Bisphosphonate Drug Therapy **Policy Number:** M-0036
Revision: 2 **Last Update: 6/4/2014**

Etidronate (Didronel®)
Ibandronate (Boniva®)
Pamidronate (Aredia®)
Zoledronic Acid

Payment will not be made for any use of these drugs outside of the criteria without prior authorization. The member may not be billed unless the member explicitly agrees in writing to be responsible for the charges in accordance with the contract/provider manual. Prior authorization will only be given if the provider demonstrates the intended use meets Medicare coverage guidelines.

Coverage Guidelines:

Etidronate
FDA
- Heterotopic ossification
- Hypercalcemia of malignancy
- Paget's disease

Off-Label
- Hypercalcemia of malignancy, Oral maintenance therapy
- Osteoporosis

Ibandronate
FDA
- Postmenopausal osteoporosis
- Postmenopausal osteoporosis; Prophylaxis

Off-Label
- Bone metastasis
- Disorder related to transplantation – Osteoporosis

- Hypercalcemia of malignancy

Pamidronate

FDA

- Bone metastasis, Osteolytic; associated with metastatic breast cancer or multiple myeloma
- Hypercalcemia of malignancy (Moderate to Severe), With adequate hydration
- Paget's disease (Moderate to Severe)

Off-Label

- Complex regional pain syndrome, type I
- Disorder of joint of spine
- Drug-induced osteoporosis; Prophylaxis - Gonad regulating hormone adverse reaction
- Hypercalcemia, Associated with tamoxifen-induced tumor flare
- Osteogenesis imperfecta
- Osteopenia (Acute); Prophylaxis - Total replacement of hip
- Osteopenia - Quadriplegic cerebral palsy
- Osteoporosis due to corticosteroids
- Postmenopausal osteoporosis

Zoledronic Acid

FDA

- Bone metastasis - Solid tumor configuration
- Hypercalcemia of malignancy
- Multiple myeloma
- Osteoporosis, in men
- Osteoporosis, Secondary prophylaxis in patients with recent low-trauma hip fracture
- Osteoporosis due to corticosteroids; Treatment and Prophylaxis
- Paget's disease
- Postmenopausal osteoporosis
- Postmenopausal osteoporosis; Prophylaxis

Off-Label

- Monoclonal gammopathy of uncertain significance, with osteopenia or osteoporosis
- Osteopenia, Secondary to androgen-deprivation therapy in prostate cancer patients; Prophylaxis
- Osteopenia, Secondary to hormone therapy in breast cancer patients; Prophylaxis
- Osteopenia, secondary to ovarian dysfunction induced by adjuvant chemotherapy in premenopausal women with early-stage breast cancer; Prophylaxis

Coding Information:

HCPCS Code(s)

J1436	INJECTION, ETIDRONATE DISODIUM, PER 300 MG
J1740	INJECTION, IBANDRONATE SODIUM, 1 MG
J2430	INJECTION, PAMIDRONATE DISODIUM, PER 30 MG
Q2051	INJECTION, ZOLEDRONIC ACID, NOT OTHER SPECIFIED, 1 MG

ICD-9 Code(s) J1436 Etidronate

198.5	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE MARROW
203.00	MULTIPLE MYELOMA, WITHOUT MENTION OF HAVING ACHIEVED REMISSION
203.01	MULTIPLE MYELOMA IN REMISSION
203.02	MULTIPLE MYELOMA, IN RELAPSE
275.42	HYPERCALCEMIA
728.10 - 728.12	CALCIFICATION AND OSSIFICATION UNSPECIFIED - TRAUMATIC MYOSITIS OSSIFICANS
731.0	OSTEITIS DEFORMANS WITHOUT BONE TUMOR
733.09	OTHER OSTEOPOROSIS
958.6	VOLKMANN'S ISCHEMIC CONTRACTURE

ICD-9 Code(s) J3489 Zolendronic acid

198.5	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE MARROW
203.00	MULTIPLE MYELOMA, WITHOUT MENTION OF HAVING ACHIEVED REMISSION
203.01	MULTIPLE MYELOMA IN REMISSION
203.02	MULTIPLE MYELOMA, IN RELAPSE
275.42	HYPERCALCEMIA
728.10 - 728.12	CALCIFICATION AND OSSIFICATION UNSPECIFIED - TRAUMATIC MYOSITIS OSSIFICANS

731.0	OSTEITIS DEFORMANS WITHOUT BONE TUMOR
733.00 - 733.09	OSTEOPOROSIS UNSPECIFIED - OTHER OSTEOPOROSIS
958.6	VOLKMANN'S ISCHEMIC CONTRACTURE

ICD-9 Code(s) J2430 Pamidronate only

198.5	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE MARROW
203.00	MULTIPLE MYELOMA, WITHOUT MENTION OF HAVING ACHIEVED REMISSION
203.01	MULTIPLE MYELOMA IN REMISSION
203.02	MULTIPLE MYELOMA, IN RELAPSE
275.42	HYPERCALCEMIA
728.10 - 728.12	CALCIFICATION AND OSSIFICATION UNSPECIFIED - TRAUMATIC MYOSITIS OSSIFICANS
731.0	OSTEITIS DEFORMANS WITHOUT BONE TUMOR
733.00 - 733.09	OSTEOPOROSIS UNSPECIFIED - OTHER OSTEOPOROSIS
756.51	OSTEOGENESIS IMPERFECTA
756.54	POLYOSTOTIC FIBROUS DYSPLASIA OF BONE
756.59	OTHER CONGENITAL OSTEODYSTROPHIES
958.6	VOLKMANN'S ISCHEMIC CONTRACTURE

ICD-9 Code(s) J1740 Ibandronate (Boniva)

198.5	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE MARROW
275.42	HYPERCALCEMIA
733.00 - 733.09	OSTEOPOROSIS UNSPECIFIED - OTHER OSTEOPOROSIS

ICD-9 Codes that DO NOT Support Medical Necessity:

733.90 DISORDER OF BONE AND CARTILAGE UNSPECIFIED

1. If bone metastasis is the condition being treated, the claim must be submitted with the ICD-9 code that reflects the reason for the service (198.5). The diagnosis of a primary malignant neoplasm must be present in the patient's progress notes, and available if requested.

2. Intravenous administration by infusion should be billed with codes 96365 for first hour and code 96366 for each additional hour. If the administration is by IV push use code 96374. Information in the medical record should support the medical necessity of this service based on the indications listed and be available on request. ICD-9 codes supporting medical necessity should be submitted on the claim.

Limitations:

Bisphosphonate drugs are available in both oral and parenteral forms. Coverage by Medicare is limited to those drugs administered parenterally (IV). The names of these drugs and their route of administration are as follows:

Alendronate sodium (Fosamax) oral
Tiludronate sodium (Skelid) oral
Risedronate sodium (Actonel) oral
Etidronate disodium (Didronel) oral and IV (J1436)
Pamidronate disodium (Aredia) IV (J2430)
Zoledronic acid, J3489
Ibandronate (Boniva) oral and IV (J1740)

Intravenous administration of bisphosphonate drug therapy is covered for FDA approved indications and for off label indications when peer reviewed literature is available that supports additional coverage.

A. Etidronate disodium (Didronel) IV (J1436), Pamidronate disodium (Aredia) IV (J2430) and Zolendronic acid (Zoledronate) (Zometa) IV (J3487), are covered for the following indications:

1. Hypercalcemia associated with malignancy (275.42). Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying complication with metastatic bone disease and hypercalcemia associated with malignancy. Most cases of hypercalcemia, associated with malignancy, occurs in patients who have breast cancer, squamous-cell tumors of the lung or head and neck, renal -cell carcinoma, and certain hematologic malignancies (multiple myeloma and some types of lymphomas).

   Bisphosphonates, in conjunction with hydration, are indicated for moderate or severe hypercalcemia associated with malignancy with or without bone metastases.

2. Cancer treatment induced bone loss (733.09)

All oncology therapies that induce hypogonadism cause osteoporosis in a large percentage of patients unless hormone replacement is carried out immediately.

Hypogonadism may occur in hormone-dependent tumors such as breast and prostate cancer; or it can be a consequence of cancer therapy in non hormone-dependant malignancies such as Hodgkin's and non-Hodgkin's lymphoma.

Cancer Treatment-Induced Bone Loss (CTIBL) in Breast and Prostate Cancer

Breast Cancer

Cytotoxic chemotherapy: There are 2 mechanisms of cytotoxic chemotherapy inducing bone loss. First, there is a direct negative effect of the cytotoxic therapy on bone cells, predominantly osteoblasts and, second, many women who are premenopausal have cytotoxic therapy effects on ovarian function, which results in gonadal loss.

In addition, in premenopausal women, surgery (oophorectomy) or radiation therapy to the ovary results in bone loss. Hormone therapy, tamoxifen in premenopausal women, and the aromatase inhibitors result in bone loss, as well as gonadotropin-releasing hormone (GnRH) antagonists/agonists, which shut off ovarian function. All of these result in estrogen depletion.

Prostate Cancer

In prostate cancer, cytotoxic therapy again has a negative effect not only on testicular function but also on bone. Surgical therapy, hormone therapy, including antiandrogens and GnRH agonists/antagonists, results in androgen depletion. The final common pathway, estrogen and androgen depletion, results in a decrease in bone mineral density.

3. Bone metastases (198.5) secondary to solid tumors, breast cancer, prostate cancer

4. Multiple Myeloma (203.00, 203.01, 203.02)

5. Osteolytic lesions due to metastases (198.5)

6. Paget's Disease of bone (osteitis deformans) (731.0)

   Intravenous bisphosphonates are indicated for moderate to severe Paget's disease of bone.

7. Prophylaxis and treatment of heterotopic ossification associated with spinal cord injury, traumatic brain injury, hip replacement, and burns. (728.10-728.12, 958.6)

   Etidronate disodium for this indication is usually given orally. It is indicated parenterally when the patient has failed a trial of the oral drug or has insurmountable issues related to absorption, compliance or dosing posture.

B. In addition to the above, Pamidronate Sodium (J2430) is covered for:

1. Osteogenesis Imperfecta (756.51)

2. Fibrous dysplasia of bone (756.54) (McCune-Albright syndrome) (756.59)

C. Ibandronate [Boniva] (effective with FDA approval 01/06/2006); Pamidronate: or Zolendronic acid (05/01/2006, off-label) Reclast® (August 17, 2007 – FDA approval) are covered for:

1. Treatment of osteoporosis (733.00 -733.09) when;

   Bisphosphonates remain the most appropriate anti-osteoporosis intervention, and there is no class contraindication or hypersensitivity to bisphosphonates, and there exists either:
   - Demonstrated intolerance or contraindication for FDA approved oral bisphosphonates and oral dosing regimens,

   or insurmountable issues related to absorption, compliance or dosing posture,

   or

   - When adequate trials of FDA-approved oral bisphosphonates result in fallen BMD and/or failure to suppress bone turnover (e.g. persisting high bone -turnover marker measurements.)

The World Health Organization (WHO) defines osteoporosis as spine, hip, or wrist bone mineral density (BMD) Tscore <-2.5 or prevalent fragility fracture; and severe osteoporosis as T-score <-2.5 and prevalent fragility fracture

Evidence in the medical record should clearly support the need for the intravenous administration of bisphosphonates for the treatment of osteoporosis.

The recommended dose of Boniva Injection for the treatment of postmenopausal osteoporosis is 3 mg every 3 months.

The recommended dose of Reclast® for treatment of postmenopausal osteoporosis is a single 5 mg infusion once a year given intravenously over no less than 15 minutes. (5 mg in a 100 mL ready to infuse solution)

D. Ibandronate [Boniva] Effective 10/16/2009

1. Hypercalcemia associated with malignancy (275.42).

2. Bone metastases (198.5) secondary to solid tumors, breast cancer, prostate cancer

E. Zoledronic acid, Reclast® - Injection is indicated for the treatment of:

1. Paget's disease of bone in men and women effective with FDA approval April 16, 2007. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase 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, to induce remission (normalization of serum alkaline phosphatase).

   A single dose of Reclast® (zoledronic acid) Injection should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.

   WPS Medicare will cover Reclast at most once per year because after a single treatment with Reclast in Paget's disease an extended remission period is observed. Re-treatment with Reclast may be considered, after one year in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

2. Osteoporosis Foundation Recommendations:

• A hip or vertebral (clinical or morphometric) fracture,
• Other prior fractures and low bone mass (T-score between -1.0 and -2.5 at the femoral neck, total hip or spine),
• T-score < -2.5 at femoral neck, total hip or spine after appropriate evaluation to exclude secondary causes,
• Low bone mass (T-score -1.0 to -2.5 at femoral neck, total hip or spine) and secondary causes associated with high risk of fracture (such as glucocorticoid use or total immobilization),
• Low bone mass (T-score between -1.0 to -2.5 at femoral neck, hip or spine) with a 10-year probability of hip fracture greater than or equal to 3% or 10-year probability of any major osteoporosis-related fracture of greater than or equal to 20% based on the US-adapted WHO algorithm (FRAX).

AND one of the following criteria:
1. Documented allergy to shellfish and/or salmon derivatives.
2. Documented intolerance of oral bisphosphonate therapy due to medical or surgical conditions including but not limited to:

• severe esophageal disease (e.g. ulcerations, strictures);
• esophageal symptoms or dysphagia severe enough to cause patient non-compliance with oral bisphosphonates;
• inability to take anything by mouth;
• inability to sit or stand for at least 30 minutes; or
• intestinal malabsorption.

3. Documented non-compliance with oral bisphosphonate treatment regimen of at least 3 months.

Precautions

Hypocalcemia may occur with Reclast therapy. To reduce the risk of hypocalcemia, all patients should receive 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following Reclast administration.

Reclast may cause fetal harm when administered to a pregnant woman. Reclast should

not be used during pregnancy.

Reclast is not recommended for use in patients with severe renal impairment (creatinine clearance <35mL/min) due to lack of adequate clinical experience in this population. Reclast has been associated with heart arrhythmia problems in the form of atrial fibrillation.

E. Bisphosphonates can impact renal function. Monitoring of renal function before during and post treatment according to labeled recommendations would be expected.

F. Monitoring with appropriate laboratory tests such as calcium, magnesium, and phosphate may be recommended.

G. The Food and Drug Administration has notified the public to the problem of osteonecrosis (also described as avascular or aseptic necrosis) of the mandible and/or maxilla, occurring in association with intravenously administered bisphosphonates.

H. A Severe anterior uveitis has been reported with use of bisphosphonate therapy.

I. The U.S. Food and Drug Administration (FDA) is updating the public regarding information previously communicated describing the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis

Atypical subtrochanteric femur fractures are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis, including Fosamax, Fosamax Plus D, Actonel, Actonel with Calcium, Boniva, Atelvia, and Reclast (and their generic products).

This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer (i.e., Didronel, Zometa, Skelid, and their generic products).

Although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use.

Bisphosphonate medications approved for the prevention and/or treatment of osteoporosis have clinical trial data supporting fracture reduction efficacy through at least 3 years of treatment and, in some cases, through 5 years.
The FDA is continuing its evaluation of data supporting the safety and effectiveness of long term use (greater than 3 to 5 years) of bisphosphonates for the treatment and prevention of osteoporosis and will provide additional guidance at the completion of our review.

Background:

Bisphosphonate drugs act to inhibit normal and abnormal bone reabsorption. This action is helpful in reducing pain, reversing hypercalcemia, preventing and reducing fractures in a range of diseases that directly or indirectly impact bone modeling and remodeling.

Definitions:

HCPCS Code—Healthcare Common Procedure Coding System - A system of letter and number codes assigned to procedures, medications, supplies and equipment used for pricing and billing.
ICD-9 Code—International Classification of Disease, 9th edition. A standardized classification of disease, injuries, and causes of death, by etiology and anatomic localization and codified into a 6-digit number, which allows clinicians, statisticians, politicians, health planners and others to speak a common language, both US and internationally.

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For the Archived Policy, please go to http://www.vivaprovider.com/Resources/CoveragePolicies.aspx and click on the Archived Policies Link.