of denosumab, raloxifene, and zoledronic acid in postmenopausal women with osteoporosis. No active-controlled RCTs were identified. Denosumab, zoledronic acid, and raloxifene were all effective in reducing the risk of vertebral fractures, both clinically and radiographically assessed, after 36 months of treatment compared with placebo. Denosumab and zoledronic acid reduced the risk of multiple vertebral fractures, hip fractures, and non-vertebral fractures. There was limited evidence for raloxifene on these outcomes, suggesting it may not be effective in preventing non-vertebral fractures, including hip fractures. The proportion of patients who died during the trials, as well as the overall incidence of serious adverse events, was not significantly different between each active drug and placebo. However, denosumab was associated with a higher incidence of cellulitis, zoledronic acid with atrial fibrillation, and raloxifene with venous thromboembolism and hot flushes compared with placebo.

Clinical Evidence

Clinical Evidence updated the review *Fracture prevention in postmenopausal women* in September 2010.[11] Key findings were:

- *Alendronate, risedronate, zoledronate, denosumab, and parathyroid hormone reduce vertebral and non-vertebral fractures compared with placebo.*
  - *Etidronate, ibandronate, pamidronate, and raloxifene reduce vertebral fractures, but have not been shown to reduce non-vertebral fractures.*
  - *Raloxifene protects against breast cancer, but increases venous thromboembolic events and stroke compared with placebo.*

- *Calcitonin may reduce vertebral fractures over 1 to 5 years, but has not been shown to reduce non-vertebral fractures.*

- *CAUTION: Hormone replacement therapy may reduce fractures, but it increases the risk of breast cancer and cardiovascular events. The risks of adverse effects of treatment are thought to outweigh the beneficial effects of hormone replacement therapy in prevention of fractures.*
- *Combined calcium plus vitamin D or vitamin D analogues alone may reduce vertebral and non-vertebral fractures, but trials have given inconclusive results.*
- *Monotherapy with calcium or vitamin D has not been shown to reduce fractures, and calcium alone may potentially be associated with an increased risk of cardiovascular adverse effects.*

UpToDate

The nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate are ibandronate) are the primary agents used for the initial treatment of Paget disease. UpToDate[7] summarized the major trials comparing the nitrogen-containing bisphosphonates. Normalization or reduction in serum alkaline phosphatase levels have been the primary end points in clinical trials of antipagetic therapies, as surrogate markers for reduction in increased bone turnover. In two identical, six-month trials involving a total of 357 patients, zoledronic acid patients achieved the primary endpoint more often than risedronate patients (96% versus 74%).[16 17] In a two-year randomized, open label trial of 72 patients, alendronate achieved biochemical remission, defined as both the serum alkaline phosphatase and urine deoxypyridinoline/creatinine ratio being in the normal range, more often than pamidronate (86% versus 56%) after one year.[18] However, the results were affected by whether or not the patients had previously been treated with pamidronate. In the 44 previously untreated patients, the biochemical remission rate of was similar (91% versus 86%). A third trial included 120 patients and at six months, zoledronic acid was associated with higher rates of both the biochemical response (97% versus 45%) and normalization of serum alkaline phosphatase (93% versus 35%) compared to pamidronate.[19] The comparisons were limited by small numbers of patients, short duration or lack of blinding and the use of surrogate endpoints. Calcitonin is the only other FDA approved drug for the treatment of patients with Paget disease who cannot tolerate bisphosphonates. Subcutaneous calcitonin was evaluated in 85 patients and found that serum alkaline phosphatase or urine hydroxyproline excretions were initially reduced by about 50%.[20] However, these parameters returned to pretreatment levels in 26% of patients and almost all of these patients developed high titer anti-calcitonin antibodies.

Lin, et al

Lin, et al reviewed four RCTs[21 22 23 24] comparing denosumab 60mg subcutaneously every six months to alendronate 70mg orally every week. The studies were systematically identified, assessed for quality and data extracted. The review provided low quality evidence there was no significant difference in fracture risk between the denosumab and alendronate at 1 year [3 studies, fixed-effects OR (95% CI): 1.42 (0.84–2.40), p = 0.19, I2 = 0%]. There was low to very low evidence of no differences in total adverse events, serious adverse events, neoplasms or infections.

CADTH

The Common Drug Review[13] systematically reviewed six denosumab RCTs of post-menopausal women with osteoporosis as determined by low BMD. Only the FREEDOM trial included incidence of new vertebral fracture as a primary outcome. The other five relied on the percentage change in BMD, adherence or percentage change in cortical thickness at distal radius. FREEDOM[25] (N=7,808) was a 36-month double-blind double-dummy parallel-group RCT comparing denosumab 60 mg subcutaneousloy every six months with placebo. In the FREEDOM trial, patients having both a

baseline and at least one follow-up spinal radiograph, the 36-month incidence of radiographically confirmed new vertebral fracture was lower for denosumab (2.3%) compared with placebo (7.2%), absolute risk reduction (ARR): 4.8%, 95% confidence interval (CI), 3.9% to 5.8%. None of the active comparator trials were powered to examine fracture. DECIDE[21] and STAND[22] reported fracture incidence as patient reported adverse events and the frequency of fracture was similar between denosumab and alendronate. Mortality, serious adverse events and withdrawal due to adverse events were similar between denosumab and placebo in the FREEDOM trial, and between denosumab and alendronate in the STAND and DECIDE trials. The Canadian Expert Drug Advisory Committee recommended denosumab coverage for women with postmenopausal osteoporosis for whom bisphosphonates are contraindicated due to hypersensitivity or abnormalities of the esophagus (e.g., esophageal stricture or achalasia), and have at least two of the following: age >75 years, a prior fragility fracture or a BMD T-score ≤ -2.5.

VA

The VA Pharmacy Benefits Management Services reviewed denosumab for formulary placement in January 2012.[14] Denosumab's FDA labeled indications are: treatment of postmenopausal women with osteoporosis, treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[26 27] The FREEDOM fracture findings were reported. In addition, denosumab was reported to be noninferior to alendronate, across all surrogate measures and superiority with respect to lumbar spine BMD and distal one third radius. Few men have received denosumab. Data is limited to treatment for bone loss resulting from androgen deprivation therapy and glucocorticoids. Denosumab's adverse effect profile includes increased risk serious events: hypocalcemia, infection, osteonecrosis of the jaw, and dermatologic reactions such as cellulitis, rash, and eczema. Unanswered safety concerns include a risk for cancers and pancreatitis. Common adverse events were back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The VA determined denosumab's place in therapy is as an alternative to zoledronic acid and subcutaneous teriparatide for patients who cannot tolerate an oral bisphosphonate, who have not had a satisfactory response to an oral bisphosphonate, or who have a contraindication to a bisphosphonate (e.g., a creatinine clearance less than 30 or 35 mL/min). Denosumab's advantages include twice yearly administration, a rapid onset of action (similar to zoledronic acid), an increase in BMD at the distal ⅓ radius, and use in patients with renal impairment. The VA lists disadvantages as the risk of serious adverse events, and whether the potential for development of neoplasms and pancreatitis is real, a higher cost.

New Guidelines:

NICE published clinical treatment guidance for denosumab for the prevention of osteoporotic fractures in postmenopausal women in October 2010.[15] The recommendations are:

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures:

- *who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments and*
- *who have a combination of T-score1, age and number of independent clinical risk factors for fracture (see section 1.3) as indicated in the following table.*

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69	– [a]	−4.5	−4.0
70–74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0

[a] Treatment with denosumab is not recommended.

Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

Recent FDA warnings:

Bisphosphonates:

The FDA has monitored the bisphosphonates for several safety issues.[6]

In September 2011 the zoledronic acid label was revised to include a contraindication in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. Kidney failure is a rare, but serious, condition associated with the use of zoledronic acid in patients with a history of or risk factors for renal impairment. Cases of acute renal failure requiring dialysis or having a fatal outcome following zoledronic acid use have been reported to FDA.

In July 2011 the FDA advised that the benefits of oral bisphosphonate drugs in reducing the risk of serious fractures in people with osteoporosis continue to outweigh the potential risks of developing esophageal cancer. There have been conflicting findings from studies evaluating this risk and it is important to note that the risk of this cancer is extremely rare, especially in women.

In October 2010 the FDA clarified recommendations regarding the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. These fractures are very uncommon (<1% of all hip and femur fractures overall). It is not clear if bisphosphonates are the cause but have been predominantly reported in patients taking bisphosphonates. These atypical fractures may be related to long-term term bisphosphonate use. Specific recommendations are:

- Be aware of the possible risk of atypical subtrochanteric and diaphyseal femur fractures in patients taking bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing bisphosphonates.
- Discuss the known benefits and potential risks of using bisphosphonates with patients.
- Evaluate any patient who presents with new thigh or groin pain to rule out a femoral fracture.

- Discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.
- Consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over 5 years.
- Report any adverse events with the use of bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Denosumab:

Denosumab carries a mandated Risk Management and Mitigation Strategy to inform healthcare providers about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw, associated with denosumab.

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