MEDICAL POLICY

POLICY TITLE	ZOLEDRONIC ACID (RECLAST®, ZOMETA®)
POLICY NUMBER	MP-2.143

Original Issue Date (Created):	**11/1/2008**
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Effective Date:	**8/1/2020**

I. POLICY

Zoledronic acid (Reclast®) injection is approved by the U.S. Food and Drug Administration (FDA) for the following indications:

- Treatment of osteoporosis in postmenopausal women.
- Prevention of osteoporosis in postmenopausal women.
- Treatment to increase bone mass in men with osteoporosis.
- Treatment and prevention of glucocorticoid-induced osteoporosis in patients.
- Treatment of Paget's disease of bone in men and women.

Zoledronic acid (Zometa®) injection is approved by the U.S. Food and Drug Administration (FDA) for the following indications:

- Hypercalcemia of malignancy
- Patients with multiple myeloma and 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.

Zoledronic acid (Reclast®) and Zometa® **are not indicated** for use in pediatric patients.

Prevention and Treatment of Osteoporosis

Zoledronic Acid (Reclast®) may be considered **medically necessary** in patients who cannot tolerate or are unresponsive to oral osteoporosis agents, are receiving supplemental calcium and vitamin D and any **ONE** of the following indications:

- Prevention of osteoporosis in postmenopausal women with osteopenia*.
- Treatment of osteoporosis** in postmenopausal women.
- Prevention of new clinical fractures for patients with a recent low-trauma hip fracture.
- Treatment to increase bone mass in men with osteoporosis**.
- Treatment and prevention of glucocorticoid osteoporosis in patients who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and are expected to be on glucocorticoids for at least 12 months.

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*Osteopenia is defined as a bone mineral density (BMD) T-score between [-1] and [-2.5] at the femoral neck or spine.

**Osteoporosis is defined as a BMD T score of [-2.5] or less at the femoral neck or spine after appropriate evaluation to exclude secondary causes.

NOTE: The inability to swallow tablets is **not a medically necessary indication** for injectable bisphosphonates as alternative preparations of oral bisphosphonates are available (e.g. liquid alendronate).

Treatment of Paget's Disease of Bone

Zoledronic Acid (Reclast®) may be considered **medically necessary** in patients with Paget's disease of bone for the following indications:

- The patient has elevations of serum alkaline phosphotase two times or higher than the upper limit of the age-specific normal reference range.
- The patient is symptomatic from active bone lesions.
- The patient is at risk for complications from their disease.

Retreatment for Paget's disease of the Bone:

Specific retreatment data are not available. However, a second course of therapy of zoledronic acid (Reclast®) may be considered **medically necessar**y for retreatment of Paget's disease of the bone for patients who have relapsed based on increased serum alkaline phosphatase, failure to achieve normalization of serum alkaline phosphatase, or in those with symptoms, as dictated by medical practice.

Treatment of Cancer Related Conditions

Zoledronic acid (Zometa®) may be considered **medically necessary** for any of the following indications:

- Hypercalcemia of malignancy (FDA defines hypercalcemia as an albumin-corrected calcium (cCa) of >12mg/dL [3.0mmol/L] using the formula: cCa in mg/dL + 0.8 (mid-range of measured albumin in mg/dL)
- Multiple Myeloma (in conjunction with standard antineoplastic therapy)
- Bone Metastases from solid tumors (in conjunction with standard antineoplastic therapy):
  - Prostate cancer (if cancer has progressed after treatment with at least one hormonal therapy)
  - Other solid tumor types

Retreatment for Cancer Related Conditions

Retreatment with zoledronic acid (Zometa®) 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to initial dose.

Treatment of Hypercalcemia Associated with Hyperparathyroidism
The safety and efficacy of zoledronic acid (Zometa®) in the treatment of hypercalcemia associated hyperparathyroidism or with other nontumor-related conditions has not been established.

The use of zoledronic acid (Reclast®, Zometa®) for non-FDA approved indications is considered **investigational**, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.
Note: For patients with late stage metastatic disease (Stage IV), please refer to MP 2.373 Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions for additional guidance

Cross-reference:

MP 2.373 - Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO: Refer to FEP Benefit Brochure for information on Specialty Drugs: https://www.fepblue.org/benefit-plans/benefit-plans-brochures-and-forms

Note The Federal Employee Program (FEP) Service Benefit Plan does not have a medical policy related to these services..

Note for Medicare Advantage:

1. FDA approved drugs used for indications other than what is indicated on the FDA approved product label may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the Medicare recognized national drug compendia, authoritative medical literature and/or accepted standards of medical practice. Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2-Unlabeled Use of Drug). *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*
2. In accordance with CMS letter issued on September 17, 2012, entitled "Prohibition on Imposing Mandatory Step Therapy for Access to Part B Drugs and Services." Step

therapy that is not part of the FDA label does not apply to Medicare Advantage Members.

III. DESCRIPTION/BACKGROUND

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Bisphosphonates

Bisphosphonates are used to treat osteoporosis and to prevent damaging changes to the bone caused by Paget's disease of the bone and bone metastases. Bisphosphonates suppress bone resorption and are the most widely used class of drugs to treat osteoporosis. Bisphosphonates may also be used for osteoporosis prevention.

Oral bisphosphonates such as Alendronate (Fosamax®) and Risedronate (Actonel®) are available in daily or weekly dosages. Ibandronate (Boniva®), another type of bisphosphonate, is available in an oral form for daily or monthly dosing. Oral bisphosphonates can cause gastrointestinal disorders and patients must remain upright for thirty minutes (Alendronate and Risedronate) or sixty minutes (Ibandronate) after swallowing the tablet whole with plain water on an empty stomach. Alendronate is also available as an oral liquid for individuals who have difficulty swallowing tablets. Injectable bisphosphonates provide an alternative for individuals who have difficulty with the dosing requirements of oral bisphosphonates.

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft and most commonly occur with minimal or no impact to the affected areas. They may be bilateral and many patients report prodromal pain in the affected areas, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of the fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Emerging evidence has also indicated a link between bisphosphonates and a rare but serious complication, osteonecrosis of the jaw. This may be more likely to occur after oral surgery.

Osteoporosis

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip and wrist. The diagnosis can be confirmed by a finding of low bone mass or by the presence or history of osteoporotic fractures. Osteoporosis is most common among post- menopausal women but can occur in men as well. Long-term glucocorticoid therapy can also lead to osteoporosis.

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Bone mineral density (BMD) is one of the key determinants for the need for drug therapy and may be classified according to the T score. A T score is the comparison of an individual's bone density to the optimal peak bone density for the individual's gender. It is reported as number of standard deviations (SD) below the average. The World Health Organization (WHO) defines osteoporosis as spine, hip, or wrist bone mineral density (BMD) 2.5 SD or more below the young adult mean (T score of [-2.5] or less). Osteopenia is a condition where bone mineral density is lower than normal but not as low as osteoporosis. It is defined as a T score between [-1.0 and -2.5].

Dual Energy X-ray Absorptiometry (DEXA) is the most commonly used technique to measure BMD. The margin of error of repeated DEXA tests is 3-5% and the average person will not have a change of this magnitude over a 3-5 year period. Also, DEXA result norms are established for each individual machine and therefore, repeat testing on another machine is not directly comparable.

Paget's Disease of the Bone

Paget's disease of the bone (osteitis deformans) is a chronic disease of the bone characterized by excessive osteoclastic bone resorption followed by excessive bone formation. Affected bones are thick but structurally weak and prone to fractures or deformity. Paget's disease occurs most frequently in the spine, skull, pelvis and bones of the lower extremities. One or more bones may be affected. Paget's disease is rarely diagnosed in people less than 40 years of age. Oral agents for the treatment of Paget's disease of the bone include Alendronate (Fosamax®) and Risedronate (Actonel®).

Cancer-Related Bone Conditions

Bone metastasis can cause bone to wear away leaving small holes called osteolytic bone lesions, and can cause abnormal weak and unstable bone formation called osteoblastic bone lesions. Common areas of metastasis include the spine, pelvis, hip, femur, and skull. Affected bones are prone to fracture resulting in pain and decreased mobility. Vertebral fractures can cause spinal cord compression and subsequent paralysis. Hypercalcemia, a late complication of cancer, can cause nausea and vomiting, dehydration, coma, and death. Bisphosphonates can also reduce blood calcium levels by preventing release of calcium from the bones.

Zoledronic Acid (Reclast®, Zometa®)

Zoledronic acid is an injectable bisphosphonate available in two different brands (zoledronic acid (Reclast®) and Zometa®) in single dose vials with doses specific to the approved indications. FDA approved indications for zoledronic acid (Reclast®) includes Paget's disease of the bone and treatment and prevention of osteoporosis. FDA approved indications for zoledronic acid (Zometa®) include treatment of hypercalcemia of malignancy (HCM) and treatment of patients with multiple myeloma or documented bone metastases from solid tumors in conjunction with standard antineoplastic therapy.

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Zoledronic acid in the brand form of zoledronic acid (Zometa®) is FDA approved only for cancer-related indications.

See the prescribing information for safety precautions, dosing and administration recommendations.

IV. RATIONALE

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For information on clinical studies for zoledronic acid (Reclast®) and (Zometa®) refer to the Prescribing Information.

V. DEFINITIONS

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ALKALINE PHOSPHATASE is an enzyme present in all tissues and in high concentration in bone, kidneys, intestines, biliary ducts, plasma, and teeth. It may be elevated in serum in some diseases of the bone and liver and some other illnesses. The normal adult value is 20 to 140 IU/L (international units per liter).

ANTINEOPLASTIC AGENTS are substances that inhibit or prevent the growth of neoplasms.

BONE RESORPTION is bone loss due to osteoclastic activity.

FRACTURE is a traumatic injury to a bone in which the continuity of the bone tissue is broken.

GLUCOCORTICOIDS are hormones that predominantly affect the metabolism of carbohydrates and, to a lesser extent, fats and proteins (and have other effects). Glucocorticoids are made in the outside portion (the cortex) of the adrenal gland and chemically classed as steroids. Cortisol is the major natural glucocorticoid. The term glucocorticoid also applies to equivalent hormones synthesized in the laboratory (e.g. prednisone).

HYPOGONADISM is the inadequate production of sex hormones.

MENOPAUSE IS the cessation of menses.

MORPHOMETRIC FRACTURE is a fracture identified by a change in the shape of a bone, rather than from pain or other symptoms.

MYELOMA is a malignant tumor composed of plasma cells of the type normally found in the bone marrow.

OFF-LABEL USE is the use of a prescription drug or medical device in the treatment of an illness or injury for which it has not been specifically approved by the FDA.

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OSTEOCLASTIC refers to osteoclasts, especially with reference to their activity in the absorption and removal of osseous (bone) tissue.

OSTEOCLASTS are large multinucleated cells formed from differentiated macrophages that are responsible for the breakdown of bone.

OSTEONECROSIS is the death of a segment of bone usually caused by insufficient blood flow to a region of the skeleton.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

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Covered when Medically Necessary:

HCPCS Code	Description
J3489	Injection, zoledronic acid, 1 mg

ICD-10-CM Diagnosis Codes	Description
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
E83.52	Hypercalcemia
M80.0	Age-related osteoporosis with current pathological fracture
M81.0	Age-related osteoporosis without current pathological fracture
M81.6	Localized osteoporosis [Lequesne]
M81.8	Other osteoporosis without current pathological fracture
M85.80	Other specified disorders of bone density and structure
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
M85.861	Other specified disorders of bone density and structure, right lower leg
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
M85.88	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
M88.821	Osteitis deformans of right upper arm
M88.822	Osteitis deformans of left upper arm
M88.831	Osteitis deformans of right forearm
M88.832	Osteitis deformans of left forearm
M88.841	Osteitis deformans of right hand
M88.842	Osteitis deformans of left hand
M88.851	Osteitis deformans of right thigh

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ICD-10-CM Diagnosis Codes	Description
M88.852	Osteitis deformans of left thigh
M88.861	Osteitis deformans of right lower leg
M88.862	Osteitis deformans of left lower leg
M88.871	Osteitis deformans of right ankle and foot
M88.872	Osteitis deformans of left ankle and foot
M88.88	Osteitis deformans of other bones
M88.89	Osteitis deformans of multiple sites
M88.9	Osteitis deformans of unspecified bone
R74.8	Abnormal levels of other serum enzymes
Z51.11	Encounter for antineoplastic chemotherapy
Z51.12	Encounter for antineoplastic immunotherapy
Z79.52	Long term (current) use of systemic steroids
Z87.310	Personal history of (healed) osteoporosis fracture
Z87.311	Personal history of (healed) other pathological fracture

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.143	**CAC 1/26/10 New policy.** Created a separate policy for Zoledronic Acid from the previous Injectable Bisphosphonate policy. Added new medical necessity criteria for the prevention of postmenopausal osteoporosis due to expanded FDA indications for Reclast®.
	CAC 1/25/11 Full review
	4/2012 Consensus review. Changed policy to be consistent with change in prescribing information. (Deleted the statement "expected to be on glucocorticoids for at least 12 months" in the indication for glucocorticoid-induced osteoporosis but criteria remains in the consideration for coverage section)
	CAC 6/4/13 Consensus review. List review. Administrative code review complete.
	12/19/2013 Admin update. New 2014 Code updates made.

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	CAC 3/25/14 Consensus review. No change to policy statements. References updated. Rationale section added.
	7/1/14 Admin update. Deleted notation regarding preauthorization requirement. All Users should refer to officially posted preauthorization resources for requirements.
	CAC 3/24/15 Consensus review. No changes to the policy statements. References updated. Medicare variation revised to address step-therapy for Reclast and use of off-label indications for both Reclast and Zometa. Coding reviewed.
	CAC 11/24/15 Minor review. For Paget's disease – removed requirement for trial of oral agents prior to administration of Zoledronic Acid (Reclast®). Other statements unchanged. Updated references. Reviewed rationale. Coding reviewed.
	CAC 11/29/16 Consensus review. Policy statements unchanged. Variation reformatting completed. References updated. Coding reviewed/updated.
	11/13/17 Consensus review. No change to policy statements. Rationale and references reviewed.
	8/3/18 Consensus review. No change to policy statements. Rationale changed – to refer to prescribing information. References updated.
	05/29/2019 Consensus review. No change to policy statements. References updated.
	09/09/2019 Admin update. Code review. Unspecified dx added. Effective 10/1/2019.
	4/10/2020 Admin update. Added note for patients with late stage metastatic disease (Stage IV), please refer to MP 2.373 Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions for additional guidance
	5/16/2020 Consensus review. Policy statement unchanged. References updated. Coding reviewed.

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