Clinical Policy: Zoledronic acid (Reclast, Zometa)
Reference Number: ERX.SPMN.108
Effective Date: 10/16
Last Review Date: 09/16

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

Policy/Criteria
It is the policy of health plans affiliated with Envolve Pharmacy Solutions® that zoledronic acid (Reclast®, Zometa®, and generic formulations) is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Reclast or generic - Osteoporosis and Paget’s Disease of the Bone (must meet all):
      1. Age ≥ 18 years;
      2. Request is for one of the following indications:
         a. Treatment of osteoporosis in postmenopausal woman:
            i. Prior to therapy, T-score ≤ -2.5 (DXA) at the femoral neck or spine or osteoporotic vertebral fracture confirmed by radiographic imaging; or
            ii. High risk of fracture, defined as a recent low-trauma hip fracture;
         b. Prevention of osteoporosis in postmenopausal woman:
            i. Prior to therapy, T-score < -1.0 (DXA) at the femoral neck or spine with a 10-year probability of hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% per the WHO Fracture Risk Assessment Tool (FRAX)7;
         c. Treatment of male with osteoporosis (if hypogonadal osteoporosis, is receiving testosterone but remains at high risk for fracture or has a contraindication to testosterone);
         d. Treatment or prevention of glucocorticoid-induced osteoporosis when either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to ≥ 7.5 mg of prednisone and is expected to remain on glucocorticoids for at least 12 months;
         e. Treatment of Paget’s disease of the bone and one of the following (i through iii):
            i. Serum alkaline phosphatase is elevated ≥ 2 times the upper limit of the age-specific normal reference range; or
            ii. Paget’s disease of the bone is symptomatic; or
            iii. At risk for complications from the disease;
      3. Had an inadequate response to oral bisphosphonate therapy (decline in BMD of ≥ 5% or continued fractures after one year of therapy), unless contraindicated or intolerant;
      4. Has been counseled on and is receiving adequate vitamin D and/or calcium supplementation, if appropriate;
      5. Prescribed dose does not exceed 5 mg;
6. If request is for Reclast, has a contraindication to or has tried and is intolerant to the generic version of Reclast;
7. Member is not concurrently using Zometa.

Approval duration:
For osteoporosis prevention- one infusion every 24 months
For all other indications - one infusion every 12 months

B. Zometa or generic - Hypercalcemia, Multiple Myeloma, Bone Metastases (must meet all):
1. Age ≥ 18 years;
2. Request is for one of the following diagnoses:
   a. Hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of ≥ 12 mg/dL per Appendix B;
   b. Multiple myeloma with active disease (per Appendix C) when used in conjunction with both of the following:
      i. Standard antineoplastic therapy;
      ii. Oral calcium supplement of 500 mg and a multiple vitamin containing 400 international units of vitamin D daily;
   c. Bone metastases from solid tumors;
      i. Used in conjunction with the following (a and b):
         1. Standard antineoplastic therapy;
         2. Oral calcium supplement of 500 mg and a multiple vitamin containing 400 international units of vitamin D daily;
      ii. If prostate cancer, documented evidence that prostate cancer has progressed after treatment with at least one hormonal therapy;
3. Prescribed dose does not exceed 4 mg;
4. If request is for Zometa, member has a contraindication to or has tried and is intolerant to the generic version of Zometa;
5. Member is not concurrently using Reclast.

Approval duration:
One infusion for hypercalcemia of malignancy
3 months for multiple myeloma and bone metastases (infusions as often as every 3 weeks)

C. Other diagnoses/indications: Refer to ERX.SPMN.16 - Global Biopharm Policy.

II. Continued Approval
A. Reclast or generic - Osteoporosis and Paget’s Disease of the Bone (must meet all):
1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria;
2. Re-treatment of Paget’s disease is limited to one of the following:
   a. Disease relapse based on increases in serum alkaline phosphatase;
   b. Failed to achieve normalization of their serum alkaline phosphatase;
   c. Member is symptomatic.
**Approval duration:**
For osteoporosis prevention - one infusion every 24 months
For all other indications - one infusion every 12 months

**B. Zometa or generic – Hypercalcemia, Multiple Myeloma, Bone Metastases (must meet all):**
1. Currently receiving the medication via health plan benefit or member has previously met all initial approval criteria;
2. Documentation supports positive response to therapy;
3. If treatment is for hypercalcemia of malignancy, meets a and b:
   a. ≥ 7 days have elapsed since last treatment;
   b. Documented evidence that serum calcium has not returned to normal or remained normal after initial treatment.

**Approval duration:**
For hypercalcemia of malignancy – one infusion
For multiple myeloma and bone metastases – 6 months (infusions as often as every 3 weeks)

**C. Other diagnoses/indications (must meet 1 or 2):**
1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy; or
2. Refer to ERX.SPMN.16 - Global Biopharm Policy.

**Background**

*Description/Mechanism of Action:*
Zoledronic acid is an inhibitor of osteoclastic bone resorption available in the following formulations (see package inserts for detailed administration instructions):
- **Reclast brand/generics:**
  - 5 mg/100 mL (single-use ready to use)
- **Zometa brand/generics:**
  - 4 mg/5 mL (single-use concentrate to be diluted)
  - 4 mg/100 mL (single-use ready to use)

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the anti-resorptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.
FDA Approved Indications:
Reclast (zoledronic acid) is a bisphosphonate/intravenous infusion solution indicated for:

- 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.
- Prevention of osteoporosis in postmenopausal women.
- Treatment to increase bone mass in men with osteoporosis.
- 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.
- Treatment of Paget’s disease of bone in men and women. Treatment is indicated in patients with Paget’s disease of bone with elevations in serum alkaline phosphatase 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.

Limitations 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 (zoledronic acid) is a bisphosphonate/intravenous infusion solution indicated for:

- 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] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin [g/dL]).
- Treatment of patients with multiple myeloma.
- 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.

Limitations of use:
- The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions have not been established.
Appendices

Appendix A: Abbreviation Key
BMD: bone mineral density
Ca: calcium
cCa: albumin-corrected calcium
CrCl: creatinine clearance
DXA: dual energy X-ray absorptiometry
FRAX: WHO Fracture Risk Assessment Tool

Appendix B: Formula for Albumin-Corrected Calcium Level
\[ cCa \text{ in mg/dL} = \text{Ca in mg/dL} + 0.8 (4.0 \text{ g/dL} - \text{patient albumin [g/dL]}) \]

Appendix C: Definition of Multiple Myeloma - Active (Symptomatic) Disease
One or more of the following:
- Hypercalcemia (> 11.5 mg/dL)
- Renal insufficiency (creatinine > 2 mg/dL) or CrCl < 40mL/min
- Anemia (hemoglobin < 10 g/dL or hemoglobin > 2 g/dL below the lower limit of normal)
- Lytic or osteopenic bone disease as evidenced by bone lesions on skeletal radiography, CT, or PET-CT
- Bone marrow clonal plasma cells ≥ 60%
- Abnormal serum free light chain ratio ≥ 100 (involved kappa) or < 0.01 (involved lambda)
- More than one focal lesion (involving bone or bone marrow) detected by PET/CT and/or whole body MRI

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>J3489</td>
<td>Injection, zoledronic acid, 1 mg</td>
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Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>07/16</td>
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Policy split from USS.CP.PHAR.20 Osteoporosis Injectable Therapy, combined with Zometa, and converted to new template.
Zometa: Removed safety criteria.
## Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Condition</th>
<th>Revisions and Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>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.</td>
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<td>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.</td>
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<td>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.</td>
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<td><strong>Reclast:</strong></td>
<td>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 &gt; 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.</td>
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References
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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