



BlueCross BlueShield
of Alabama

Name of Policy:

Zoledronic Acid (Reclast[®]) Injection

Policy #: 355

Category: Pharmacy

Latest Review Date: May 2011

Policy Grade: **Active Policy but no longer scheduled for regular literature reviews and updates.**

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

The National Osteoporosis Foundation reports that approximately 22 million women in the U.S. have osteopenia, putting them at increased risk of osteoporosis, a disease that causes bones to break more easily. Osteoporosis is a major public health threat affecting an estimated 10 million men and women in the U.S.

Zoledronic acid is a bisphosphonic acid, which is an inhibitor of osteoclastic bone resorption. The principle pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. It also inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. Zoledronic acid (Reclast®) is a single-dose intravenous infusion. It is contraindicated in patients with hypocalcemia or with hypersensitivity to any component of Reclast. It should not be given to patients with severe renal impairment, if creatinine clearance <35 ml/minute.

Policy:

Zoledronic Acid (Reclast®) Injection meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications:

- Treatment of osteoporosis in post-menopausal women
- Treatment to increase bone mass in men with osteoporosis
- Treatment and prevention of glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months
- Treatment of Paget's disease of bone in men and women
- For the prevention of new clinical fractures in patients who have recently had a low-trauma hip fracture
- Post-menopausal women with osteopenia for the prevention of osteoporosis.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Reid, et al (2005) reported on the efficacy of zoledronic acid, administered as a single IV infusion, to treat Paget's disease. In two randomized, double-blind trials of six months duration, they compared one 15 minute infusion of 5mg of zoledronic acid with 60 days of oral risedronate (Actonel) (30mg/day). The results showed that at six months, 96% of patients (16% of 176) receiving zoledronic acid had a therapeutic response, as compared with 74.3% of patients (127 of

171) receiving risedronate. Alkaline phosphatase levels normalized in 89% of patients in the zoledronic acid group and 58% of patients in the risedronate group. Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 days). The investigators reported that the physical-component summary score of the Medical Outcomes Study 36-item Short-Form General Health Survey, a measure of the quality of life, increased significantly from baseline at three months and six months in the zoledronic acid group and differed significantly from those in the risedronate group at three months. The pain scores improved in both groups. During post-trial follow-up, (median 190 days), 21 of 82 patients in the risedronate group had a loss of therapeutic response, as compared with one of 113 patients in the zoledronic acid group.

Keating and Scott (2007) published a review on the use of zoledronic acid to treat Paget's disease. They stated that results of well designed clinical trials show that a single intravenous dose of zoledronic acid (5mg) is effective and well tolerated in the treatment of Paget's disease of bone. This approach was associated with a significantly higher therapeutic response rate and a more rapid reduction in bone turnover than achieved with 60 days of oral risedronic acid. Also, biochemical remission was sustained after 24 months of follow-up in zoledronic acid recipients. The authors noted that preliminary results suggest that zoledronic acid is a cost-effective option and an important first-line treatment for Paget's disease of bone.

Zoledronic acid has been shown to increase bone density and decrease fracture risk in women with post-menopausal osteoporosis. Black, et al (2007) reported on the results of the HORIZON Pivotal Fracture Trial, a double-blind, randomized controlled clinical trial of a once-yearly infusion of zoledronic acid on fracture risk over a three-year period. In this study, 3889 patients were randomly assigned to receive a single 15-minute infusion of zoledronic acid (5 mg) and 3876 were assigned to receive placebo at baseline, at 12 months, and at 24 months. The patients were followed until 36 months. The investigators reported that treatment with zoledronic acid reduced the risk of vertebral fracture by 70% during a three year period, as compared with placebo (3.3% in the zoledronic acid group vs. 10.9% in the placebo group). It also reduced the risk of hip fracture by 41% (1.4% in the zoledronic acid group vs. 2.5% in the placebo group). Non-vertebral fractures were reduced by 25%, clinical fractures by 33%, and clinical vertebral fractures by 77%. The investigators also found that zoledronic acid was also associated with a significant improvement in bone mineral density and bone metabolism markers. Adverse events, including changes in renal function, were similar in the two study groups. However, serious atrial fibrillation occurred more frequently in the zoledronic acid group (in 50 vs. 20 patients). The investigators concluded that a once-yearly infusion of zoledronic acid during a three year period significantly reduced the risk of vertebral, hip, and other fractures.

Lyles, et al (2007) reported on a randomized, double-blind, placebo-controlled study to examine whether zoledronic acid would improve clinical features and mortality following hip fracture. A total of 1065 patients were assigned to receive yearly intravenous zoledronic acid (5mg dose) and 1062 patients were assigned to receive placebo. The infusions were first administered within 90 days after surgical repair of a hip fracture. The mean follow-up was 1.9 years. The primary end point was a new clinical fracture. The rates of any new clinical fracture were 8.6% in the zoledronic acid group and 13.9% in the placebo group, a 35% risk reduction with zoledronic acid. The respective rates of a new clinical vertebral fracture were 1.7% and 3.8%. The

respective rates of new non-vertebral fractures were 7.6% and 10.7%. In the safety analysis, 101 of 1054 patients in the zoledronic acid group (9.6%) and 141 of 1057 patients in the placebo group (13.3%) died, a reduction of 28% in deaths from any cause in the zoledronic acid group. The most frequent adverse events in patients receiving zoledronic acid were pyrexia, myalgia, and bone and musculoskeletal pain. No cases of osteonecrosis of the jaw were reported, and no adverse effects on the healing of fractures were noted. The rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the two groups. The authors concluded that an annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival.

In December 2008, the U.S. Food and Drug Administration (FDA) approved once-yearly zoledronic acid infusions for the treatment of low bone mass in men with osteoporosis. The FDA approval was based on data from a two year, double-blind trial of more than 300 men with osteoporosis. There were 153 osteoporotic men who received a 15-minute infusion of zoledronic acid once per year and 148 other osteoporotic men who received weekly oral alendronate for two years. The results showed that the men who were treated with zoledronic acid increased their lumbar spine bone mineral density (BMD) by a mean of 6.1% over two years. This change in BMD was similar to the 6.2% increase in the alendronate group. Each patient also received 1000 mg calcium and 800-1000 IV of Vitamin D each day. In the first three days of the trial, treatment with zoledronic acid was associated with myalgia (17%), fever (16%), fatigue (12%), arthralgia (11%), pain (10%), chills (10%), headache (10%) and influenza-like illness (9%). No patients developed osteonecrosis of the jaw. There was one death in each group. The two groups had similar rates of serious adverse events. This trial was sponsored by Novartis, the company that manufactures Reclast® (Zoledronic acid).

Reid, et al (2009) reported on a one year, randomized, double-blind study to assess whether one intravenous infusion of zoledronic acid (5mg) was non-inferior to daily oral risedronate (5mg) for prevention and treatment of glucocorticoid-induced osteoporosis. There were 833 patients randomized to receive zoledronic acid (n = 416) or risedronate (n = 417). Patients were allocated to prevention or treatment subgroups dependent on the duration of glucocorticoid use immediately preceding the study. The treatment subgroup consisted of those treated for more than three months (272 patients on zoledronic acid and 273 on risedronate), and the prevention subgroup of those treated for less than three months (144 patients on each drug). The results showed that a single yearly infusion of zoledronic acid significantly increased lumbar spine bone mineral density at 12 months in both the treatment group (Reclast 4.1%, risedronate 2.7%) and the prevention group (Reclast 2.6%, risedronate 0.6%). Adverse events were more frequent in patients given zoledronic acid, largely due to transient symptoms during the first 3 days after infusion.

The efficacy and safety of Reclast in postmenopausal women with osteopenia was assessed in a two-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged ≥ 45 years, who were stratified by years since menopause: Stratum I women < 5 years from menopause (n = 224); Stratum II women ≥ 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 5mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day. The primary efficacy variable was the percent change of bone mineral density (BMD) at 24 months relative to baseline.

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 $p < 0.0001$).

2011 Update

A literature search found no new relevant clinical studies. The policy statement remains unchanged.

Key Words:

Zoledronic Acid, Reclast®, osteoporosis, bisphosphonates, Paget's disease, osteopenia

Approved by Governing Bodies:

April 2007—Reclast was approved for the treatment of Paget's disease of bone.

August 2007—Reclast was approved as a once-yearly treatment for post-menopausal osteoporosis.

June 2008—The treatment of post-menopausal osteoporosis indication was broadened to include the prevention of new clinical fractures in patients who have recently had a low trauma hip fracture.

December 2008—Reclast was approved as a once-yearly treatment to increase bone mass in men with osteoporosis.

March 2009—Reclast was approved as a once-yearly injection to treat and prevent osteoporosis caused by glucocorticoids for patients expected to be on glucocorticoids for at least 12 months.

June 2009—Reclast was approved as a once every 2 year infusion for the prevention of osteoporosis in post-menopausal women.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan.

Pre-certification requirements: Not applicable

Current Coding:

HCPCS Codes:

J3489 Injection, zoledronic acid, 1 mg (**effective 01/01/2014**)

Previous Coding:

HCPCS Codes:

J3488 Injection, Zoledronic Acid (Reclast), 1 mg (**deleted 12/31/2013**)

References:

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Policy History:

Medical Policy Group, May 2009 (3)

Medical Policy Administration Committee, July 2009

Available for comment July 1-August 14, 2009

Medical Policy Group, May 2011 (3): Updated Key Points

Medical Policy Group, September 2012: **Effective September 14, 2012 this policy is no longer scheduled for regular literature reviews and updates.**

Medical Policy Group, January 2014 (1): 2014 Coding Update: new HCPCS code, J3489, added to coding section, effective 01/01/2014; deleted code J3488 moved to previous coding section, effective 01/01/2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.