

Zoledronic acid: **Zometa®; Reclast®** (Intravenous)

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I. Length of Authorization

Zometa:

- Hypercalcemia of Malignancy: Coverage is provided for up to 2 doses for 12 months and may NOT be renewed.
- All other indications: Coverage is provided for 12 months and may be renewed.

Reclast:

- Fracture risk reduction following alternative osteoporosis class therapy: Coverage will be provided for 12 months and may NOT be renewed.
- Prevention of osteoporosis in post-menopausal women: Coverage is provided for 24 months and may be renewed.
- All other indications: Coverage is provided for 12 months and may be renewed

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

Zometa

Indication	Quantity Limit
Hypercalcemia of malignancy	4 mg bottle/vial per 7 days x 2 doses only
Multiple myeloma, bone metastases from solid tumors, Systemic mastocytosis	4 mg bottle/vial every 21 days
Breast cancer (bone loss prevention and risk reduction of distant metastasis)	4 mg bottle/vial every 168 days (6 months)
Prostate cancer (bone loss prevention)	4 mg bottle/vial every 84 days (3 months)
Langerhans Cell Histiocytosis	4 mg bottle/vial every 28 days

Reclast

Indication	Quantity Limit
Prevention of osteoporosis in post-menopausal women	5 mg solution every 730 days (24 months)
All other indications	5 mg solution every 365 days (12 months)

B. Max Units (per dose and over time) [HCPCS Unit]:

Zometa

Indication	Max Units
Hypercalcemia of malignancy	4 billable units every 7 days for 2 doses only
Multiple myeloma, bone metastases from solid tumors, systemic mastocytosis	4 billable units every 21 days
Breast cancer (bone loss prevention and risk reduction of distant metastasis)	4 billable units every 168 days (6 months)
Prostate cancer (bone loss prevention)	5 billable units every 84 days (3 months)
Langerhans Cell Histiocytosis	4 billable units every 28 days

Reclast

Indication	Max Units
Paget's Disease	5 billable units for 2 doses
Prevention of osteoporosis in post-menopausal women	5 billable units every 730 days (24 months)
Fracture risk reduction following alternative osteoporosis class therapy	5 billable units for 1 dose
Treatment of osteoporosis/Treatment and prevention of glucocorticoid-induced osteoporosis	5 billable units every 84 days (3 months)

III. Initial Approval Criteria ^{1,2}

- Patient is at least 18 years of age; **AND**

Zometa

Universal Criteria ^{1,31,37}

- Patient does not have hypocalcemia and will be adequately supplemented with calcium and vitamin D (*Note: excludes when use is for hypercalcemia of malignancy*); **AND**
- Patient must have a CrCl \geq 30 mL/min; **AND**
- Will not be used in combination with Reclast, other bisphosphonates, denosumab, romosozumab, or parathyroid hormone analogs/related peptides; **AND**

Coverage is provided in the following conditions:

Hypercalcemia of malignancy † Φ¹

- Patient has an albumin-corrected serum calcium level of ≥ 12 mg/dL

Multiple myeloma † ‡^{1,5}

Bone metastases from solid tumors †¹

- Used in conjunction with standard antineoplastic therapy

Prostate Cancer ‡^{3,41}

- Used for prevention of bone loss associated with androgen deprivation therapy (ADT)

Breast Cancer ‡^{3,42}

- Patient is post-menopausal (natural or induced); **AND**
 - Patient is receiving adjuvant aromatase inhibition therapy; **AND**
 - Used to maintain or improve bone mineral density and reduce risk of fractures; **OR**
 - Patient is receiving adjuvant therapy; **AND**
 - Used for risk reduction of distant metastasis in patients with a high-risk tumor

Systemic Mastocytosis ‡^{3,26,33}

- Used for the treatment of osteopenia or osteoporosis

Langerhans Cell Histiocytosis ‡^{3,34}

- Patient has multifocal bone disease OR unifocal isolated bone disease

Reclast

Universal Criteria^{2,31,37}

- Confirmation patient is receiving calcium and Vitamin D supplementation if dietary intake is inadequate; **AND**
- Patient must not have hypocalcemia; **AND**
- Patient must have a CrCl ≥ 35 mL/min and no evidence of acute renal impairment; **AND**
- Will not be used in combination with Zometa, other bisphosphonates, denosumab, romosozumab, or parathyroid hormone analogs/related peptides; **AND**

Coverage is provided in the following conditions:

Treatment and prevention of postmenopausal osteoporosis †^{2,25,28,32,38,39}

- Patient experienced severe intolerance, ineffective response±, or has contraindications* to oral bisphosphonate therapy; **OR**
- Patient had a prior fragility fracture or is at especially high fracture risk**

Treatment to increase bone mass in men with osteoporosis † 2

- Patient experienced severe intolerance, ineffective response±, or has contraindications* to oral bisphosphonate therapy; **OR**
- Patient had a prior fragility fracture or is at especially high fracture risk**

Treatment and prevention of glucocorticoid-induced osteoporosis † 2

- Patient experienced severe intolerance, ineffective response±, or has contraindications* to oral bisphosphonate therapy; **OR**
- Patient had a prior fragility fracture or is at especially high fracture risk ¥

Treatment of Paget's disease of bone in men and women † 2

- Serum alkaline phosphatase is two times or higher than the upper limit of the age-specific reference range; **OR**
- Patient is symptomatic; **OR**
- Patient is at risk for complications from their disease

Fracture risk reduction following alternative osteoporosis class therapy ‡ 25,28,30,32,40,41

- Patient is discontinuing osteoporosis therapy with denosumab, romosozumab, or parathyroid hormone analogs/related peptides due to a reduction in fracture risk (i.e., no longer high or very high risk); **AND**
- Used to prevent accelerated bone mineral density decline and loss of fracture efficacy

± Ineffective response is defined as one or more of the following: 28,30,37

- o Decrease in T-score in comparison with baseline T-score from DXA scan
- o Patient has a new fracture while on bisphosphonate therapy

** High risk for fractures include, but are not limited to, one or more of the following: 28,37

- o History of an osteoporotic fracture as an adult
- o Parental history of hip fracture
- o Low BMI
- o Rheumatoid arthritis
- o Alcohol intake (3 or more drinks per day)
- o Current smoking
- o History of oral glucocorticoids ≥5 mg/d of prednisone (or equivalent) for >3 months (ever)

* Examples of contraindications to oral bisphosphonate therapy include the following: 29

- o Documented inability to sit or stand upright for at least 30 minutes
- o Documented pre-existing esophageal disorder such as achalasia, esophageal stricture, esophageal varices, or Barrett's esophagus
- o Surgical anastomoses are present in the GI tract after certain types of bariatric surgery (e.g., Roux-en-Y gastric bypass)

¥ Increased risk for glucocorticoid-induced osteoporosis fracture: 40

- o Prior osteoporotic fracture
- o High-dose glucocorticoid use (i.e., prednisone [or equivalent] ≥30 mg/d >30 d or ≥5 g/year)
- o FRAX glucocorticoid adjusted 10-year risk of major osteoporotic fracture ≥20% or hip >3%
- o T-score by DXA of ≤-2.5 measured at the lumbar spine, femoral neck, total hip, or forearm at the 33% (one-third) radius site

◊ Note: If glucocorticoid dose is >7.5 mg/day, multiply the FRAX 10-year risk of major osteoporotic fracture by 1.15 and the hip fracture risk by 1.2 (e.g., if hip fracture risk is 2.0% multiply by 1.2 = 2.4% risk)

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); ◊ Orphan Drug

IV. Renewal Criteria ^{1,2}

Coverage can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in the initial criteria section; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: renal impairment, osteonecrosis of the jaw, atypical femoral fractures, hepatic impairment, hypocalcemia, incapacitating pain in the bone, joint, and/or muscle, bronchoconstriction, etc.; **AND**

Zometa ^{1,27,30,41,42}

- Disease response as indicated by the following:
 - Multiple Myeloma, Bone metastases from solid tumors:
 - Absence/delay in skeletal-related events (e.g., pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)
 - Hypercalcemia of Malignancy: May not be renewed
 - Breast Cancer (bone loss prevention), Prostate Cancer (bone loss prevention), and Systemic Mastocytosis:
 - Absence of fractures; **OR**
 - Increase in bone mineral density compared to pretreatment baseline
 - Breast Cancer (risk reduction of distant metastasis):
 - Prevention of bone recurrence; **OR**
 - Stabilization of disease from baseline; **OR**
 - Absence/delay in skeletal-related events (e.g., pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)
 - Langerhans Cell Histiocytosis:
 - Improvement in bone pain; **OR**
 - Improvement/resolution in active bone lesions compared to pretreatment baseline

Reclast ^{2,25,30,32}

- Disease response as indicated by the following:
 - Fracture Risk Reduction Following Alternative Osteoporosis Class Therapy:
 - May not be renewed
 - Osteoporosis indications:

- Absence of fractures; **OR**
- Increase in bone mineral density compared to pretreatment baseline; **AND**
 - Patients who have received 3 years of bisphosphonate therapy should be re-evaluated with a DXA or serum marker for bone turnover [i.e., serum C-terminal crosslinking telopeptide (CTX)]; **AND**
 - Those patients at low-to-moderate risk of fractures should be considered for a temporary discontinuation of bisphosphonate for up to 5 years (re-assess risk at 2 to 4 year intervals to determine if earlier re-initiation is necessary)
- Paget's Disease:
 - Patient previously experienced therapeutic response to treatment (i.e., normalization of serum alkaline phosphatase (SAP) or a reduction of $\geq 75\%$ from baseline in total SAP excess (defined as the difference between the measured level and midpoint of normal range); **AND**
 - Patient is having a relapse of disease based on increases in SAP; **OR**
 - Patient has symptomatic disease; **OR**
 - Patients failed to achieve normalization of SAP

V. Dosage/Administration

Zometa 1,6,10-12,13,27,35,36,41,21

Indication	Dose*
Hypercalcemia of malignancy	4 mg IV for 1 dose, may be repeated after 7 days if serum calcium does not return to normal. Renal function must be carefully monitored in all patients receiving therapy and serum creatinine must be assessed prior to retreatment.
Breast cancer (bone loss prevention and risk reduction of distant metastasis)	4 mg IV every 6 months
Prostate cancer (bone loss prevention)	4 mg IV every 3 months
Multiple myeloma & bone metastases from solid tumors	4 mg IV every 3 to 4 weeks <u>OR</u> 4 mg every 12 weeks
Systemic mastocytosis	4 mg IV every 3 to 4 weeks
Langerhans Cell Histiocytosis	4 mg IV every 4 weeks

*Decrease dose based upon CrCl (mL/min): 3.5 mg for CrCl 50-60; 3.3 mg for CrCl 40-49; 3 mg for CrCl 30-39

Reclast 2,30,40

Indication	Dose
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Paget's Disease	5 mg IV for 1 dose, may be repeated if symptomatic, relapsed or partial response following previous dose.
Fracture risk reduction following alternative osteoporosis class therapy	5mg IV for one dose
Prevention of osteoporosis in post-menopausal women	5 mg IV every 24 months
Treatment and prevention of glucocorticoid-induced osteoporosis	5 mg IV every 12 months
Treatment of osteoporosis	5 mg IV every 12 months

VI. Billing Code/Availability Information

HCPCS Code:

- J3489 – Injection, zoledronic acid, 1 mg; 1 billable unit = 1 mg

NDC(s):

- Zometa 4 mg/100 mL single-dose ready-to-use bottle*§: 00078-0590-xx
- Zometa 4 mg/5 mL single-dose vial of concentrate*§: 00078-0387-xx
- Reclast 5 mg/100 mL ready-to-infuse solution§: 00078-0435-xx

* No longer commercially available

§ Generic formulation available from various manufacturers

VII. References

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Appendix 1 – Covered Diagnosis Codes

Zometa

ICD-10	ICD-10 Description
C00-C14	Malignant neoplasms of lip, oral cavity, and pharynx
C15-C26	Malignant neoplasms of digestive organs
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50.011-C50.929	Malignant neoplasms of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system

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ICD-10	ICD-10 Description
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C7A.00-C7A.8	Malignant neuroendocrine tumors
C7B.00-C7B.8	Secondary neuroendocrine tumors
C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C79.51	Secondary malignant neoplasm of bone
C81	Hodgkin lymphoma
C82	Follicular lymphoma
C83	Non-follicular lymphoma
C84	Mature T/NK-cell lymphomas
C85	Other specified and unspecified types of non-Hodgkin lymphoma
C86	Other specified types of T/NK-cell lymphoma
C88	Malignant immunoproliferative diseases and certain other B-cell lymphomas
C90.00	Multiple myeloma not having reached remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having reached remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having reached remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having reached remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C94.30	Mast cell leukemia not having achieved remission
C94.31	Mast cell leukemia, in remission
C94.32	Mast cell leukemia, in relapse
C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.2	Malignant mast cell neoplasm
C96.20	Malignant mast cell neoplasm, unspecified
C96.21	Aggressive systemic mastocytosis
C96.22	Mast cell sarcoma
C96.29	Other malignant mast cell neoplasm
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis

ICD-10	ICD-10 Description
C96.7	Other specified malignant neoplasms of lymphoid, haematopoietic and related tissue
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms, except benign neuroendocrine tumors
D3A.00-D3A.8	Benign neuroendocrine tumors
D37	Neoplasm of uncertain behavior of oral cavity and digestive organs
D38	Neoplasm of uncertain behavior of middle ear and respiratory and intrathoracic organs
D39	Neoplasm of uncertain behavior of female genital organs
D40	Neoplasm of uncertain behavior of male genital organs
D41	Neoplasm of uncertain behavior of urinary organs
D42	Neoplasm of uncertain behavior of meninges
D43	Neoplasm of uncertain behavior of brain and central nervous system
D44	Neoplasm of uncertain behavior of endocrine glands
D47.02	Systemic mastocytosis
D48	Neoplasm of uncertain behavior of other and unspecified sites
D49.0-D49.9	Neoplasms of unspecified behavior
E83.52	Hypercalcemia
M80.8B2A- M80.8B2S	Osteoporosis with current pathological fracture
M80.8B9A- M80.8B9S	Osteoporosis with current pathological fracture
M81.6	Localized osteoporosis
M81.8	Other osteoporosis without current pathological fracture
M85.80	Other specified disorders of bone density and structure, unspecified site
M85.811	Other specified disorders of bone density and structure, right shoulder
M85.812	Other specified disorders of bone density and structure, left shoulder
M85.821	Other specified disorders of bone density and structure, right upper arm
M85.822	Other specified disorders of bone density and structure, left upper arm
M85.831	Other specified disorders of bone density and structure, right forearm
M85.832	Other specified disorders of bone density and structure, left forearm
M85.841	Other specified disorders of bone density and structure, right hand
M85.842	Other specified disorders of bone density and structure, left hand
M85.851	Other specified disorders of bone density and structure, right thigh
M85.852	Other specified disorders of bone density and structure, left thigh
M85.859	Other specified disorders of bone density and structure, unspecified thigh
M85.861	Other specified disorders of bone density and structure, left hand

ZOLEDRONIC ACID (Zometa®, Reclast®) Prior Auth Criteria

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ICD-10	ICD-10 Description
M85.862	Other specified disorders of bone density and structure, left lower leg
M85.871	Other specified disorders of bone density and structure, right ankle and foot
M85.872	Other specified disorders of bone density and structure, left ankle and foot
M85.9	Disorder of bone density and structure, unspecified
M89.9	Disorder of bone, unspecified
M94.9	Disorder of cartilage, unspecified
Z79.810	Long term (current) use of selective estrogen receptor modulators (SERMs)
Z79.811	Long term (current) use of aromatase inhibitors
Z79.899	Other long term (current) drug therapy
Z85	Personal history of malignant neoplasm
Z85.3	Personal history of malignant neoplasm of breast
Z85.46	Personal history of malignant neoplasm of prostate
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Dual coding requirements:

Prevention of bone loss in men receiving androgen deprivation therapy for prostate cancer:

- Primary code: M85.80, M85.811, M85.812, M85.821, M85.822, M85.831, M85.832, M85.841, M85.842, M85.851, M85.852, M85.861, M85.862, M85.871, M85.872, M89.9 or M94.9 plus: C61 OR Z85.46 **and** Z79.899

Prevention of aromatase inhibitor induced bone loss in breast cancer:

- Primary code: M85.80, M85.811, M85.812, M85.821, M85.822, M85.831, M85.832, M85.841, M85.842, M85.851, M85.852, M85.861, M85.862, M85.871, M85.872, M89.9 or M94.9 plus: C50.011-C50.922 OR Z85.3 **and** Z79.810 OR Z79.811

Reclast

ICD-10	ICD-10 Description
C61	Malignant neoplasm of prostate
M80.00XA-M80.08XS	Age-related osteoporosis with current pathological fracture
M80.8B2A-M80.8B2S	Osteoporosis with current pathological fracture
M80.8B9A-M80.8B9S	Osteoporosis with current pathological fracture
M81.0	Age-related osteoporosis without current pathological fracture
M81.6	Localized osteoporosis
M81.8	Other osteoporosis without current pathological fracture
M85.80	Other specified disorders of bone density and structure, unspecified site
M85.851	Other specified disorders of bone density and structure, right thigh
M85.852	Other specified disorders of bone density and structure, left thigh
M85.859	Other specified disorders of bone density and structure, unspecified thigh

ICD-10	ICD-10 Description
M85.88	Other specified disorders of bone density and structure, other site
M85.89	Other specified disorders of bone density and structure, multiple sites
M85.9	Disorder of bone density and structure, unspecified
M88.0	Osteitis deformans of skull
M88.1	Osteitis deformans of vertebrae
M88.811	Osteitis deformans of right shoulder
M88.812	Osteitis deformans of left shoulder
M88.819	Osteitis deformans of unspecified shoulder
M88.821	Osteitis deformans of right upper arm
M88.822	Osteitis deformans of left upper arm
M88.829	Osteitis deformans of unspecified upper arm
M88.831	Osteitis deformans of right forearm
M88.832	Osteitis deformans of left forearm
M88.839	Osteitis deformans of unspecified forearm
M88.841	Osteitis deformans of right hand
M88.842	Osteitis deformans of left hand
M88.849	Osteitis deformans of unspecified hand
M88.851	Osteitis deformans of right thigh
M88.852	Osteitis deformans of left thigh
M88.859	Osteitis deformans of unspecified thigh
M88.861	Osteitis deformans of right lower leg
M88.862	Osteitis deformans of left lower leg
M88.869	Osteitis deformans of unspecified leg
M88.871	Osteitis deformans of right ankle
M88.872	Osteitis deformans of left ankle
M88.879	Osteitis deformans of unspecified ankle
M88.88	Osteitis deformans of other bone
M88.89	Osteitis deformans of multiple sites
M88.9	Osteitis deformans of unspecified bone
M89.9	Disorder of bone, unspecified
M94.9	Disorder of cartilage, unspecified
Z85.46	Personal history of malignant neoplasm of prostate

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCA/LCD):

Medicare Part B Covered Diagnosis Codes		
Jurisdiction	NCD/LCA/LCD Document (s)	Contractor
5, 8	A56907	Wisconsin Physicians Service, Inc.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC