Reference number(s)
4796-A

STANDARD MEDICARE PART B MANAGEMENT

MIACALCIN (calcitonin [salmon] injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Miacalcin injection is indicated for the treatment of symptomatic Paget's disease of bone in patients with moderate to severe disease characterized by polyostotic involvement with elevated serum alkaline phosphatase and urinary hydroxyproline excretion. There is no evidence that the prophylactic use of calcitonin salmon is beneficial in asymptomatic patients. Miacalcin injection should be used only in patients who do not respond to alternative treatments or for whom such treatments are not suitable.
2. Miacalcin injection is indicated for the early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as intravenous fluids and furosemide, oral phosphate or corticosteroids, or other agents.
3. Miacalcin injection is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause. The evidence of efficacy for calcitonin-salmon injection is based on increases in total body calcium observed in clinical trials. Fracture reduction efficacy has not been demonstrated. Miacalcin injection should be reserved for patients for whom alternative treatments are not suitable.

B. Compendial Uses

1. Aneurysmal bone cyst
2. Adjunct for cancer pain
3. Central giant cell reparative granuloma of jaw
4. Complex regional pain syndrome type I
5. Reduction of bone fractures risk in perimenopausal women with osteoporosis and men with osteoporosis
6. Osteogenesis imperfecta
7. Osteoporosis due to long-term corticosteroid therapy
8. Postoperative phantom limb
9. Prophylaxis of premenopausal osteoporosis due to estrogen deficiency

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Paget's disease of bone
Authorization of 12 months may be granted for treatment of Paget's disease of bone when all of the following criteria are met:
1. Member has symptomatic Paget's disease of bone (e.g., bone pain, bowing of lower extremity, hearing loss, heart failure, increased cardiac output, osteoarthritis) prior to therapy.
2. Member has failed prior treatment with an injectable bisphosphonate (e.g., pamidronate, zoledronic acid) or is intolerant to previous injectable therapy

B. Hypercalcemia
Authorization of 1 month may be granted for treatment of hypercalcemic emergency when Miacalcin is used in combination with other agent(s) to reduce serum calcium levels.

C. **Aneurysmal bone cyst**
Authorization of 6 months may be granted for the treatment of aneurysmal bone cysts.

D. Adjunctive treatment for cancer pain
Authorization of 12 months may be granted for treatment of pain control in patients with malignant bone metastasis when used an adjunct to morphine treatment.

E. **Central giant cell reparative granuloma of jaw**
Authorization of 12 months may be granted for pediatric patients for the treatment of central giant cell reparative granuloma of the jaw (CGCG).

F. **Complex regional pain syndrome type I**
Authorization of 6 months may be granted for complex regional pain syndrome Type I.

G. Osteogenesis imperfecta
Authorization of 12 months may be granted for decreasing bone fracture rates in patients with osteogenesis imperfecta.

H. **Postoperative phantom limb pain**
Authorization of 12 months may be granted for the treatment of post-operative phantom limb pain.

I. **Prophylaxis of premenopausal osteoporosis due to estrogen deficiency**
Authorization of 12 months may be granted to female members for prophylaxis of premenopausal osteoporosis when all the following are met:
1. Member has an estrogen deficiency
2. Member has a contraindication to estrogen replacement therapy

J. Osteoporosis treatment
Authorization of 12 months may be granted for the treatment of osteoporosis in men or postmenopausal osteoporosis.

K. **Treatment of men and women with glucocorticoid-induced osteoporosis**

Authorization of 12 months may be granted for the treatment of glucocorticoid-induced osteoporosis.

L. **Prevention of perimenopausal osteoporosis**
Authorization of 12 months may be granted for the prevention of perimenopausal osteoporosis.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Paget's disease of bone, Aneurysmal bone cyst, Adjunctive treatment for cancer pain, Central giant cell reparative granuloma of jaw, Complex regional pain syndrome type I, Osteogenesis imperfecta, Postoperative phantom limb pain, Prophylaxis of Premenopausal osteoporosis due to estrogen deficiency, Osteoporosis treatment, Glucocorticoid-induced osteoporosis, Prevention of perimenopausal osteoporosis
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Miacalcin
2. The member is receiving the requested medication for an indication listed in Section II
3. The member is receiving benefit from therapy.

B. Hypercalcemia
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Miacalcin.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Miacalcin are covered in addition to the following:
1. Aneurysmal bone cyst
2. Adjunct for cancer pain
3. Central giant cell reparative granuloma of jaw
4. Complex regional pain syndrome type I
5. Reduction of bone fractures risk in perimenopausal women with osteoporosis and men with osteoporosis
6. Osteogenesis imperfecta
7. Osteoporosis due to long-term corticosteroid therapy
8. Postoperative phantom limb
9. Prophylaxis of premenopausal osteoporosis due to estrogen deficiency

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Miacalcin to treat aneurysmal bone cyst can be found in a study by Szendroi et al. Seven patients with aneurysmal bone cysts (ABC) were treated with salmon calcitonin, 100 international units three times weekly, by direct administration into the cyst. A total of fifteen doses were administered. The six ABCs determined to be hypovascular responded well, with demonstrable ossification of the cysts. The seventh patient with ABC had a hypervascular lesion, treated initially with superselective embolization. This patient then received the calcitonin regimen but failed to respond to either regimen.

Support for using Miacalcin as an adjunct for cancer pain can be found in several studies. A double-blind study by Fiore et al of 9 patients evaluated treatment response to severe oncological pain. Four patients were administered salmon calcitonin epidurally (15 international units), 3 received human calcitonin epidurally (60 mcg or 9 international units), and the remaining 2 patients received human calcitonin by the subarachnoid route (6 mcg or 0.9 international units). Five patients served as controls. Thirty minutes after epidural administration, 5 of 7 patients subjectively noted good pain relief; however, the duration of action was only 1 hour or less with human calcitonin and very prolonged (up to 12 hours) with salmon calcitonin. The subarachnoid route produced an analgesic effect within minutes, but it was short lasting.
Rossano et al published a study of 20 patients using 100 international units of epidurally administered salmon calcitonin. During the 10 treatment days, there was a significant difference in the mean total morphine consumption between the calcitonin and placebo groups. The data suggests that chronic administration of epidural salmon calcitonin can potentiate morphine's analgesic effect, which should reduce the need for morphine-based analgesics.
Finally, Mystakidou et al used subcutaneous, high-dose calcitonin, as an adjunct to morphine treatment, to treat metastatic bone pain in advanced cancer patients. Twenty-two patients who had been pain-free for at least 18 days with continuous subcutaneous morphine treatment but in whom pain then reappeared were given subcutaneous calcitonin 400 international units per day by continuous infusion with the established dose of morphine. Pain scores were significantly reduced at 12, 24, and 48 hours and at 7 days compared to baseline. At 7 days, 7 patients were free of pain. In 3 patients, satisfactory analgesia was not achieved with calcitonin and required an increase in the morphine dose. Plasma beta-endorphin levels increased from baseline levels by 23%, 75%, 109%, and 147% at 12, 24, and 48 hours and 7 days, respectively. There was a statistically significant correlation (p less than 0.005) between beta-endorphin levels and the reduction in pain scores at 12 hours.

Support for using Miacalcin to treat central giant cell reparative granuloma of jaw can be found in two reported cases (Pogrel et al). Calcitonin treatment resolved central giant cell granulomas (CGCG) of the mandible in a 13-year-old girl and an 11-year-old girl. CGCG was histologically confirmed in both cases and was recurring after aggressive curettage in one case and rapidly enlarging after steroid treatment in the other. Calcitonin was tried for this condition because of its histologic similarity to "brown tumor" of hyperparathyroidism, although neither serum calcium concentration nor parathyroid hormone status were abnormal in these cases. Both girls were started on 100 units of subcutaneous human calcitonin per day, which was continued for 11 and 10 months, respectively, until human calcitonin became unavailable in the United States. One girl was switched to subcutaneous salmon calcitonin 100 units per day for another 10 months, and the other to intranasal salmon calcitonin 200 units per day for 9 months. The 11-year-old, who had experienced pain with the growing lesion, had relief from pain within 3 days. However, there was no radiological evidence of improvement in either case until 4 months. After termination of treatment, biopsies showed only fibrous tissue and an almost total absence

of giant cells. A year after treatment, both girls were well, without evidence of recurrence. However, 26 months after termination of treatment, one of the girls developed a biopsy-proven CGCG of the anterior mandible that appeared to be separate from the previous lesion. Calcitonin was to be tried again but had not been at the time of this publication.

Support for using Miacalcin to treat complex regional pain syndrome type I can be found in a study by Hamamci et al. Forty-one patients with hemiplegia and stage 1-2 reflex sympathetic dystrophy (now known as Complex Regional Pain Syndrome Type 1) were given daily intramuscular injections of either salmon calcitonin 100 international units (n=25) or physiological saline 1 ml (n=16) for 4 weeks. Although no difference in pain scores was evident between the groups at one week, by 4 weeks the calcitonin group had significantly less pain than the saline group. Range of motion improved significantly in both groups over the 4 weeks, but improvement in shoulder flexion was significantly greater in the calcitonin group than in the saline group.

Support for using Miacalcin to reduce the bone fracture risk in perimenopausal women with osteoporosis and men with osteoporosis can be found in a study by Kanis and McCloskey. An analysis of 16 trials in which calcitonin was compared to placebo, no therapy, calcium alone, or calcium with vitamin D and in which fractures were counted, the number of vertebral and non-vertebral fractures was lower in those who received calcitonin treatment than in those who did not. Patient populations included post-menopausal women with osteoporosis, perimenopausal women, men with osteoporosis, and men and women taking corticosteroids. Studies ranged in duration from 6 months to 3 years. Fractures per 100 patient years were 6.94 and 16.56 for the calcitonin and non-calcitonin groups, respectively.

Support for using Miacalcin to treat osteogenesis imperfecta can be found in a study by Nishi et al. Annual bone fracture rates were significantly decreased from baseline in 10 patients with osteogenesis imperfecta who were receiving salmon calcitonin by both subcutaneous and intranasal routes. The study design did not, however, include a control group.

Support for using Miacalcin to treat osteoporosis caused by long-term corticosteroid therapy can be found in a randomized, placebo-controlled trial by Ringe. Thirty-six chronic obstructive lung disease patients with a mean daily intake of prednisone 16 milligrams were administered 100 international units of salmon calcitonin every other day subcutaneously (18 patients) or served as controls (18 patients). After 6 months of therapy, there was significant pain relief in the calcitonin group, as well as a 2.7% increase in the mineral content of the distal radius as compared to a decrease of 3.5% in the control group.

Support for using Miacalcin to treat postoperative phantom limb can be found in a study by Jaeger and Maier. Highly significant reductions or complete elimination of early postoperative phantom limb pain was demonstrated in a double-blind, placebo-controlled crossover study of 21 patients with major amputations who received a salmon calcitonin 200 international unit infusion. Placebo infusions resulted in no significant reductions in pain. Calcitonins appear to be highly effective in managing early postoperative phantom limb pain.

Support for using Miacalcin as prophylaxis against premenopausal osteoporosis due to estrogen deficiency can be found in a small, randomized study by Mazzuoli and colleagues. As an alternative to estrogen replacement therapy, a randomized, double-blind study of 28 ovariectomized women found that administration of 100 MRC units of salmon calcitonin given intramuscularly every other day prevented significant changes in bone mineral content (BMC) from occurring, while patients receiving placebo had significant decreases in BMC after only 6 months. These results indicate that for women in whom estrogen replacement therapy is contraindicated, salmon calcitonin can, at least over the short term, inhibit bone resorption; long term studies as well as studies using better tolerated routes of administration are needed.

VI. REFERENCE

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