Clinical Policy Title: Infusible pharmaceuticals for bone pain management

Clinical Policy Number: 00.02.06

Effective Date: June 1, 2014
Initial Review Date: February 19, 2014
Most Recent Review Date: February 15, 2017
Next Review Date: February 2018

Policy contains:
- Cancers metastatic to bone.
- Non-cancer bone diseases.
- Bisphosphonates.
- Radiation and radioisotopes.

Related policies:

CP# 18.04.02  Hierarchy of chronic pain management

ABOUT THIS POLICY: AmeriHealth Caritas District of Columbia has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas District of Columbia’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas District of Columbia when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas District of Columbia’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas District of Columbia’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas District of Columbia will update its clinical policies as necessary. AmeriHealth Caritas District of Columbia’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas District of Columbia considers the use of the specific treatments or infusible pharmaceuticals listed below to be clinically proven and, therefore, medically necessary when the following criteria are met:

<table>
<thead>
<tr>
<th>Pharmaceutical or Treatment</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Bone metastases from prostate cancer.</td>
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<tr>
<td></td>
<td>Bone metastases from lung cancer.</td>
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<tr>
<td></td>
<td>Multiple myeloma.</td>
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<tr>
<td></td>
<td>Osteogenesis imperfecta.</td>
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<tr>
<td>Zolendronate</td>
<td>Bone metastases from breast cancer.</td>
</tr>
<tr>
<td></td>
<td>Painful bone metastases.</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Painful bone metastases.</td>
</tr>
<tr>
<td>Samarium-153 lexidronam</td>
<td>Osteoblastic metastatic bone cancer.</td>
</tr>
</tbody>
</table>

Limitations:

Coverage of specific pharmaceuticals and/or treatments is subject prior authorization by plan criteria. Prior authorization criteria for the pharmaceuticals listed in this coverage policy is set forth in Appendix A.

There is currently insufficient medical evidence to determine the medical necessity of calcitonin for metastatic bone pain.
Alternative covered services:

Physician office visits, standard chemotherapy, analgesics.

Background:

A debilitating form of pain emanating from the skeletal system, bone pain is classified as deep somatic pain. It is often difficult to localize, associated with a variety of pathologies, and can severely impair quality of life. Underlying diagnoses include cancers metastatic to bone and non-cancer conditions, such as osteoarthritis, Paget’s disease, sickle cell disease, and osteogenesis imperfecta.

Bone is a common site of metastases from carcinomas of the prostate, breast, lung, kidney, bladder, and thyroid, and for lymphomas and sarcomas. Prostate, lung, and breast primaries account for 80 percent of metastases to bone, which are more common than primary bone tumors. The bone sites most often involved with metastases are vertebrae, proximal femur, pelvis, ribs, sternum, proximal humerus, and skull. Lesions may be asymptomatic, or may produce pain, swelling, nerve root or spinal cord compression, pathologic fracture, or replacement of marrow. When bone destruction is prominent, symptoms of hypercalcemia may be present.

Treatment (with curative or palliative intent) for bone metastases depends on the underlying malignancy and symptoms, and may include local radiation therapy, hormone inhibition (anti-androgens for prostate cancer or anti-estrogens for breast), bone-seeking isotopes with both tumor and symptom effects, bisphosphonates (osteoporosis drugs), or prophylactic internal fixation (when the integrity of a weight-bearing bone is threatened).

There is currently insufficient medical evidence to determine the medical necessity of calcitonin for metastatic bone pain.

Searches:

AmeriHealth Caritas District of Columbia searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

Searches were conducted on December 15, 2016. Search terms were: “bone pain” and “metastatic bone pain.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
• **Economic analyses such as cost-effectiveness**, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Single and multiple fraction radiation delivery schedules are equally effective.

No specific radioisotope is superior to other radioisotopes; and most bisphosphonates are equivalent.

Many interventions for metastatic bone pain require further research: optimal agent in a specific class, dose, timing, and impact on other outcomes, e.g., survival.

Research on pain management in non-cancer indications (osteogenesis imperfecta; sickle cell disease) is too limited for recommendations on specific strategies.

**Policy updates:**

A new guideline from the Sociedad Española de Oncología Médica (SEOM) reviews bone metastases pathogenesis, clinical presentations, lab tests, imaging techniques for diagnosis and response assessment, bone-targeted agents, and local therapies, as radiation and surgery, and establishes recommendations for the management of patients with metastases to bone.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grávalos (2016)</td>
<td>Key points:</td>
</tr>
</tbody>
</table>
| SEOM clinical guideline for bone metastases from solid tumors | • Bone-targeted therapies include zoledronic acid, a potent biphosphonate, and denosumab.  
• Radium 233, an alpha-particle emitter, increases overall survival in patients with bone metastases from resistant castration prostate cancer.  
• Multidisciplinary approach is essential and bone surgery and radiotherapy should be integrated in the treatment of bone metastases when necessary. |
| Hayes (2013)              | Key points:                                                                                      |
| Magnetic resonance-guided focused ultrasound therapy            | • Magnetic resonance-guided focused ultrasound for painful bone metastases.  
• Small uncontrolled case series, three of which reported patients who had previously failed conventional radiation.  
• On restudy did not report previous treatment failure. |
| Heidenreich (2013)        | Key points:                                                                                      |
| Guidelines on prostate cancer                                     | • Guidelines on prostate cancer management of bone metastases.  
• Therapy of symptomatic bone metastases toward quality of life.  
• Bone-protective agents may be offered.  
• Randomized controlled trials (RCTs) and systematic reviews through 2012.  
• Direct therapy of symptomatic bone metastases toward quality of life.  
• Bone-protective agents may be offered. |
<p>| Zhu (2013)                | Key points:                                                                                      |
|                           |                                                                                                    |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Key points</th>
</tr>
</thead>
</table>
| Zolendronate for metastatic bone disease and pain | - Zolendronate for metastatic bone disease and pain.  
- RCTs through October 2011.  
- 12 trials (4,450 subjects).  
- Significant reduction in pain and skeletal events up to 24 months.  
- Well tolerated. |
| Chow (2012) Update on the systematic review of palliative radiotherapy trials for bone metastases | - Palliative radiotherapy trials for bone metastases.  
- RCTs in any language through 2010: single versus multiple fraction radiation.  
- 25 studies.  
- Overall and complete responses similar, but higher re-treatment rates for single fraction. |
- RCTs through 2011.  
- Seven trials (9,518 subjects).  
- Zolendronate has clear effect on fractures and may contribute to overall survival. |
- RCTs without language restriction through 2011.  
- 12 trials (1,750 subjects).  
- Reduced skeletal events and in conjunction with other treatments reduced pain.  
- Some suggestion that survival was prolonged. |
- RCTs through October 2011.  
- 20 trials (6,692 subjects).  
- Bisphosphonates reduce pathological vertebral fracture, pain and other skeletal-related events without significant adverse events.  
- No evidence for superiority of any specific agent, although zolendronate is superior to etidronate and placebo alone (but not to pamidronate or clodronate for improving survival or fractures). |
- RCTs through April 2011.  
- 34 trials (2,806 subjects).  
- In women with clinically evident bone metastases, oral, and IV bisphosphonates reduced risk of skeletal-related events and delayed time to their development; some agents also reduced pain.  
- Optimal timing and duration of treatment remains uncertain, and there is insufficient evidence to support routine use.  
- Large in-progress trials should clarify outstanding issues. |
<table>
<thead>
<tr>
<th>article</th>
<th>Key points:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid in the management of skeletal metastases for prostate cancer</td>
<td>• Benefits from literature combine with costs from France, Germany, Portugal, and Netherlands.</td>
</tr>
<tr>
<td></td>
<td>• Results suggest zoledronic acid is highly cost effective compared to placebo in these European nations.</td>
</tr>
<tr>
<td>Roqué i Figuls (2011)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Radioisotopes for metastatic bone pain</td>
<td>• Radioisotopes for metastatic bone pain.</td>
</tr>
<tr>
<td></td>
<td>• RCTs through October 2010: strontium-89; Samarium-153; rhenium-186; phosphorus-32 versus placebo or another isotope.</td>
</tr>
<tr>
<td></td>
<td>• 15 studies (1,146 subjects).</td>
</tr>
<tr>
<td></td>
<td>• No significant differences among treatments.</td>
</tr>
<tr>
<td></td>
<td>• Radioisotopes may provide complete pain relief over one to six months with no increase in analgesic use but severe adverse effects (leucopenia and thrombocytopenia) are common.</td>
</tr>
<tr>
<td>Phillipi (2008)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Bisphosphonate therapy for osteogenesis imperfecta</td>
<td>• Bisphosphonates for osteogenesis imperfect.</td>
</tr>
<tr>
<td></td>
<td>• RCTs and quasi through August 2008.</td>
</tr>
<tr>
<td></td>
<td>• Eight trials (403 subjects).</td>
</tr>
<tr>
<td></td>
<td>• Data for oral versus placebo could not be aggregated.</td>
</tr>
<tr>
<td></td>
<td>• One trial favored bisphosphonates for reduced fractures; no differences in remaining three trials.</td>
</tr>
<tr>
<td></td>
<td>• Evidence suggests that oral or IV agents increase bone mineral density, although unclear if fracture risk is reduced.</td>
</tr>
<tr>
<td></td>
<td>• Additional research (optimal method of delivery, duration, long-term safety) is needed.</td>
</tr>
<tr>
<td>Botteman (2006)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Cost-effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases</td>
<td>• Cost-effectiveness of bisphosphonates for breast cancer with bone metastases:</td>
</tr>
<tr>
<td></td>
<td>• Effective from studies published 1987 through 2005.</td>
</tr>
<tr>
<td></td>
<td>• Resource use from published studies 2001 through 2004.</td>
</tr>
<tr>
<td></td>
<td>• Decision analytic model compared six strategies over 10 years.</td>
</tr>
<tr>
<td></td>
<td>• Zolendronate is cost effective compared to no treatment and all other bisphosphonates; its use should improve outcomes and reduce costs</td>
</tr>
<tr>
<td>Dunlop (2006)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Pain management for sickle cell disease in children and adults</td>
<td>• Pain management for sickle cell disease.</td>
</tr>
<tr>
<td></td>
<td>• RCTs through June 2002.</td>
</tr>
<tr>
<td></td>
<td>• Nine studies.</td>
</tr>
<tr>
<td></td>
<td>• Small number of trials, subjects, and heterogeneity precluded meta-analysis.</td>
</tr>
<tr>
<td></td>
<td>• Too few trials for meaningful comparisons among treatments: more research needed.</td>
</tr>
<tr>
<td>Hayes (2006)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Bone pain due to osteoblastic metastatic bone cancer</td>
<td>• Samarium Sm-153 lexidronam for bone pain from osteoblastic metastatic bone cancer.</td>
</tr>
<tr>
<td>Martinez-Zapata (2006)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Calcitonin for metastatic bone pain</td>
<td>• Calcitonin for metastatic bone pain.</td>
</tr>
<tr>
<td></td>
<td>• RCTs through October 2011.</td>
</tr>
</tbody>
</table>
- Two studies (90 subjects): too few for meta-analysis.
- Limited evidence does not support use of calcitonin.

**References**

**Professional society guidelines/other:**

Hayes, Inc. Magnetic resonance guided focused ultrasound therapy (MRgFUS) (Exablate; Insightec Ltd.) for palliation of painful bone metastases. Health Technology Brief. September 27, 2013.

Hayes, Inc. Quadramet® (Samarium Sm-153 lexidronam (Cytogen Corp) for bone pain due to osteoblastic metastatic bone cancer. Health Technology Brief. Published 2006; reviewed 2008.


National Institute for Health and Clinical Excellence (NICE). Adalimumab for the treatment of adults with psoriasis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008a (technology...
appraisal guidance no. 146).


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**


L35457 Nerve Blockade for Treatment of Chronic Pain and Neuropathy. CMS Medicare Coverage Database website. [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35457&ver=24&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=pain&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAACAAAAAA&details.aspx?LCDId=35457&ver=24&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=pain&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAACAAAAAA](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35457&ver=24&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=pain&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAACAAAAAA). Accessed December 15, 2016.


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>C90.00</td>
<td>Multiple Myeloma</td>
<td></td>
</tr>
<tr>
<td>C79.51</td>
<td>Bone metastasis from prostate</td>
<td></td>
</tr>
<tr>
<td>C79.51</td>
<td>Bone metastasis from lung</td>
<td></td>
</tr>
<tr>
<td>C79.51</td>
<td>Bone metastasis from breast</td>
<td></td>
</tr>
<tr>
<td>C79.51</td>
<td>Osteoblastic metastatic bone cancer</td>
<td></td>
</tr>
<tr>
<td>G89.3</td>
<td>Neoplasm related pain (acute) (chronic)</td>
<td></td>
</tr>
<tr>
<td>Q78.8</td>
<td>Osteogenesis imperfecta</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9600</td>
<td>Strontium-89, therapeutic, per millicurie</td>
<td></td>
</tr>
<tr>
<td>A9604</td>
<td>Samarium-153, therapeutic, per dose</td>
<td></td>
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</tbody>
</table>

**Appendix A**
PerformRx Formulary Criteria

PERFORMRX PRIOR AUTHORIZATION PROTOCOL FOR INJECTABLE BISPHOSPHONATES

Preferred Agent (requires prior authorization)
Pamidronate disodium (Aredia®): 3mg/ml, 6 mg/ml, 9 mg/ml liquid in 10 ml vials, 30 mg, 90 mg vials

Non-preferred Agents (requires prior authorization) Zoledronic Acid (Zometa®): 4 mg/5 ml vial
Ibandronate sodium (Boniva® Injection): 3 mg/ml single-use
Denosumab (Xgeva®): 120mg/1.7ml

Initial Approval:
The request for the medication is for an Food and Drug Administration (FDA) approved indication, or is used for a medical condition that is supported by the medical compendium (Micromedex, American Hospital Formulary Service (AHFS), DrugPoints, Drug Package Insert) as defined in the Social Security Act 1927 or per the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), National Osteoporosis Foundation (NOF), or the National Institutes of Health (NIH) Consensus Panel standard of care guidelines.

If the medication request is for Zoledronic Acid (Zometa®), Denosumab (Xgeva®) or Ibandronate (Boniva® Injection) or any other brand only available injectable bisphosphonate for treating a medical condition other than postmenopausal osteoporosis or bone metastasis in prostate cancer, the patient has a documented (consistent with pharmacy claims data) treatment failure (See Definition of End Points for additional information) after receiving an adequate trial (including dates, 3 months or more of therapy) of generic Pamidronate (Aredia®) or has a documented medical reason (intolerance, hypersensitivity, contraindication, etc.) for not utilizing generic Pamidronate (Aredia®) to manage their medical condition.

FOR ANY REQUEST FOR BONIVA INJECTION FOR THE TREATMENT OF OSTEOPOROSIS PLEASE REFER TO THE SEPARATE BONIVA INJECTION PROTOCOL.

Prescribed dosing of medication is within FDA approved indications or is supported by the medical compendium as defined by the Social Security Act or per the NCCN, ASCO, NOF or NIH standard of care guidelines.

If all of the above conditions are met, the request will be approved for up to 3 months or as recommended per FDA approved indications or as defined by the medical compendium as defined above or per the NCCN, ASCO, NOF or NIH standard of care guidelines; if all of the above criteria are not met, the request is referred to a Medical Director for medical necessity review.

Reauthorization of Medication:
The prescribing physician has provided documentation as to the clinical benefits of the medication supporting continued treatment, OR the medication is being continued in accordance with the recommended time as defined by FDA drug package insert, or per recommendations of the medical compendium as described above, or per the NCCN, ASCO, NOF or NIH standard of care guidelines.

Prescribed dosing of medication is within FDA approved indications or supported by the medical compendium as defined by the Social Security Act or per the NCCN, ASCO, NOF or NIH standard of care guidelines.

If all of the above conditions are met, the request will be approved for up to 3 months or as recommended per FDA approved indications or as defined by the medical compendium as defined above or per the NCCN, ASCO, NOF or NIH standard of care guidelines; if all of the above criteria are not met, the request is referred to a Medical Director for medical necessity review.

FDA APPROVED INDICATIONS AND DOSING: Pamidronate disodium (Aredia®):

Hypercalcemia of Malignancy – in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases.

For patients with moderate hypercalcemia (corrected serum calcium of approximately 12-13.5 mg/dL) the recommended dose is 60 to 90 mg given as a single dose, intravenous infusion over 2–24 hours.
For patients with severe hypercalcemia (corrected serum calcium >13.5 mg/dL) the recommended dose is 90 mg given as a single dose intravenous infusion over 2 – 24 hours. Longer infusions (i.e. >2 hours) may reduce the risk for renal toxicity, particularly in patients with preexisting renal insufficiency.

A limited number of patients have received more than one treatment for hypercalcemia. Retreatment with Aredia, in patients who show complete or partial response initially, may be carried out if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. The dose and manner of retreatment is identical to that of the initial treatment.

Paget’s disease – is indicated for the treatment of patients with moderate to severe Paget’s disease of bone. The effectiveness of Aredia was demonstrated primarily in patients with serum alkaline phosphatase > 3 times the upper limit of normal.

The recommended dose is 30 mg daily, administered as a 4 hour infusion on 3 consecutive days for a total dose of 90mg. A limited number of patients have received more than one treatment in clinical trials. When clinically indicated, patients should be retreated at the dose of initial therapy.

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma – in conjunction with standard antineoplastic therapy are indicated for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma.

The recommended dose for patients with osteolytic bone lesions of multiple myeloma is 90mg administered as a 4 hour infusion given on a monthly basis. Limited information is available on the use of Aredia in patients with a serum creatinine 3.0g/dl.

The recommended dose for patients with osteolytic bone metastases of bone cancer is 90 mg administered over a 2 hour infusion given every 3-4 weeks.

Zoledronic Acid (Zometa ®):

Hypercalcemia of Malignancy – is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of >12 mg/dl \{3.0 mmol/L\} using the formula: cCa in mg/dl = Ca in mg/dl +0.8 (mid-range of measure albumin in mg/dl). The maximum recommended dose is 4 mg. The 4 mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes. Patients who receive Zometa should have their serum creatinine assessed prior to each treatment. Dose adjustments are not necessary in treating patients with hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy. Multiple Myeloma and Bone Metastases of Solid Tumor is indicated for the treatment of patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

The recommended dose for patients with a CrCl > 60 mL/min is 4 mg infused over no less than 15 minutes every 3-4 weeks. The optimal duration of therapy is not known. Patients should also be administered an oral calcium supplement of 500mg and a multiple vitamin containing 400 IU of vitamin D daily. Upon initiation of treatment the recommended dose for patients with reduced renal function should be:

<table>
<thead>
<tr>
<th>Baseline Creatinine Clearance (mL/min)</th>
<th>Recommended Dose of Zometa</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>4 mg</td>
</tr>
<tr>
<td>50 – 60</td>
<td>3.5 mg</td>
</tr>
<tr>
<td>40 – 49</td>
<td>3.3 mg</td>
</tr>
<tr>
<td>30 – 39</td>
<td>3 mg</td>
</tr>
</tbody>
</table>

Ibandronate sodium (Boniva® Injection):

Osteoporosis – is indicated for the treatment of osteoporosis in postmenopausal women.

The recommended dose is 3 mg every 3 months administered intravenously over a 15 to 30 second period.

Denosumab (Xgeva®):

Bone Metastasis from Solid Tumors – indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

The recommended dose is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.
Glossary:

Definition of End Points: Intermediate outcomes in metastatic bone disease include biomarkers, radiographic criteria for bone response or progression, and in the adjuvant setting, bone mineral density. Non-fatal skeletal-related complications can be measured as meaningful endpoints to treatment such fractures, spinal cord compression, hypercalcemia and pain. A change in frequency of these events should be combined to demonstrate an improvement in quality of life. Skeletal related events (SREs) divided by the time on drug therapy can be used as a composite end point. Examples of SREs are pathologic fracture, spinal cord collapse/compression, or requiring surgery or therapeutic radiation therapy for bone pain or bone-related cause. Time to first SRE after starting drug therapy is a reliable endpoint. Clinical endpoints for osteoporosis include bone mineral density score, x-ray, fracture history, height loss, and markers of bone formation or pain score. No evidence of improved or stable bone mineral density detected by X-ray or densitometry after 12 months of drug therapy or an osteoporotic fracture, height loss or kyphosis [indicative of vertebral (spinal fracture)] after 6 months or more of drug therapy can be considered treatment failure.

Definition of Hypercalcemia

| Normal serum calcium (Ca) level is 8-10 mg/dL (2-2.5 mmol/L) |
| Mild: Total Ca 10.5-11.9 mg/dL (2.5-3 mmol/L) |
| Moderate: Total Ca 12-13.9 mg/dL (3.5-5 mmol/L) |
| Hypercalcemia is defined as a serum calcium level greater than 10.5 mg/dL (>2.5 mmol/L) |
| Hypercalcemic crisis: Total Ca 14-16 mg/dL (3.5-4 mmol/L) |

For every 1 g/dL (1 g/L) drop in serum albumin below 4 g/dL (40 g/L), measured serum calcium decreases by 1.8 mg/dL (0.02 mmol/L).

Therefore, if albumin level < 4 g/dL (40 g/L) need to correct calcium based on the following formulas: Corrected Ca = (4g/dL - (plasma albumin) X 0.8 + serum calcium, g/dL) or Corrected Ca = serum calcium, mmol/L = ([40-(plasma albumin)] X 0.02)

Osteonecrosis of the Jaw (ONJ): may remain asymptomatic for many weeks or months and is typically identified by exposed bone in the oral cavity upon clinical presentation. The lesions become symptomatic when infection or trauma is involved at the site or surrounding areas. Signs and symptoms include localized pain; soft-tissue swelling and inflammation, loosening of previously stable teeth, drainage and exposed bone. These symptoms most commonly occur at the site of previous tooth extraction or dental-surgical interventions.

References:
Boniva® Injection Prescribing Information. Roche Pharmaceuticals, July 2009.
Coldwell, B. Head LR. White D. et al. Guidelines for the use of zoledronic acid for the treatment of tumor-induced hypercalcemia QEI health sciences