Zoledronic Acid (Zometa®, Reclast®)

NDC CODE(S)

00078-0435-XX Reclast 5 MG/100ML Solution (NOVARTIS)
00409-4215-XX ZOLEDRONIC ACID 4MG/5ML Concentrate (Hospira)
00409-4215-XX ZOLEDRONIC ACID 4MG/5ML Solution (Hospira)
00409-4228-XX ZOLEDRONIC ACID 5MG/100ML Solution (Hospira)
00409-4229-XX ZOLEDRONIC ACID 4MG/100ML Solution (Hospira)
16714-0815-XX ZOLEDRONIC ACID 4MG/5ML Concentrate (Northstar Rx)
16729-0242-XX ZOLEDRONIC ACID 4MG/5ML Solution (Accord Healthcare)
23155-0170-XX ZOLEDRONIC ACID 4MG/5ML Solution (Heritage Pharmaceuticals)
25021-0801-XX ZOLEDRONIC ACID 4MG/5ML Solution (Sagent Pharmaceutical)
25021-0826-XX ZOLEDRONIC ACID 4MG/100ML Solution (NovaPlus/Sagent Pharmaceutical)
25021-0826-XX ZOLEDRONIC ACID 4MG/100ML Solution (Sagent Pharmaceutical)
25021-0830-XX ZOLEDRONIC ACID 5MG/100ML Solution (Sagent Pharmaceutical)
43598-0330-XX ZOLEDRONIC ACID 4MG/5ML Solution (NovaPlus/Dr. Reddy's)
43598-0331-XX ZOLEDRONIC ACID 5MG/100ML Solution (Dr. Reddy's Lab)
50742-0416-XX ZOLEDRONIC ACID 4MG/5ML Solution (Ingenus Pharmaceuticals)
51991-0064-XX ZOLEDRONIC ACID 5MG/100ML Solution (Breckenridge)
51991-0065-XX ZOLEDRONIC ACID 4MG/5ML Solution (Breckenridge)
54288-0100-XX ZOLEDRONIC ACID 4MG/5ML Solution (BPI Labs LLC)
55111-0685-XX ZOLEDRONIC ACID 4MG/5ML Solution (Dr. Reddy's Laboratories Inc.)
55111-0688-XX ZOLEDRONIC ACID 5MG/100ML Solution (Dr. Reddy's Lab)
55150-0266-XX ZOLEDRONIC ACID 4MG/5ML Solution (Auromedics Pharma)
63323-0961-XX ZOLEDRONIC ACID 4MG/5ML Solution (Fresenius KABI USA)
63323-0966-XX ZOLEDRONIC ACID 5MG/100ML Solution (Fresenius KABI USA)
67457-0390-XX ZOLEDRONIC ACID 4MG/5ML Solution (Mylan Institutional)
67457-0619-XX ZOLEDRONIC ACID 5MG/100ML Solution (Mylan Institutional)
67457-0794-XX ZOLEDRONIC ACID 5MG/100ML Solution (Mylan Institutional)
67457-0920-XX ZOLEDRONIC ACID 4MG/5ML Concentrate (NOVAPLUS/MYLAN INSTITUTIONAL)
68001-0437-XX ZOLEDRONIC ACID 4MG/5ML Solution (BLUE POINT LABORATORIES)
70860-0210-XX ZOLEDRONIC ACID 4MG/100ML Solution (Athenex Pharmaceutical)
70860-0802-XX ZOLEDRONIC ACID 5MG/100ML Solution (Athenex Pharmaceutical)

DESCRIPTION

Zoledronic acid is a bisphosphonate which inhibits osteoclast-mediated bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action:

Bisphosphonates show selective action on bone due to their high affinity for mineralized bone. Zoledronic acid is drawn to bone in areas of high bone turnover where its main target is the osteoclast. It binds to mineralized bone targeting the osteoclast. Within the osteoclast it inhibits the action of the enzyme farnesyl pyrophosphate synthase, resulting in disruption of the osteoclast cytoskeleton and cell death. This action prevents the increased osteoclastic activity and accompanying skeletal calcium release of certain tumors and other conditions.

POLICY

- Zoledronic acid is considered ***medically necessary*** for the treatment/prevention of the following if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  Aromatase inhibitor-associated bone loss (AIBL)

Bone metastases
Hypercalcemia
Multiple myeloma
Osteopenia/Osteoporosis
Paget's disease (osteitis deformans)
Langerhans Cell Histiocytosis

- Zoledronic acid for the treatment/prevention of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

- Reclast/Zometa should not be used in combination with one another, other bisphosphonates, denosumab, romosozumab, or parathyroid hormone analogs/related peptides; **AND**
- Patient does not have hypocalcemia (supplement adequately with calcium and vitamin D); **AND**

Zometa

- Patient must have a CrCl ≥ 30 mL/min; **AND**

Hypercalcemia of malignancy

Multiple myeloma

Bone metastases from solid tumors (in conjunction with standard antineoplastic therapy)

Prevention of skeletal related events in men with castration-recurrent prostate cancer

Prevention of bone loss associated with aromatase inhibitor therapy for breast cancer in postmenopausal women or premenopausal women on adjuvant ovarian suppression

Prevention of bone loss associated with androgen deprivation therapy in men with prostate cancer

Treatment of osteopenia/osteoporosis in patients with systemic mastocytosis

Langerhans Cell Histiocytosis

Reclast

- Patient must have a CrCl ≥ 35 mL/min and no evidence of acute renal impairment; **AND**

Treatment and prevention of postmenopausal osteoporosis

- 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

Note: patients discontinuing treatment with denosumab due to a reduction in fracture risk (i.e., no longer high or very high risk) require subsequent antiresorptive therapy in order to prevent accelerated bone mineral density loss

*and increase in fracture risk. **One** administration is allowed for this use prior to temporary discontinuation of intravenous antiresorptive therapy.*

Treatment to increase bone mass in men with osteoporosis

- 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

- 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

- 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

Prevention or treatment of osteoporosis in men with prostate cancer during androgen deprivation therapy

±Ineffective response defined as one or more of the following:
• Decrease in T-score in comparison with baseline T-score from DXA scan • Patient has a new fracture while on bisphosphonate therapy
***Examples of contraindications to oral bisphosphonate therapy include the following:**
• Documented inability to sit or stand upright for at least 30 minutes • Documented pre-existing gastrointestinal disorder such as inability to swallow, Barrett's esophagus, esophageal stricture, dysmotility, or achalasia

RENEWAL 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 (e.g., renal toxicity, osteonecrosis of the jaw, atypical femoral fractures, hypocalcemia, incapacitating pain in the bone/joint/muscle, etc.); **AND**

Reclast

- Disease response as indicated by the following:
  - 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 reevaluated 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: normalization of serum alkaline phosphatase (SAP) or a reduction of ≥ 75% from baseline in total SAP excess (defined as the difference between the measured level and midpoint of normal range)

Zometa

- Disease response as indicated by the following:
  - Bone metastases/MM: absence/delay in skeletal-related events (e.g., pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)
  - Hypercalcemia of Malignancy: corrected serum calcium ≤ 11.5 mg/dL
  - Prevention of bone loss/SRE in cancer patients/Osteoporosis or Osteopenia in Systemic Mastocytosis:
    - Absence of fractures; **OR**
    - Increase in bone mineral density compared to pretreatment baseline;
  - Langerhans Cell Histiocytosis:
    - Improvement in bone pain; OR
    - Improvement/resolution in active bone lesions compared to pretreatment baseline

DOSAGE/ADMINISTRATION

Zometa:

INDICATION	DOSE
Hypercalcemia of malignancy	4 mg IV x 1 dose, may be repeated after 7 days if serum calcium does not return to normal
Prevention of aromatase inhibitor-induced bone loss in breast cancer	4 mg IV every 6 months
Prevention of androgen deprivation-induced bone loss in prostate cancer	4 mg IV every 3 months
Multiple myeloma & bone metastases from solid tumors	4 mg IV every 3 to 4 weeks **OR** 4 mg every 12 weeks
Treatment of osteopenia/osteoporosis in systemic mastocytosis	4 mg IV every 3 to 4 weeks
Langerhans Cell Histiocytosis	4 mg IV every month

*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:

INDICATION	DOSE
Active Paget's Disease	5 mg IV x 1 dose
Prevention of osteoporosis in post-menopausal women	5 mg IV every 2 years
Prevention of glucocorticoid-induced osteoporosis	5 mg IV every year
Treatment of osteoporosis	5 mg IV every year

Prevention of androgen deprivation-induced bone loss in prostate cancer	5 mg IV every year

LENGTH OF AUTHORIZATION

Zometa:

- Coverage is provided for 12 months and may be renewed.

Reclast:

- 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 (unless otherwise specified).

DOSING LIMITS

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

Zometa	
Indication	**Max Units**
Hypercalcemia of malignancy	4 billable units per 7 days
Multiple myeloma, bone metastases from solid tumors, & osteopenia/osteoporosis in systemic mastocytosis	4 billable units every 21 days
Prevention of bone loss in breast cancer	4 billable units every 168 days (6 months)
Prevention of bone loss in prostate cancer & Prevention or treatment of osteoporosis in prostate cancer	4 billable units every 84 days (3 months)
Langerhans Cell Histiocytosis	4 billable units every 28 days
Reclast	
Indication	**Max Units**
Prevention of osteoporosis in postmenopausal women	5 billable units every 730 days (24 months)
All other indications	5 billable units every 365 days (12 months)

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

1. Zometa [package insert]. Stein, Switzerland; Novartis Pharmaceuticals; December 2018. Accessed February 2021. (obsolete)
2. Reclast [package insert]. East Hanover, NJ; Novartis Pharmaceuticals; April 2020. Accessed February 2021.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Zoledronic Acid. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed February 2021.
4. Berenson JR, Boccia R, Lopez T, et al. Results of a Multicenter Open-Label Randomized Trial Evaluating Infusion Duration of Zoledronic Acid in Multiple Myeloma Patients (the ZMAX Trial). J Support Oncol. 2011;9(1):32-40.
5. Black DM, Delmas PD, Eastell R, et al. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. New Engl J Med. 2007;356(18):1809-1822.
6. Eidtmann H, de Boer R, Bundred N, et al. Efficacy of Zoledronic Acid in Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole: 36-Month Results of the ZO-FAST Study. Ann Oncol. 2010;21(11):2188-2194.
7. McClung M, Miller P, Recknor C, et al. Zoledronic Acid for the Prevention of Bone Loss in Postmenopausal Women With Low Bone Mass: A Randomized Controlled Trial. Obstet Gynecol. 2009;114(5):999-1007.
8. Michaelson MD, Kaufman DS, Lee H, et al. Randomized Controlled Trial of Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Agonist-Induced Bone Loss in Men With Prostate Cancer. J Clin Oncol. 2007;25(9):1038-1042.
9. Reid DM, Devogelaer JP, Saag K, et al. Zoledronic Acid and Risedronate in the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (HORIZON): A Multicentre, Double-Blind, Double-Dummy, Randomised Controlled Trial. Lancet. 2009;373(9671):1253-1263.
10. Smith MR, Eastham J, Gleason DM, et al. Randomized Controlled Trial of Zoledronic Acid to Prevent Bone Loss in Men Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer. J Urol. 2003;169(6):2008-2012.
11. Bhoopalam, N. et al. Intravenous zoledronic acid to prevent osteoporosis in a veteran population with multiple risk factors for bone loss on androgen deprivation therapy. J Urol. 2009 Nov;182(5):2257-64. Epub 2009 Sep 16.
12. Bundred, N.J. et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer. 2008 Mar 1;112(5):1001-10.
13. Brufsky A, Harker WG, Beck JT, et al, “Zoledronic Acid Inhibits Adjuvant Letrozole-Induced Bone Loss in Postmenopausal Women With Early Breast Cancer,” J Clin Oncol 2007, 25(7):829-36.
14. Himelstein AL, Qin R, Novotny PJ, et al. “CALBG 70604 (Alliance): A randomized phase III study of standard dosing vs longer interval dosing of zoledronic acid in metastatic cancer. J Clin Oncol 33, 2015 (suppl; abstr 9501).
15. WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and management of osteoporosis: report of a WHO scientific group. (WHO technical report series; 921). Geneva, Switzerland: WHO; 2000.

16. Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health care level. Technical Report. World Health Organization Collaborating Center for Metabolic Bone Diseases. University of Sheffield, UK; 2007.
17. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014.
18. Camacho PM, Petak SM, Binkley N, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016. Endocr Pract. 2016 Sep ; 22(Suppl 4):1-42.
19. Hortobagyi GN, Van Poznak C, Harker WG, et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol. 2017 Jan 26. doi: 10.1001/jamaoncol.2016.6316.
20. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 2017 Jan 3;317(1):48-58. doi: 10.1001/jama.2016.19425.
21. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. DOI: 10.1200/JCO.2016.70.7257 Journal of Clinical Oncology - published online before print March 6, 2017.
22. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. J Bone Oncol. 2017 Mar 23;7:1-12
23. Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians. Ann Intern Med. 2017 May 9. doi: 10.7326/M15-1361.
24. Jeremiah MP, Unwin BK, Greenawald MH, et al. Diagnosis and Management of Osteoporosis. Am Fam Physician. 2015 Aug 15;92(4):261-8.
25. Eastell R, Rosen CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. J Clin Endo Metab, Vol 104, Iss 5, May 2019, pps 1595–1622, https://doi.org/10.1210/jc.2019-00221.
26. Rossini M, Zanotti R, Viapiana O, et al. Zoledronic acid in osteoporosis secondary to mastocytosis. Am J Med. 2014 Nov;127(11):1127.e1-4.
27. Chellapandian d, Makras P, Kaltsas G, et al. Bisphosphonates in Langerhans Cell Histiocytosis: An International Retrospective Case Series. Mediterr J Hematol Infect Dis. 2016 Jul 1;8(1):e2016033. doi: 10.4084/MJHID.2016.033. eCollection 2016
28. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Systemic Mastocytosis 1.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
29. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Histiocytic Neoplasms 1.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network,
30. Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
31. Lexi-Comp Online. (2021, February). AHFS DI. *Zoledronic acid*. Retrieved April 15, 2021 from Lexi-Comp Online with AHFS.
32. MICROMEDEX Healthcare Series. Drugdex Drug Evaluations. (2020, October). *Zoledronic acid*. Retrieved April 15, 2021 from MICROMEDEX Healthcare Series.

BlueCross BlueShield of Tennessee

Policy

Medical Policy Manual **Approved Revision: Do Not Implement until 8/31/21**

EFFECTIVE DATE 8/31/2021

ID_MRx