Clinical Policy: Zoledronic Acid (Reclast, Zometa)
Reference Number: ERX.SPA.66
Effective Date: 10.01.16
Last Review Date: 02.19

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Zoledronic acid (Reclast®, Zometa®) is a bisphosphonate.

FDA Approved Indication(s)
Reclast is indicated:
- For the treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Reclast reduces the incidence of fractures (hip, vertebral, and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Reclast reduces the incidence of new clinical fractures;
- For the prevention of osteoporosis in postmenopausal women;
- For the treatment to increase bone mass in men with osteoporosis;
- For the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months;
- For the treatment of Paget's disease of bone in men and women with elevations in serum alkaline phosphatase (ALP) of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease.

Limitation(s) of use: The safety and effectiveness of Reclast for the treatment of osteoporosis is based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

Zometa is indicated:
- For the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of greater than or equal to 12 mg/dL (3.0 mmol/L);
- For the treatment of patients with multiple myeloma;
- 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.

Limitation(s) of use: The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions have not been established.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Reclast and Zometa are medically necessary when the following criteria are met:
I. Initial Approval Criteria

A. Osteoporosis and Paget’s Disease of Bone (must meet all):
   1. Request is for Reclast for one of the following indications (a, b, or c):
      a. Osteoporosis;
      b. Prevention of osteoporosis;
      c. Paget’s disease of bone;
   2. For osteoporosis-related indications, member meets one of the following (a or b):
      a. Prescribed by or in consultation with one of the following specialists: a gynecologist, endocrinologist, rheumatologist, geriatrician, orthopaedist, or physiatrist;
      b. Failure of a 12-month trial of an oral bisphosphonate (alendronate is preferred) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   3. Not currently receiving therapy with Zometa;
   4. Dose does not exceed 5 mg.

Approval duration:
- Postmenopausal osteoporosis prevention – 24 months (one infusion)
- All other indications – 12 months (one infusion)

B. Hypercalcemia, Multiple Myeloma, and Bone Metastases (must meet all):
   1. Request is for Zometa for one of the following indications (a, b, or c):
      a. Hypercalcemia of malignancy evidenced by an albumin-corrected calcium (cCa) ≥ 12 mg/dL (see Appendix D);
      b. Multiple myeloma when used in conjunction with standard antineoplastic therapy;
      c. Bone metastases from solid tumors and both of the following (i and ii):
         i. Member is currently receiving standard antineoplastic therapy;
         ii. If prostate cancer, documented evidence that prostate cancer has progressed after treatment with at least one hormonal therapy (see Appendix D);
   2. Not currently receiving therapy with Reclast;
   3. Dose does not exceed 4 mg.

Approval duration:
- Hypercalcemia of malignancy – 1 week (one infusion)
- Multiple myeloma and bone metastases – 3 months (one infusion every 3 weeks)

C. Other diagnoses/indications
   1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Osteoporosis and Paget’s Disease of Bone (must meet all):
   1. Request is for Reclast;
   2. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   3. For osteoporosis-related indications, member is responding positively to therapy;
   4. For Paget’s disease, disease has relapsed or progressed (e.g., increases in or failure to achieve normalization of serum ALP, radiographic progression of disease);
   5. If request is for a dose increase, new dose does not exceed 5 mg.

Approval duration:
- Postmenopausal osteoporosis prevention – 24 months (one infusion)
- All other indications – 12 months (one infusion)

B. Hypercalcemia, Multiple Myeloma, and Bone Metastases (must meet all):
   1. Request is for Zometa;
   2. Currently receiving the medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   3. For hypercalcemia of malignancy, member meets both of the following (a and b):
C. Clinical Policy

a. At least 7 days have elapsed since last treatment;
b. Documented evidence that serum calcium has not returned to normal or remained normal after initial treatment;
4. For multiple myeloma and bone metastases, member continues to receive standard antineoplastic therapy and is responding positively to therapy with Zometa (e.g., no significant toxicity);
5. If request is for a dose increase, new dose does not exceed 4 mg.

Approval duration:

Hypercalcemia of malignancy – 1 week (one infusion)
Multiple myeloma and bone metastases – 6 months (one infusion every 3 weeks)

C. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
ALP: alkaline phosphatase
BMD: bone mineral density
CrCl: creatinine clearance
cCa: albumin-corrected calcium
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>alendronate (Fosamax®)</td>
<td>Osteoporosis 10 mg PO QD or 70 mg PO q week</td>
<td>Osteoporosis 10 mg/day or 70 mg/week</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoid-induced osteoporosis 5 mg PO QD or 10 mg PO QD (in postmenopausal women not receiving estrogen)</td>
<td>Glucocorticoid-induced osteoporosis 5 mg/day or 10 mg/day (in postmenopausal women not receiving estrogen)</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis prophylaxis 5 mg PO QD or 35 mg PO q week</td>
<td>Osteoporosis prophylaxis 5 mg/day or 35 mg/week</td>
</tr>
<tr>
<td></td>
<td>Paget’s disease 40 mg PO QD for 6 months; may re-treat if needed</td>
<td>Paget’s disease 40 mg/day</td>
</tr>
<tr>
<td>Fosamax® Plus D (alendronate/cholecalciferol)</td>
<td>Osteoporosis 70 mg alendronate/2,800 units cholecalciferol or 70 mg alendronate/5,600 units cholecalciferol PO q week</td>
<td>Osteoporosis 70 mg alendronate/5,600 units cholecalciferol/week</td>
</tr>
<tr>
<td>risedronate (Actonel®, Atelvia®)</td>
<td>Osteoporosis (including prophylaxis)</td>
<td>Osteoporosis (including prophylaxis)</td>
</tr>
</tbody>
</table>
### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid (Reclast)</td>
<td>Treatment of postmenopausal osteoporosis, treatment to increase bone mass in men with osteoporosis, and</td>
<td>5 mg IV once a year</td>
<td>5 mg/year</td>
</tr>
</tbody>
</table>

**Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.**

**Appendix C: Contraindications/Boxed Warnings**

- **Contraindication(s):** hypersensitivity; Reclast only – hypocalcemia, creatinine clearance < 35 mL/min and in those with evidence of acute renal impairment
- **Boxed warning(s):** none reported

**Appendix D: General Information**

- The World Health Organization uses the following classifications for osteoporosis and osteopenia:

<table>
<thead>
<tr>
<th>Category</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1.0 or above</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-2.5 or below</td>
</tr>
</tbody>
</table>

- Formula for albumin-corrected calcium level: \( cCa \) in mg/dL = Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin [g/dL])
- Hormonal therapy for prostate cancer includes regimens containing luteinizing hormone-releasing hormone (LHRH) agonists (e.g., goserelin, histrelin, leuprolide, triptorelin), LHRH antagonists (e.g., degarelix), antiandrogens (e.g., nilutamide, flutamide, bicalutamide, enzalutamide), and/or an androgen biosynthesis inhibitor (e.g., abiraterone) per NCCN guidelines.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>treatment and prevention of glucocorticoid-induced osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prevention of postmenopausal osteoporosis</td>
<td>5 mg IV once every 2 years</td>
<td>5 mg/2 years</td>
</tr>
<tr>
<td></td>
<td>Treatment of Paget’s disease of bone</td>
<td>5 mg IV once; re-treatment may be considered</td>
<td>5 mg</td>
</tr>
<tr>
<td>Zoledronic acid (Zometa)</td>
<td>Hypercalcemia of malignancy</td>
<td>4 mg as a single-use IV infusion; may re-treat with 4 mg after a minimum of 7 days</td>
<td>4 mg/infusion</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma and bone metastases from solid tumors</td>
<td>4 mg as a single-use IV infusion every 3 to 4 weeks</td>
<td>4 mg/3 weeks</td>
</tr>
</tbody>
</table>

VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid (Reclast)</td>
<td>Ready-to-infuse solution: 5 mg/100 mL</td>
</tr>
<tr>
<td>Zoledronic acid (Zometa)</td>
<td>Ready-to-infuse solution: 4 mg/100 mL, Single-use via concentrate: 4 mg/5 mL</td>
</tr>
</tbody>
</table>

VII. References

### Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>07.16</td>
<td>09.16</td>
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</tbody>
</table>

Policy split from USS.CP.PHAR.20 Osteoporosis Injectable Therapy, combined with Zometa, and converted to new template.

**Zometa:**
- Removed safety criteria.
- Hypercalcemia of malignancy: initial renal dose adjustment and co-administration with saline hydration criteria removed; max dose added; re-auth max total doses removed; signs of jaw osteonecrosis removed; renal deterioration removed; approval changed from 3 to 6 months.
- Multiple myeloma: initial definition of MM active (symptomatic) disease added; modified dosing criteria to max of ≤ 4 mg; lytic destruction of bone/spine compression/osteopenia criteria removed; re-auth 2 year treatment limit criteria removed; signs of jaw osteonecrosis criteria removed; renal deterioration criteria removed since tx interruption vs. hard stop; approval changed to 6 months.
- Bone metastases from solid tumors: initial modified dosing criteria to max dose of ≤ 4 mg; criteria for prostate cancer added as noted in PI; re-auth 2 year treatment limit criteria removed; signs of jaw osteonecrosis criteria removed; renal deterioration criteria removed; approval changed to 6 months.

**Reclast:**
- Removed safety criteria.
- For men with osteoporosis: criteria distinguished between primary osteoporosis and hypogonadal osteoporosis; testosterone requirement maintained for hypogonadal osteoporosis but year-long therapy prior to Reclast removed. Added “at femoral neck or spine” for T score.
- Removed requirement must be > 50 in cases where osteoporosis diagnosis relies on history of an osteoporotic fracture. Added additional criteria if purpose is prevention of osteoporosis per UpToDate and FRAX. Added definition of bisphosphonate trial failure. Calcium/vitamin D requirement language edited to be less specific. Approval duration broken up across indications. Edited to allow continued therapy for Paget’s disease in some cases per PI.

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>06.17</td>
<td>08.17</td>
</tr>
</tbody>
</table>

Converted to new template. Added maximum dose to continued therapy.

Osteoporosis and Paget’s disease: Removed high risk of fracture (recent low-trauma hip fracture). Added “at total hip” to T score. Added requirement for T score/history of fracture to confirm diagnosis of male osteoporosis, and combined treatment of osteoporosis of postmenopausal women and males. Removed requirement for administration of calcium/vitamin D if appropriate. Added contraindication of CrCl < 35 as it can lead to hospitalization. For Paget’s disease, removed requirement for trial/failure of an oral bisphosphonate.

Hypercalcemia, multiple myeloma, and bone metastases: Removed requirement that multiple myeloma must be active, and deleted appendix C (definition of active MM). Added requirement for member to continue to be receiving oral calcium and vitamin D to continued therapy.

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.17.17</td>
<td>02.18</td>
</tr>
</tbody>
</table>

1Q18 annual review:
- Converted to new template. Modified diagnoses and removed requirements for evidence of diagnoses for Reclast indications. Removed age
requirement. Modified criteria to add specialist requirement or trial and failure of a bisphosphonate (alendronate is preferred) for osteoporosis-related indications. Removed definition of treatment failure. Modified approval duration of 24 months to apply only to postmenopausal osteoporosis prevention. Removed requirements for calcium and vitamin D supplementation. Added requirement for continuation of standard antineoplastic therapy for multiple myeloma and bone metastases. Modified approval duration for Other diagnoses/indications to 6 months. Updated appendices.

1Q 2019 annual review: no significant changes; added geriatrician prescriber option; removed previous requirement that physiatrist prescriber applies only to postmenopausal osteoporosis; references reviewed and updated.

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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