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Policy Number: C16790-A

Intravenous Bisphosphonates

PRODUCTS AFFECTED

Boniva (ibandronate) SOLN, pamidronate Inj, Reclast (zoledronic acid), Zometa (zoledronic acid), zoledronic acid, ibandronate SOLN

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive

DIAGNOSIS:
See FDA and compendial approved off-labeled uses

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. OSTEOPOROSIS AND OSTEOPOROSIS PROPHYLAXIS:
1. Documented diagnosis of ANY of the following (i) postmenopausal osteoporosis in women, (ii) postmenopausal woman at risk for a fracture, (iii) osteoporosis in men or (iv) man being treated with androgen deprivation therapy for metastatic prostate cancer requiring prophylaxis therapy for osteoporosis [Zometa or generic equivalent only], (v) osteoporosis prevention in

postmenopausal women taking aromatase inhibitors for breast cancer [Zometa or generic equivalent only], (vi) osteoporosis prevention for members taking prednisone or its equivalent at a dose of > 5 mg/day for at least 3 months
AND

2. Prescriber attests that member has been counseled to concurrently take calcium (1000 mg) and vitamin D (400-1200 international units) supplements in conjunction with bisphosphonate therapy
AND
3. Any of the following criteria are met: Member has a diagnosis of esophageal stricture, achalasia, or other severe esophageal dysmotility disorder; OR Member has a history of severe malabsorption making use of oral bisphosphonates ineffective; OR Member has an inability to stand or sit upright for 60 minutes; OR Member has tried and is intolerant to two (2) or more oral bisphosphonates.
AND
4. Prescriber attests that member will be evaluated and monitored following the FDA labeled monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.
AND
5. FOR IBANDRONATE: Member has a diagnosis of osteoporosis AND Prescriber attests to a trial and failure or labeled contraindication of Reclast (zoledronic acid SOLN 5MG/100ML)

B. FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS ONLY:

1. Request is for ibandronate (Boniva) or zoledronic acid (Reclast)
AND
2. Documentation of history of prednisone or its equivalent at a dose of > 5 mg/day for > 3 months
AND
3. (a) The member has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist)
OR
(b) The member has had an osteoporotic fracture or a fragility fracture of the spine, hip, proximal humerus, pelvis, or distal forearm
OR
(c) Fracture Risk Assessment Tool (FRAX) (GC-adjusted) 10-year risk of major osteoporotic fracture score of 20% or greater OR FRAX (GC-adjusted) 10-year risk of hip fracture score of 3% or greater indicating member is at high risk for fracture
AND
4. Documentation of a trial and failure of one oral generic bisphosphonate therapy, unless contraindicated or intolerant.
AND
5. Prescriber attests that member will be evaluated and monitored following the FDA labeled monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.
AND
6. FOR IBANDRONATE: Prescriber attestation of a trial and failure or labeled contraindication of Reclast (zoledronic acid SOLN 5MG/100ML).

C. BONE METASTASES AND MULTIPLE MYELOMA:

1. Request is for pamidronate, ibandronate (Boniva) or zoledronic acid (Zometa)
AND
2. Documented diagnosis of bone metastases from a solid tumor or multiple myeloma
AND
3. Prescriber attests that member will be evaluated and monitored following the FDA labeled

monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment. In patients with multiple myeloma; Monitor serum creatinine (prior to each dose), serum calcium (regularly); vitamin D levels (intermittently), spot urine sample for albuminuria (every 3 to 6 months; for unexplained albuminuria, obtain 24 urine collection to assess urinary albumin; reassess every 3 to 4 weeks with 24-hour urine collection for total protein and urine protein electrophoresis until renal function returns to baseline)
AND

4. Dose requested aligns with manufacturer recommendation based on creatinine clearance (see Appendix)
AND
5. FOR PAMIDRONATE: Prescriber attestation of a trial and failure or labeled contraindication of Zometa (zoledronic acid 4 mg)
AND
6. FOR IBANDRONATE: Diagnosis of breast cancer and prescriber attestation of a trial and failure or labeled contraindication of Zometa (zoledronic acid 4 mg).

D. HYPERCALCEMIA OF MALIGNANCY:

1. Request is for pamidronate or zoledronic acid (Zometa)
AND
2. Documented serum creatinine, calcium, and albumin level dated within the past 90 days along with height and weight to calculate creatinine clearance
Hypercalcemia = [total albumin-corrected calcium >12 mg/dL [3 mmol/L] or serum ionized calcium > 8 mg/dL [2 mmol/L])
AND
3. Dose requested aligns with manufacturer recommendation based on creatinine clearance (see Appendix)
AND
4. FOR PAMIDRONATE: Prescriber attestation of a trial and failure or labeled contraindication of Zometa (zoledronic acid 4 mg)

E. PAGET'S DISEASE:

1. Documented diagnosis of Paget’s disease
AND
2. Request is for pamidronate or zoledronic acid (Reclast)
AND
3. Prescriber attests that member will be evaluated and monitored following the FDA labeled monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.
AND
4. Dose requested aligns with manufacturer recommendation based on creatinine clearance (see Appendix)
AND
5. FOR PAMIDRONATE: Prescriber attestation of a trial and failure or labeled contraindication of Reclast (zoledronic acid SOLN 5MG/100ML)

F. OSTEOGENESIS IMPERFECTA:

1. Documentation of a diagnosis of osteogenesis imperfecta.
AND
2. Request is for pamidronate.
AND
3. Prescriber attests that member will be evaluated and monitored following the FDA labeled

monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.

E. HYPERCALCEMIA ASSOCIATED WITH PRIMARY HYPERPARATHYROIDISM OR ENDSTAGE RENAL FAILURE, (INCLUDING MEMBERS WITH SECONDARY HYPERPARATHYROIDISM)

1. Documented diagnosis hypercalcemia associated with of one (1) of the following: (i) primary hyperparathyroidism or (ii) End Stage Renal Failure
   AND
2. Request is for pamidronate
   AND
3. Prescriber attests that member will be evaluated and monitored following the FDA labeled monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.
   AND
4. Provider attests that member has been unable to reduce serum calcium with standard care (e.g., restricting calcium-based binders, calcitriol or vitamin D analogs, or the use of calcimedins.)

CONTINUATION OF THERAPY:

A. ALL INDICATIONS:

1. Chart notes showing member's positive response to therapy or stabilization of disease
   AND
2. Prescriber attests that member will continue to be evaluated and monitored following the FDA labeled monitoring recommendations; Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment. In patients with multiple myeloma; Monitor serum creatinine (prior to each dose), serum calcium (regularly); vitamin D levels (intermittently), spot urine sample for albuminuria (every 3 to 6months; for unexplained albuminuria, obtain 24 urine collection to assess urinary albumin; reassess every 3 to 4 weeks with 24-hour urine collection for total protein and urine protein electrophoresis until renal function returns to baseline)
   AND
3. FOR OSTEOPOROSIS INDICATIONS – prescriber attests to monitoring the bone mineral density every 1 – 3 years.

DURATION OF APPROVAL:

Bone metastases and multiple myeloma: Initial authorization: 6 months, Continuation of Therapy:12 months
Hypercalcemia: Initial authorization: Up to 3 months, Continuation of Therapy: up to 3 months
Osteoporosis, Osteogenesis Imperfecta, and Paget's Disease- Initial authorization: 1 year, Continuation of Therapy: for up to 1year

PRESCRIBER REQUIREMENTS:

Osteoporosis: No requirements
All other indications: Prescribed by, or in consultation with, a board-certified endocrinologist, oncologist, or another applicable specialist.

Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

AGE RESTRICTIONS:

Osteogenesis imperfecta: no limit**.**

All other indications: 18 years of age and older

QUANTITY:
Bone Metastasis and Multiple Myeloma:
Boniva or generic equivalent (ibrandronate): 6 mg IV every 3 to 4 weeks
Pamidronate: 90 mg IV once every 3 to 4 weeks
Zometa or generic equivalent: 4 mg IV every 3 to 4 weeks or every 12 weeks

Hypercalcemia of Malignancy
Pamidronate: 60 mg or 90 mg IV infusion as a single dose, minimum of 7 days before retreatment
Zometa or generic equivalent: 4 mg IV as single dose, minimum of 7 days before retreatment

Osteogenesis Imperfecta:
Pamidronate: 3 mg/kg/cycle, repeated every 4 to 6 months

Paget's Disease:
Reclast or generic equivalent: 5 mg IV as a single dose
Pamidronate: 30mg IV once daily for 3 days

Treatment or Prevention of Glucocorticoid Induced
Osteoporosis: Boniva or generic equivalent (treatment): 2 mg IV every 3 months
Reclast or generic equivalent: 5mg IV x 1 dose for 1 year

Treatment and Prevention of Osteoporosis:
Boniva or generic equivalent (treatment): 3 mg IV every 3 months
Reclast or generic equivalent: 5mg IV x 1 dose for 1 year
Zometa or generic equivalent for prevention due to androgen deprivation: 4 mg every 3 to 6 months
Zometa or generic equivalent for prevention due to aromatase inhibitors: 4 mg every 6 months

Hypercalcemia due to Hyperparathyroidism:
Pamidronate: 15 to 90 mg as a single dose

Maximum Quantity Limits – Per FDA Label for product

PLACE OF ADMINISTRATION:
Boniva (ibandronate) and Reclast (zoledronic acid):
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.
Pamidronate and Zometa (zoledronic acid):
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

Note: Site of Care Utilization Management Policy applies for Boniva (ibandronate) and Reclast (zoledronic acid). For information on site of care, see
Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous Infusion

DRUG CLASS:
Bisphosphonate derivative

FDA-APPROVED USES:
Boniva (ibandronate): Indicated for the treatment and prevention of postmenopausal osteoporosis.

Pamidronate: Indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases, members with moderate to severe Paget's disease of bone, osteolytic bone metastases of breast cancer or osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy *Limitations of use*
Safety and efficacy of pamidronate disodium in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor related conditions have not been established

Reclast (zoledronic acid): indicated for: Treatment and prevention of postmenopausal osteoporosis, Treatment to increase bone mass in men with osteoporosis, Treatment and prevention of glucocorticoid-induced osteoporosis, Treatment of Paget's disease of bone in men and women *Limitations of Use*
Optimal duration of use has not been determined. For members at low risk for fracture, consider drug discontinuation after 3 to 5 years of use

Zometa (zoledronic acid): indicated for the treatment of; Hypercalcemia of malignancy, with multiple myeloma and members 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.
Important limitation of use: The safety and efficacy of Zometa has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia.

COMPENDIAL APPROVED OFF-LABELED USES:
Boniva (ibandronate): For the treatment of hypercalcemia of malignancy, For the prevention of adverse skeletal events due to bone metastases† in selected cancer patients (e.g., breast cancer)
Pamidronate: For hypercalcemia associated with primary hyperparathyroidism, or hypercalcemia associated with end-stage renal failure including members with secondary hyperparathyroidism, For the treatment of osteogenesis imperfecta
Reclast (zoledronic acid): NA
Zometa (zoledronic acid): for osteoporosis prevention in postmenopausal women taking letrozole for early breast cancer, for osteoporosis prevention in men with prostate cancer receiving androgen deprivation therapy, For the adjuvant treatment of early breast cancer in women with postmenopausal reproductive hormone levels

APPENDIX

APPENDIX:
Renal Impairment dosage adjustments for Multiple Myeloma or Bone Metastases of Solid Tumors Indications:
NOTE: Zoledronic acid is not recommended in patients with bone metastases who have severe renal impairment; patients with SCr > 3 mg/dl were excluded from clinical trials.
CrCl > 60 ml/min: No dosage adjustment needed
CrCl 50—60 ml/min: Reduce dose to 3.5 mg IV
CrCl 40—49 ml/min: Reduce dose to 3.3 mg IV
CrCl 30—39 ml/min: Reduce dose to 3 mg IV.
CrCl < 30 ml/min: Use not recommended due to lack of clinical data

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
The World Health Organization (WHO) has defined osteoporosis on the basis of bone mineral density (BMD) measurements to help identify individuals at risk. The bone density Dual X-ray Absorptiometry

(DXA) test is one that measures the bone mineral density and compares it to an established norm or standard resulting in a score. The results are compared to the ideal or peak bone mineral density of a healthy 30-yearold adult called a T-score. A T-score is the number of standard deviations (SD) the BMD measurement is above or below the young adult mean bone mineral density.

A T-score between +1 and –1 is considered normal or healthy. A T-score between –1 and –2.5 indicates that you have low bone mass (osteopenia), although not low enough to be diagnosed with osteoporosis. A T-score of –2.5 or lower indicates that you have osteoporosis. The greater the negative number, the more severe the osteoporosis. Bisphosphonate drugs (i.e., zoledronic acid [Reclast™], ibandronate sodium [Boniva]) act to inhibit osteoclast-mediated bone resorption and are used to treat post-menopausal osteoporosis by increasing bone mass. These medications may be administered orally (daily, weekly, or monthly) or by intravenous injection.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of ibandronate, pamidronate, and zoledronic acid are considered experimental/ investigational and therefore, will follow Molina's Off-Label policy

OTHER SPECIAL CONSIDERATIONS:

Hypocalcemia may worsen during treatment. Patients must be adequately supplemented with calcium and vitamin D. Pregnancy: Ibandronate is not indicated for use in women of reproductive potential. Patients with creatinine clearance less than 30 mL/min and in those with evidence of acute renal impairment is a contraindication.

Reclast/Zometa Products Containing Same Active Ingredient: Patients receiving Zometa should not receive Reclast. Hypocalcemia may worsen during treatment. Patients must be adequately supplemented with calcium and vitamin D

Renal Impairment: A single dose should not exceed 5 mg and the duration of infusion should be no less than 15 minutes. Renal toxicity may be greater in patients with underlying renal impairment or with other risk factors, including advanced age or dehydration. Monitor creatinine clearance before each dose. Adjust dose as appropriate for renal function and disease state. Patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment is a contraindication for use in Paget's Disease or Osteoporosis related indications. Osteonecrosis of the Jaw (ONJ) has been reported. All patients should have a routine oral exam by the prescriber prior to treatment. Atypical Femur Fractures have been reported. Patients with thigh or groin pain should be evaluated to rule out a femoral fracture. Pregnancy: Reclast can cause fetal harm.

Women of childbearing potential should be advised. Severe Bone, Joint, and Muscle Pain may occur. Withhold future doses of Reclast if severe symptoms occur

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1740	Inj. ibandronate 1mg
J2430	Inj. pamidronate per 30mg
J3489	Inj. zoledronic acid 1mg

AVAILABLE DOSAGE FORMS:

Boniva SOLN 3MG/3ML
Ibandronate Sodium SOLN 3MG/3ML
Pamidronate Disodium SOLN 30MG/10ML
Pamidronate Disodium SOLN 6MG/ML
Pamidronate Disodium SOLN 90MG/10ML
Pamidronate Disodium SOLR 30MG
Pamidronate Disodium SOLR 90MG
Reclast SOLN 5MG/100ML
Zoledronic Acid CONC 4MG/5ML
Zoledronic Acid SOLN 4MG/100ML
Zoledronic Acid SOLN 5MG/100ML
Zoledronic Acid SOLR 4MG
Zometa CONC 4MG/5ML
Zometa SOLN 4MG/100ML

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Prescriber Requirements References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file