

Clinical Policy: Zoledronic Acid (Reclast, Zometa)

Reference Number: CP.PHAR.59

Effective Date: 03.11

Last Review Date: 02.20

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)

[Revision Log](#)

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:

- Postmenopausal osteoporosis (PMO) - treatment: 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;
- PMO - prevention: For the prevention of osteoporosis in postmenopausal women;
- Male osteoporosis - treatment: For the treatment to increase bone mass in men with osteoporosis;
- Glucocorticoid-induced osteoporosis - prevention and treatment: For the treatment and prevention of GIO 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;
- Paget disease: 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:

- Hypercalcemia of malignancy: 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);
- Multiple myeloma (MM): For the treatment of patients with multiple myeloma;
- Solid tumors: 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.

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It is the policy of health plans affiliated with Centene Corporation® that Reclast and Zometa are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Osteoporosis (must meet all):

1. Request is for Reclast;
2. Prescribed for one of the following uses (a or b):
 - a. Treatment or prevention of PMO or GIO;
 - b. Treatment of male osteoporosis;
3. Age \geq 18 years or documentation of closed epiphyses on x-ray;
4. Failure of a 12-month trial of oral bisphosphonate therapy (*Appendix B; alendronate is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for oral bisphosphonates*
5. Reclast is not prescribed concurrently with Zometa;
6. Dose does not exceed 5 mg.

Approval duration:

Medicaid/HIM – osteoporosis treatment: 12 months (one infusion); osteoporosis prevention: 24 months (one infusion)

Commercial – 6 months or to the member’s renewal date, whichever is longer

B. Paget Disease (must meet all):

1. Request is for Reclast
2. Diagnosis of Paget disease of the bone;
3. Age \geq 18 years or documentation of closed epiphyses on x-ray;
4. Failure of a 12-month trial of oral bisphosphonate therapy (*Appendix B; alendronate is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced (*Appendix E*);
**Prior authorization may be required for oral bisphosphonates*
5. Reclast is not prescribed concurrently with Zometa;
6. Dose does not exceed 5 mg.

Approval duration:

Medicaid/HIM – 12 months (one infusion)

Commercial – 6 months or to the member’s renewal date, whichever is longer

C. Hypercalcemia of Malignancy (must meet all):

1. Request is for Zometa;
2. Diagnosis of hypercalcemia of malignancy;
3. Prescribed by or in consultation with an oncologist;
4. Age \geq 18 years or documentation of closed epiphyses on x-ray;
5. Albumin-corrected calcium \geq 12 mg/dL;
7. Zometa is not prescribed concurrently with Reclast;
8. Dose does not exceed 4 mg.

Approval duration:

Medicaid/HIM – 1 week (one infusion)

Commercial – 6 months or to the member’s renewal date, whichever is longer

D. Multiple Myeloma or Solid Tumor (must meet all):

1. Request is for Zometa;
2. Diagnosis of one of the following (a or b):
 - a. MM;
 - b. Bony metastasis from solid tumor (e.g., breast, kidney, lung, prostate, thyroid);
3. Member is at risk for a skeletal-related event (e.g., pathologic fracture, radiation therapy or surgery to bone, spinal cord compression);
4. Prescribed by or in consultation with an oncologist;
5. Age \geq 18 years or documentation of closed epiphyses on x-ray;
6. Zometa is not prescribed concurrently with Reclast;
7. Dose does not exceed 4 mg.

Approval duration:

Medicaid/HIM – 3 months (one infusion every 3 weeks)

Commercial – 6 months or to the member’s renewal date, whichever is longer

E. Prostate/Breast Cancer - Fracture Prevention (off-label) (must meet all):

1. Request is for Zometa;
2. One of the following diagnoses (a or b):
 - a. Prostate cancer and member is receiving androgen deprivation therapy (e.g., leuprolide (Lupron®), bicalutamide (Casodex®), Nilandron®);
 - b. Breast cancer and member is receiving adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors such as anastrozole (Arimidex®), exemestane (Aromasin®) or letrozole (Femara®));
3. Prescribed by or in consultation with an oncologist;
4. Age \geq 18 years or documentation of closed epiphyses on x-ray;
5. Zometa is not prescribed concurrently with Reclast;
6. Request meets one of the following (a or b):*
 - a. Dose does not exceed 4 mg;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration:

Medicaid/HIM – 3 months (one infusion every 3 weeks)

Commercial – 6 months or to the member’s renewal date, whichever is longer

F. Systemic Mastocytosis (off-label) (must meet all):

1. Request is for Zometa;
2. Diagnosis of systemic mastocytosis;
3. Member has osteopenia or osteoporosis with bone pain;
4. Prescribed by or in consultation with an oncologist;
5. Age \geq 18 years or documentation of closed epiphyses on x-ray;
6. Zometa is not prescribed concurrently with Reclast;
7. Request meets one of the following (a or b):*
 - a. Dose does not exceed 4 mg;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration:

Medicaid/HIM – 3 months (one infusion every 3 weeks)

Commercial – 6 months or to the member’s renewal date, whichever is longer

G. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Osteoporosis and Paget Disease of Bone (must meet all):

1. Request is for Reclast;

2. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 5 mg.

Approval duration:

Medicaid/HIM – osteoporosis treatment and Paget disease: 12 months (one infusion); osteoporosis prevention: 24 months (one infusion)

Commercial – 6 months or to the member’s renewal date, whichever is longer

B. Oncology-Related Indications (must meet all):

1. Request is for Zometa;
2. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Zometa for a covered indication and has received this medication for at least 30 days;
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following (a or b):*
 - a. New dose does not exceed 4 mg;
 - b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:

Medicaid/HIM – hypercalcemia of malignancy: 1 week (one infusion); all other indications: 12 months (one infusion every 3 weeks)

Commercial – 6 months or to the member’s renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BMD: bone mineral density

FDA: Food and Drug Administration

GIO: glucocorticoid-induced osteoporosis

MM: multiple myeloma

PMO: postmenopausal osteoporosis

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.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Oral bisphosphonates		
alendronate (Fosamax [®])	Treatment/prevention: PMO Treatment: GIO, male osteoporosis Treatment: Paget disease <i>See prescribing information for dose.</i>	Varies
Fosamax [®] Plus D (alendronate / cholecalciferol)	Treatment: PMO, male osteoporosis <i>See prescribing information for dose.</i>	
risedronate (Actonel [®] , Atelvia [®])	Actonel: Treatment/prevention: PMO, GIO Treatment: male osteoporosis Treatment: Paget disease Atelvia: Treatment: PMO <i>See prescribing information for dose.</i>	
ibandronate (Boniva [®])	Treatment/prevention: PMO <i>See prescribing information for dose.</i>	

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 to any product component
 - Reclast: hypocalcemia, creatinine clearance < 35 mL/min, acute renal impairment
- Boxed warning(s): none reported

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Zoledronic acid (Reclast)	Treatment: PMO, male osteoporosis Treatment/prevention: GIO	5 mg IV once a year	5 mg/year
	Prevention: PMO	5 mg IV once every 2 years	5 mg/2 years
	Paget disease	5 mg IV once; retreatment may be considered	5 mg
Zoledronic acid (Zometa)	Hypercalcemia of malignancy	4 mg as a single-use IV infusion; may re-treat with 4 mg after a minimum of 7 days	4 mg/infusion

Drug Name	Indication	Dosing Regimen	Maximum Dose
	MM Solid tumor - bone metastasis	4 mg as a single-use IV infusion every 3 to 4 weeks	4 mg/3 weeks

VI. Product Availability

Drug Name	Availability
Zoledronic acid (Reclast)	Ready-to-infuse solution: 5 mg/100 mL
Zoledronic acid (Zometa)	Ready-to-infuse solution: 4 mg/100 mL Single-use vial concentrate: 4 mg/5 mL

VII. References

1. Reclast Prescribing Information. East Hanover, NJ: Novartis Pharmaceutical Corporation; July 2017. Available at <http://www.reclast.com>. Accessed October 14, 2019.
2. Zometa Prescribing Information. East Hanover NJ: Novartis Pharmaceuticals Corporation; December 2018. Available at <http://www.pharma.us.novartis.com/product/pi/pdf/Zometa.pdf>. Accessed October 15, 2019.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. URL: <http://www.clinicalpharmacology.com>.

Osteoporosis Diagnosis, Fracture Risk, and Treatment

4. Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*; 2019, 104: 1595–1622.
5. Camacho PM, Petak SM, Brinkley N et al. AACE/ACE Guidelines- American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Diagnosis and Treatment of Postmenopausal Osteoporosis. *Endocrine Practice* Vol 22 (suppl 4) September 2016.
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7. Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. *Osteoporos Int* (2014) 25:1439–1443. DOI 10.1007/s00198-014-2655-z.
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Male Osteoporosis

9. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guidelines. *J Clin Endocrinol Metab* 2012;97(6):1802-1822.

Glucocorticoid-Induced Osteoporosis

10. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol*. 2017; 69(8): 1521-1537.

Paget Disease

11. Singer FR, Bone HG, Hosking DJ, et al. Paget’s disease of the bone: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2014; 99(12): 4480-4422.

Oncology

12. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed October 14, 2019.

13. National Comprehensive Cancer Network. Breast Cancer Version 3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 14, 2019.

14. National Comprehensive Cancer Network. Prostate Cancer Version 4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed October 14, 2019.

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.

HCPCS Codes	Description
J3489	Injection, zoledronic acid, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>Zometa criteria</p> <p>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.</p> <p>Multiple myeloma initial - definition of MM active (symptomatic) disease added; modified dosing criteria to max of ≤ 4mg; 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.</p> <p>Bone metastases from solid tumors - initial: modified dosing criteria to max dose of ≤ 4mg; 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.</p>	01.16	2.16
<p>Reclast criteria split from CP.PHAR.20.Osteoporosis Inj policy. For men, criteria changed to require testosterone only for hypogonadal rather than primary osteoporosis, removed year-long testosterone therapy prior to Reclast.</p>	3.16	03.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>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. Certain conditions representing potential contraindications to therapy are and other safety criteria removed as the PI does not instruct that they be ruled out prior to initiating therapy or specify a test and measureable outcome by which to do so. Retained contraindication that are objective and verifiable and should be checked prior to therapy per PI (Hypocalcemia & CrCl) Added additional criteria if purpose is prevention of osteoporosis per UpToDate and FRAX. Added definition of bisphosphonate trial failure and, if contraindication/intolerance, that it be to one of the two oral drugs listed 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.</p>		
<p>Removed age restriction. Added maximum dose to continued therapy. Certain conditions representing potential contraindications to therapy and other safety criteria removed. 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. 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). Removed CrCl < 30 (a warning) and hypercalcemia associated with hyperparathyroidism (a limitation of use) from contraindications. Added requirement for member to continue to be receiving oral calcium and vitamin D to continued therapy. Added reasons to discontinue to continued therapy</p>	02.17	03.17
<p>1Q18 annual review: policies combined commercial and Medicaid; converted to new template; modified diagnoses and removed requirements for evidence of diagnoses for Reclast</p>	11.22.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
indications; modified age requirement. Modified criteria to add specialist requirement or trial and failure of a bisphosphonate (alendronate is preferred). Removed definition of treatment failure; removed contraindication of hypocalcemia; modified approval duration of 24 months to apply only to postmenopausal osteoporosis prevention; modified approval duration for other diagnoses/indications to 12 months; removed requirements for calcium and vitamin D supplementation; modified definitions for positive response to therapy; added requirement for continuation of standard antineoplastic therapy for multiple myeloma and bone metastases; references reviewed and updated.		
1Q 2019 annual review: added HIM line of business; modified Paget’s disease to only require diagnosis; added geriatrician prescriber option; removed previous requirement that physiatrist prescriber applies only to postmenopausal osteoporosis; modify approval duration for Commercial to “6 months or to the member’s renewal date, whichever is longer”; references reviewed and updated.	11.01.18	02.19
1Q 2020 annual review: removed HIM disclaimer for HIM NF drugs; Reclast: closed epiphyses added if less than 18 years; Paget disease - continuation criteria removed for individualization of therapy; Zometa: oncology - examples of skeletal related event and solid tumor added; oncologist and age added; NCCN recommended breast/prostate cancer and systemic mastocytosis uses added; hypercalcemia continuation of therapy criteria removed given response fluidity; references reviewed and updated.	11.19.19	02.20

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage

decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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