Drug Use Research & Management Program
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Month/Year of Review: May 2014
Date of Last Review: September 2012
PDL Class: Bone Metabolism Agents for Osteoporosis or Paget's Disease
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

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

Current PA Criteria: Appendix 1: Non-preferred drugs require PA to ensure appropriate drug use and safety of bone resorption suppression agents by authorizing utilization in specified patient populations.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of bone metabolism agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Previous 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.

Conclusions:

- There is no new comparative evidence that changes the previous conclusions.
- No further review of research needed at this time and review comparative costs.

Previous 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.

Reason for Review:

Routine scan of the literature for new developments.

Background:

Osteoporosis is a skeletal disease of decreasing bone mass resulting in diminished bone strength and increased risk of fractures.[1] 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.[1] This process is known as remodeling and is orchestrated and targeted to a particular site that is in need for repair by osteocytes.[1] When this system is out of balance, bone loss occurs.[2] 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.[3]

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.[3] 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.[3] 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.[3] 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.[2] 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[4] 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.[5]

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.[6] It is a fairly common finding in aging bone, with estimates ranging from 2.3 - 9% in older patients within affected populations.[7] Many patients with Paget's Disease are asymptomatic but others exhibit pain and deformities.[6] Fractures, bone tumors, neurologic disease, cardiac disease, and abnormalities in calcium and phosphate balance can also occur.[6] The goals of treatment are to reduce pain, normalize bone remodeling and slow disease progression.[6] 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 March 2014 Week 4 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.

Systematic Reviews:
Murad et al.[8] published a network meta-analysis of drug treatments to prevent fragility fractures. The systematic review included RCTs through December 2011 that enrolled patients at risk for fragility fractures treated with bisphosonates, teriparatide, selective estrogen receptor modulators, denosumab or calcium and vitamin D. Studies were evaluated for quality by two independently working reviewers and determined to be of low to moderate risk of bias but imprecise due to the small number of fracture events overall. Teriparatide, bispohosphonates and denosumab were the most effective in reducing the risk of fragility fractures. Raloxifene was less effective. But, differences in efficacy across the drugs was small (e.g. Hip Fracture OR 0.42 95% CI 0.1-1.82 for teriparatide versus 0.45 95% CI 0.27-0.68 for alendronate). Calcium and vitamin D were only effective in combination to reduce hip fracture risk (OR 0.81 95% CI 0.68-0.96).

CADTH published a rapid review of denosumab and zoledronic acid for postmenopausal osteoporosis who have failed or discontinued previous bisphosphonate therapy.[9] The literature search included all study designs published between January 2007 and May 2012. Studies were appraised using established quality appraisal methods. The drugs were found safe and effective for patients who were intolerant or failed bisphosphonates based upon BMD outcomes but they could not rule out residual bisphosphonate activity in all studies.

A non-systematic review of osteoporosis treatment in men identified RCTs evaluating bisphosphonates, denosumab and teriparatide effect on vertebral and non-vertebral fractures.[10] Alendronate, risedronate, zoledronic acid and teriparatide each have evidence of vertebral fracture reduction when used as primary prevention in men with osteoporosis. Denosumab evidence of vertebral fracture reduction is limited to those with secondary osteoporosis from androgen deprivation therapy.

A meta-analysis used adjusted indirect comparisons and mixed treatment comparison methods to compare treatments in the absence of head-to-head trials. It identified RCTs published through November 4, 2009 that evaluated osteoporosis drugs with fracture outcomes. The trials were reviewed for quality using Jadad scoring. Thirty-four studies met inclusion criteria. The authors compared denosumab to individual bisphosphonates, raloxifene and teriparatide. It was not statistically different than any comparator for clinical vertebral or non-vertebral fractures. It was statistically better than raloxifene, alendronate, risedronate and bisphosphates as a group if the outcome was restricted to new vertebral fractures. The clinical significance of this statistically determined difference is limited by the assumptions of the model and the selection of studies for inclusion and should be interpreted cautiously.

New Guidelines:

The American College of Obstetricians and Gynecologists published a Practice Bulletin on osteoporosis management in September 2012.[11] This is a comprehensive treatment guideline for women. Bisphosphonates are recommended first line but raloxifene is an alternative for younger postmenopausal women also wanting breast cancer protection. It is recommended that bisphosphonate selection be based only patient preference for route of delivery and insurance coverage. Denosumab is recommended for high risk patients unable to tolerated bisphosphonates. Teriparatide is reserved for severe osteoporotic patients who have experienced fractures. Calcitonin is not recommended except for lower risk patients unable to tolerate bisphosphonates. Combination therapy is not recommended. Bisphosphonate treatment interruption should be considered after 5-10 years of use.

Osteoporosis International published the European Guidelines in October 2012.[12] Much of the guideline focuses on fracture risk assessment. The guidelines identify alendronate, risedronate, zoledronic acid and denosumab with evidence of reducing vertebral and non-vertebral fracture. Alendronate is recommended first-line based upon cost.

The Endocrine Society published clinical guidelines for Osteoporosis in Men in June 2012.[13] The guidelines recommend selection of and FDA approved agent for men (alendronate, risedronate, zoledronic acid or teriparatide) be individualized based upon severity of osteoporosis, comorbid conditions and cost. Men with recent hip fracture are recommended zoledronic acid. Denosumb is recommended only for men receiving androgen deprivation therapy.

Recent FDA warnings:

In April 2013[14] all bisphosphonate drugs underwent labeling changes to include the risk of osteonecrosis of the jaw may increase with duration of exposure and that there has be post-marketing reports of asthma exacerbations. There have been fatal cases of anaphylaxis reported with the use of ibandronate injection.

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Appendix 1 – Current PA Criteria:

Bone Resorption Suppression and Related Agents

Goal(s):

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

Initiative:

- Prior Authorization

Length of Authorization: Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPH; Deny, (Not covered by the OHP)

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform provider of covered alternatives in class.	No: Go to #4.
4. Is the request for raloxifene (Evista)?	Yes: Go to #5.	No: go to #6.
5. Is the patient pregnant and/or at increased risk of thromboembolism or stroke?	Yes: Deny (Medical Appropriateness). Inform provider of pregnancy category X and black box warning of thromboembolism and stroke risk.	No: Approve for shorter of 1 ear or length of prescription.
6. Is the request for teriparatide (Forteo) and is the patient at high risk for fractures? Examples include: • Postmenopausal women with osteoporosis • Men with primary or hypogonadal osteoporosis • Osteoporosis associated with sustained glucocorticoid therapy	Yes: Go to #7	No: Go to #8
7. Is the patient also taking a bisphosphonate, a pediatric or young adult patient with open epiphyses, at increased risk of osteosarcoma or a history of skeletal malignancies, metabolic bone disease, underlying hypercalcemic disorders, or unexplained elevations of alkaline phosphatase?	Yes: Deny, (Medical Appropriateness)	No: Approve for shorter of 1 year or length of prescription
8. RPH Only All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.	If above the line and clinic provides supporting literature: approve for length of treatment	If below the line: Deny (Not covered by the OHP).

P&T / DUR Action: 9/16/10 (KS)
Revision(s):
Initiated: 1/1/11