MEDICAL POLICY

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

Original Issue Date (Created):	**November 1, 2008**
Most Recent Review Date (Revised):	**March 25, 2014**
Effective Date:	**July 7, 2014**

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.

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.

*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.

Treatment of Paget's Disease of Bone

Zoledronic Acid (Reclast®) may be considered **medically necessary** in patients with Paget's disease of bone who cannot tolerate or are unresponsive to oral agents **and** any **ONE** of 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.

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 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 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 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.

Cross-reference:

MP- 2.220 Bone Turnover Markers
MP -2.131 Ibandronate (Boniva®) Injection
MP - 2.142 Pamidronate (Aredia®)
MP - 5.001 Bone Mineral Density Studies

II. PRODUCT VARIATIONS

TOP

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N]	Capital Cares 4 Kids	[N]	Indemnity
[N]	PPO	[N]	SpecialCare
[N]	HMO	[N]	POS
[N]	SeniorBlue HMO	[Y]	FEP PPO*

[N] SeniorBlue PPO

*The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

III. DESCRIPTION/BACKGROUND

TOP

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.

Note: The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

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

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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.

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 (Reclast® and Zometa®) in single dose vials with doses specific to the approved indications. FDA approved indications for Reclast® includes Paget's disease of the bone and treatment and prevention of osteoporosis. FDA approved indications for 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.

The recommended dose of Reclast® for the treatment of Paget's disease is a single 5 mg intravenous infusion. Data for retreatment of Paget's disease is limited. The recommended dose of Reclast® for the treatment of osteoporosis is 5 mg intravenously once a year administered over no less than 15 minutes in an outpatient infusion center. The recommended dose of Reclast® for the prevention of osteoporosis in postmenopausal women is 5 mg intravenously every two years and 5 mg intravenously once a year for the prevention of glucocorticoid –induced osteoporosis

Zoledronic Acid in the brand form of Zometa® is FDA approved only for cancer-related indications. The recommended dose is 4 mg administered intravenously. Dosing frequency varies by clinical condition.

IV. RATIONALE

TOP

Zoledronic Acid (Reclast)

Treatment of Postmenopausal Osteoporosis
Study 1: The efficacy and safety of Reclast in the treatment of postmenopausal osteoporosis was demonstrated in Study 1, a randomized, double-blind, placebo-controlled, multinational study of 7736 women aged 65-89 years (mean age of 73) with either: a femoral neck BMD T-score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). Women were stratified into two groups: Stratum I: no concomitant use of osteoporosis therapy or Stratum II: baseline concomitant use of osteoporosis therapies which included calcitonin, raloxifene, tamoxifen, and hormone replacement therapy, but excluded other bisphosphonates.

Women enrolled in Stratum I (n=5661) were evaluated annually for incidence of vertebral fractures. All women (Strata I and II) were evaluated for the incidence of hip and other clinical fractures. Reclast was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 international units of vitamin D supplementation per day.

The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years and the incidence of hip fractures over a median duration of 3 years. The diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the radiologist and quantitative morphometric criterion. The morphometric criterion required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height.

Effect on Vertebral Fractures

Reclast significantly decreased the incidence of new vertebral fractures at one, two, and three years as shown in Table 5.

Table 5. Proportion of Patients with New Morphometric Vertebral Fractures

Outcome	Reclast (%)	Placebo (%)	Absolute Reduction in Fracture Incidence % (95% CI)	Relative Reduction in Fracture Incidence % (95% CI)
At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)*
At least one new vertebral fracture (0–2 years)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)*
At least one new vertebral fracture (0–3 years)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)*

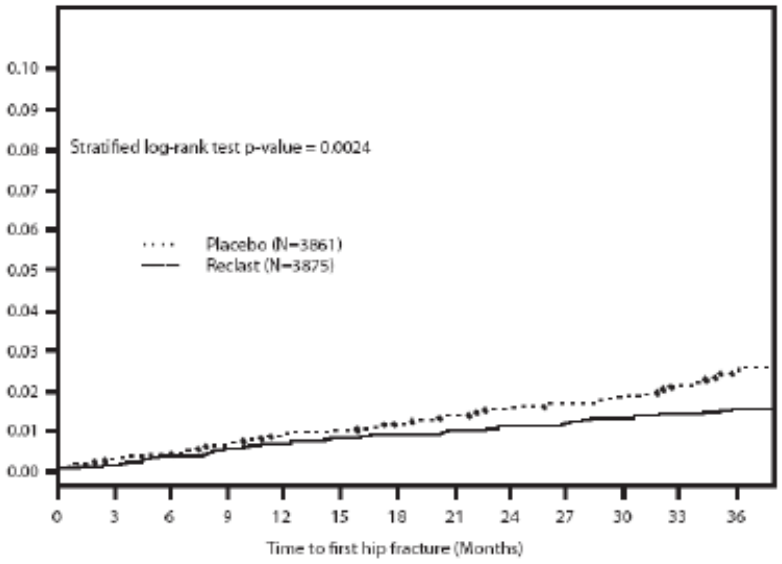
*p<0.0001

The reductions in vertebral fractures over three years were consistent (including new/worsening and multiple vertebral fractures) and significantly greater than placebo regardless of age, geographical region, baseline body mass index, number of baseline vertebral fractures, femoral neck BMD T-score, or prior bisphosphonate usage.

Effect on Hip Fracture over 3 years

Reclast demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The hip fracture event rate was 1.4% for Reclast-treated patients compared to 2.5% for placebo-treated patients.

Figure 1. Cumulative Incidence of Hip Fracture Over 3 Years



The reductions in hip fractures over three years were greater for Reclast than placebo regardless of femoral neck BMD T-score.

Effect on All Clinical Fractures

Reclast demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical (symptomatic) vertebral and non-vertebral fractures (excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures). All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 6.

Table 6. Between–Treatment Comparisons of the Incidence of Clinical Fracture Variables Over 3 Years

Outcome	Reclast (N= 3875) Event Rate n (%)+	Placebo (N= 3861) Event Rate n (%)+	Absolute Reduction in Fracture Incidence % (95% CI)+	Relative Risk Reduction in Fracture Incidence % (95% CI)
Any clinical fracture (1)	308 (8.4)	456 (12.8)	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture (2)	19 (0.5)	84 (2.6)	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture (3)	292 (8.0)	388 (10.7)	2.7 (1.4, 4.0)	25 (13, 36)*

*p-value < 0.001, **p-value <0.0001
+ Event rates based on Kaplan-Meier estimates at 36 months
(1) Excluding finger, toe, and facial fractures
(2) Includes clinical thoracic and clinical lumbar vertebral fractures
(3) Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

Effect on Bone Mineral Density (BMD)
Reclast significantly increased BMD at the lumbar spine, total hip and femoral neck, relative to treatment with placebo at time points 12, 24, and 36 months. Treatment with Reclast resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, and 5.1% at the femoral neck, over 3 years as compared to placebo.

Bone Histology

Bone biopsy specimens were obtained between Months 33 and 36 from 82 postmenopausal patients with osteoporosis treated with 3 annual doses of Reclast. Of the biopsies obtained, 81 were adequate for qualitative histomorphometry assessment, 59 were adequate for partial quantitative histomorphometry assessment, and 38 were adequate for full quantitative histomorphometry assessment. Micro CT analysis was performed on 76 specimens. Qualitative, quantitative and micro CT assessments showed bone of normal architecture and quality without mineralization defects.

Effect on Height

In the 3-year osteoporosis study, standing height was measured annually using a stadiometer. The Reclast group revealed less height loss compared to placebo (4.2 mm vs. 7.0 mm, respectively [$p<0.001$]).

Study 2: The efficacy and safety of Reclast in the treatment of patients with osteoporosis who suffered a recent low-trauma hip fracture was demonstrated in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50-95 years (mean age of 74.5). Concomitant osteoporosis therapies excluding other bisphosphonates and parathyroid hormone were allowed. Reclast was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes. The study continued until at least 211 patients had confirmed clinical fractures in the study population. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 international units orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 international units of vitamin D supplementation per day for at least 14 days prior to the study drug infusions. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Reclast significantly reduced the incidence of any clinical fracture by 35%. There was also a 46% reduction in the risk of a clinical vertebral fracture (Table 7).

Table 7. Between-Treatment Comparisons of the Incidence of Key Clinical Fracture Variables

Outcome	Reclast (N=1065) Event Rate n (%)+	Placebo (N=1062) Event Rate n (%)+	Absolute Reduction in Fracture Incidence % (95% CI) +	Relative Risk Reduction in Fracture Incidence % (95% CI)
Any clinical fracture (1)	92 (8.6)	139 (13.9)	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture (2)	21 (1.7)	39 (3.8)	2.1 (0.5, 3.7)	46 (8, 68)*

*p-value <0.05, **p-value <0.005
+ Event rates based on Kaplan-Meier estimates at 24 months
(1) Excluding finger, toe and facial fractures
(2) Including clinical thoracic and clinical lumbar vertebral fractures

Effect on Bone Mineral Density (BMD)

Reclast significantly increased BMD relative to placebo at the hip and femoral neck at all timepoints (12, 24, and 36 months). Treatment with Reclast resulted in a 6.4% increase in BMD at the total hip and a 4.3% increase at the femoral neck over 36 months as compared to placebo.

Prevention of Postmenopausal Osteoporosis

The efficacy and safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged greater than or equal to 45 years, who were stratified by years since menopause: Stratum I women less than 5 years from menopause (n=224); Stratum II women greater than or equal to 5 years from menopause (n=357). Patients within Stratum I and II were randomized to one of three treatment groups: (1) Reclast given at randomization and at Month 12 (n=77) in Stratum I and (n=121) in Stratum II; (2) Reclast given at randomization and placebo at Month 12 (n=70) in Stratum I and (n=111) in Stratum II; and (3) Placebo given at randomization and Month 12 (n=202). Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 international units vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline.

Effect on Bone Mineral Density (BMD)

Reclast significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 6.3% increase in

BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

Reclast also significantly increased total hip BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 2.6% increase in BMD in Stratum I patients and 2.1% in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.1% decrease in BMD in Stratum I patients and 1.0% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 4.7% increase in BMD in Stratum I patients and 3.2% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

Osteoporosis in Men

The efficacy and safety of Reclast in men with osteoporosis or significant osteoporosis secondary to hypogonadism, was assessed in a randomized, multicenter, double-blind, active controlled, study of 302 men aged 25-86 years (mean age of 64). The duration of the trial was two years. Patients were randomized to either Reclast which was administered once annually as a 5 mg dose in 100 mL infused over 15 minutes for a total of up to two doses, or to an oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 international units of vitamin D supplementation per day.

Effect on Bone Mineral Density (BMD)

An annual infusion of Reclast was non-inferior to the oral weekly bisphosphonate active control based on the percentage change in lumbar spine BMD at Month 24 relative to baseline (Reclast: 6.1% increase; active control: 6.2% increase).

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The efficacy and safety of Reclast to prevent and treat glucocorticoid-induced osteoporosis (GIO) was assessed in a randomized, multicenter, double-blind, stratified, active controlled study of 833 men and women aged 18-85 years (mean age of 54.4 years) treated with greater than or equal to 7.5 mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy: less than or equal to 3 months prior to randomization (prevention subpopulation), and greater than 3 months prior to randomization (treatment subpopulation). The duration of the trial was one year. Patients were randomized to either Reclast which was administered once as a 5 mg dose in 100 mL infused over 15 minutes, or to an oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 international units of vitamin D supplementation per day.

Effect on Bone Mineral Density (BMD)

In the GIO treatment subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to the active control at one year (Reclast 4.1%, active control 2.7%) with a treatment difference of 1.4% ($p<0.001$). In the GIO prevention subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to active control at one year (Reclast 2.6%, active control 0.6%) with a treatment difference of 2.0% ($p<0.001$).

Bone Histology

Bone biopsy specimens were obtained from 23 patients (12 in the Reclast treatment group and 11 in the active control treatment group) at Month 12 treated with an annual dose of Reclast or daily oral active control. Qualitative assessments showed bone of normal architecture and quality without mineralization defects. Apparent reductions in activation frequency and remodeling rates were seen when compared with the histomorphometry results seen with Reclast in the postmenopausal osteoporosis population. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

Treatment of Paget's Disease of Bone

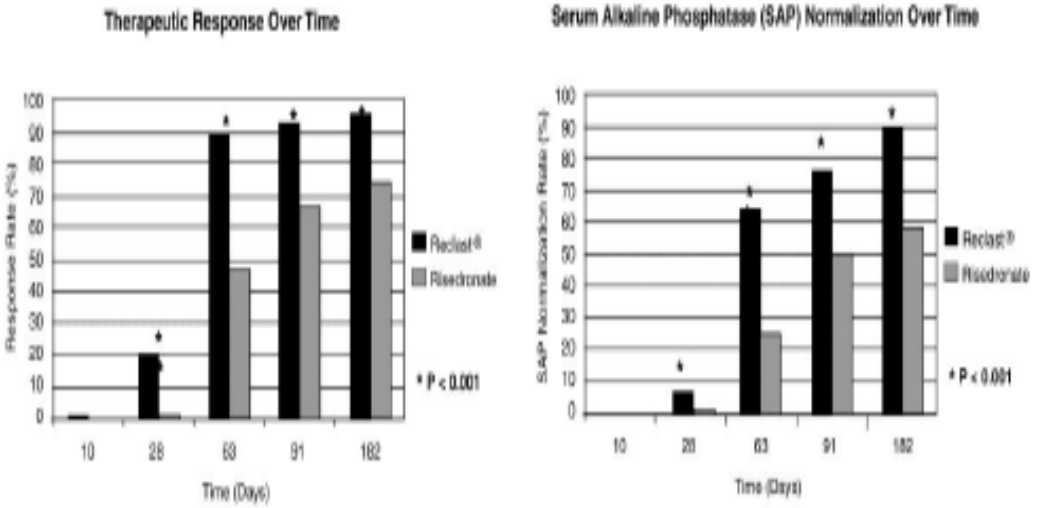
Reclast was studied in male and female patients with moderate to severe Paget's disease of bone, defined as serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry. Diagnosis was confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg Reclast vs. oral daily doses of 30 mg risedronate for 2 months was demonstrated in two identically designed 6-month randomized, double blind trials. The mean age of patients in the two trials was 70. Ninety-three percent (93%) of patients were Caucasian. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of normal range.

In both trials Reclast demonstrated a superior and more rapid therapeutic response compared with risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of formation (SAP, serum N-terminal propeptide of type I collagen [P1NP]) and resorption (serum CTx 1 [cross-linked C-telopeptides of type I collagen] and urine $^{\alpha}$--CTx).

The 6-month combined data from both trials showed that 96% (169/176) of Reclast-treated patients achieved a therapeutic response as compared with 74% (127/171) of patients treated with risedronate. Most Reclast patients achieved a therapeutic response by the Day 63 visit. In addition, at 6 months, 89% (156/176) of Reclast-treated patients achieved normalization of SAP levels, compared to 58% (99/171) of patients treated with risedronate ($p<0.0001$) (see Figure 2).

Figure 2. Therapeutic Response/Serum Alkaline Phosphatase (SAP) Normalization Over Time



The therapeutic response to Reclast was similar across demographic and disease-severity groups defined by gender, age, previous bisphosphonate use, and disease severity. At 6 months, the percentage of Reclast-treated patients who achieved therapeutic response was 97% and 95%, respectively, in each of the baseline disease severity subgroups (baseline SAP less than 3xULN, greater than or equal to 3xULN) compared to 75% and 74%, respectively, for the same disease severity subgroups of risedronate-treated patients.

In patients who had previously received treatment with oral bisphosphonates, therapeutic response rates were 96% and 55% for Reclast and risedronate, respectively. The comparatively low risedronate response was due to the low response rate (7/23, 30%) in patients previously treated with risedronate. In patients naïve to previous treatment, a greater therapeutic response was also observed with Reclast (98%) relative to risedronate (86%). In patients with symptomatic pain at screening, therapeutic response rates were 94% and 70% for Reclast and risedronate respectively. For patients without pain at screening, therapeutic response rates were 100% and 82% for Reclast and risedronate respectively.
Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with Reclast 5 mg. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect.

Zoledronic Acid (Zometa)

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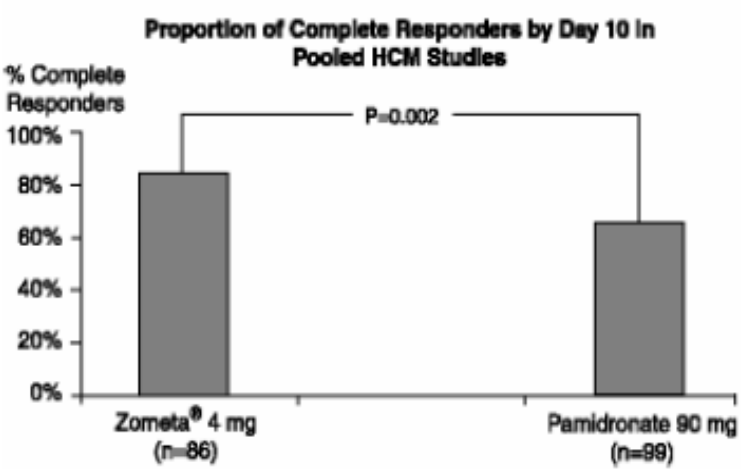
Hypercalcemia of Malignancy

Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes. The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were black, and 4% were of other races. 60% of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of greater than or equal to 12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to less than or equal to 10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a preplanned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (P=0.002) (see Figure 1). In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.

Figure 1



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value less than 11.6 mg/dL (less than 2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 11.

Table 11: Secondary Efficacy Variables in Pooled HCM Studies

		Zometa 4 mg		**Pamidronate 90 mg**
Complete Response	**N**	**Response Rate**	**N**	**Response Rate**
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of Response	**N**	**Median Duration (Days)**	**N**	**Median Duration (Days)**
Time to Relapse	86	30*	99	17
Duration of Complete Response	76	32	69	18

*P less than 0.05 versus pamidronate 90 mg.

Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 12 describes an overview of the efficacy population in three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer, and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, including NSCLC, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, GI/genitourinary cancer, head and neck cancer, and others. These trials were comprised of a core phase and an extension phase. In the solid tumor, breast cancer and multiple myeloma trials, only the core phase was evaluated for efficacy as a high percentage of patients did not choose to participate in the extension phase. In the prostate cancer trials, both the core and extension phases were evaluated for efficacy showing the Zometa effect during the first 15 months was maintained without decrement or improvement for another 9 months. The design of these clinical trials does not permit assessment of whether more than one-year administration of Zometa is beneficial. The optimal duration of Zometa administration is not known.

The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8 mg Zometa treatment arm were switched to 4 mg due to toxicity. Patients who were randomized to the Zometa 8 mg group are not included in these analysis.

Table 12: Overview of Efficacy Population for Phase III Studies

Patient Population	**No. of Patients**	**Zometa Dose**	**Control**	**Median Duration (Planned Duration) Zometa 4 mg**
Multiple myeloma or metastatic breast cancer	1,648	4 and 8* mg Q3-4 weeks	Pamidronate 90 mg Q3-4 weeks	12.0 months (13 months)
Metastatic prostate cancer	643	4 and 8* mg Q3 weeks	Placebo	10.5 months (15 months)
Metastatic solid tumor other than breast or prostate cancer	773	4 and 8* mg Q3 weeks	Placebo	3.8 months (9 months)

*Patients who were randomized to the 8 mg Zometa group are not included in any of the analyses in this package insert are not included in these analyses.

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study and

time to the first SRE. Results for the two Zometa placebo-controlled studies are given in Table 13.

Table 13: Zometa Compared to Placebo in Patients with Bone Metastases from Prostate Cancer or Other Solid Tumors

	I. Analysis of Proportion of Patients with a SRE1				II. Analysis of Time to the First SRE		
Study	**Study Arm & Patient Number**	**Proportion**	**Difference2 & 95% CI**	**P-value**	**Median (Days)**	**Hazard Ratio3 & 95% CI**	**P-value**
Prostate Cancer	Zometa 4 mg (n=214)	33%	-11% (-20%, -1%)	0.02	Not Reached	0.67 (0.49, 0.91)	0.011
	Placebo (n=208)						
Solid Tumors	Zometa 4 mg (n=257)	38%	-7% (-15%, 2%)	0.13	230	0.73 (0.55, 0.96)	0.023
	Placebo (n=250)	44%		163			

1SRE=Skeletal-Related Event
2Difference for the proportion of patients with a SRE of Zometa 4 mg versus placebo.
3Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus placebo.

In the breast cancer and myeloma trial, efficacy was determined by a noninferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1,128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI = 7.3%, 18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 14.

Table 14: Zometa Compared to Pamidronate in Patients with Multiple Myeloma or Bone Metastases from Breast Cancer

	I. Analysis of Proportion of Patients with a SRE1				II. Analysis of Time to the First SRE		
Study	**Study Arm & Patient Number**	**Proportion**	**Difference2 & 95% CI**	**P-value**	**Median (Days)**	**Hazard Ratio3 & 95% CI**	**P-value**
Multiple Myeloma & Breast Cancer	Zometa 4 mg (n=561)	44%	-2% (-7.9%, 3.7%)	0.46	373	0.92 (0.77, 1.09)	0.32
	Pamidronate (n=555)	46%			363		

1SRE=Skeletal-Related Event
2Difference for the proportion of patients with a SRE of Zometa 4 mg versus pamidronate 90 mg.
3Hazard ratio for the firstmg.

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.

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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.

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 contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

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Capital'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. Capital 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.

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

HCPCS Code	Description
J3489	INJECTION, ZOLEDRONIC ACID, 1 MG

ICD-9-CM Diagnosis Code*	Description
162.3	MALIGNANT NEOPLASM OF UPPER LOBE, BRONCHUS, OR LUNG
162.4	MALIGNANT NEOPLASM OF MIDDLE LOBE, BRONCHUS, OR LUNG
162.5	MALIGNANT NEOPLASM OF LOWER LOBE, BRONCHUS, OR LUNG
162.8	MALIGNANT NEOPLASM OF OTHER PARTS OF BRONCHUS OR LUNG
162.9	MALIGNANT NEOPLASM OF BRONCHUS AND LUNG, UNSPECIFIED SITE
174.0-174.9	MALIGNANT NEOPLASM OF FEMALE BREAST
175.0-175.9	MALIGNANT NEOPLASM OF MALE BREAST
185.	MALIGNANT NEOPLASM OF PROSTATE
203.00	MULTIPLE MYELOMA, WITHOUT MENTION OF HAVING ACHIEVED REMISSION
203.01	MULTIPLE MYELOMA IN REMISSION
275.42	HYPERCALCEMIA
731.0 – 731.1	OSTEITIS DEFORMANS WITHOUT MENTION OF BONE TUMOR
733.00	UNSPECIFIED OSTEOPOROSIS
733.01	SENILE OSTEOPOROSIS
733.02	IDIOPATHIC OSTEOPOROSIS
733.03	DISUSE OSTEOPOROSIS
733.09	OTHER OSTEOPOROSIS

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung

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ICD-10-CM Diagnosis Code*	Description
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast

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

ICD-10-CM Diagnosis Code*	Description
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
C61	Malignant neoplasm of prostate
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
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

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

ICD-10-CM Diagnosis Code*	Description
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 lower leg
M88.871	Osteitis deformans of right ankle and foot
M88.872	Osteitis deformans of left ankle and foot
M88.879	Osteitis deformans of unspecified ankle and foot
M88.88	Osteitis deformans of other bones
M88.89	Osteitis deformans of multiple sites
M88.9	Osteitis deformans of unspecified bone
M81.0	Age-related osteoporosis without current pathological fracture
M81.8	Other osteoporosis without current pathological fracture
M81.6	Localized osteoporosis [Lequesne]
M81.8	Other osteoporosis without current pathological fracture

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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X. POLICY HISTORY

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MP 2.143	**CAC 1/26/10** 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. 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 list review. Administrative code review complete.
	12/19/2013- New 2014 Code updates made.
	CAC 3/25/14 Consensus. No change to policy statements. References updated. Rationale section added.
	Admin change 7-1-14 – deleted notation regarding preauthorization requirement. All Users should refer to officially posted preauthorization resources for requirements.

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