AETNA BETTER HEALTH®
Clinical Policy Bulletin:
Pamidronate (Aredia)

Number: 0672

Policy

Aetna considers pamidronate (Aredia) medically necessary for treatment of any of the following indications:

Chronic nonbacterial osteomyelitis; or
Complex regional pain syndrome refractory to other treatments; or
Hypercalcemia of malignancy; or
Low bone mass or osteoporotic fractures following organ transplantation; or
Osteogenesis imperfecta, severe cases presenting with bone pain and repeated fractures; or
Osteolytic bone metastases or bone pain from cancer; or
Osteopenia in quadriplegic cerebral palsy; or
Paget's disease (osteitis deformans), symptomatic and characterized by abnormal and accelerated bone metabolism in 1 or more bones, where oral bisphosphonates have been ineffective. (Signs and symptoms may include bone pain, deformity, and/or fractures; increased concentrations of serum alkaline phosphatase and/or urinary hydroxyproline; neurologic disorders associated with skull lesions and spinal deformities; and elevated cardiac output and other vascular disorders associated with increased vascularity of bones); or
Refractory immobilization hypercalcemia; or
Treatment of children with osteoporosis due to immobilization.

Aetna considers pamidronate experimental and investigational for all other indications, including any of the following because its effectiveness for these indications has not been established:

Prevention and treatment of osteoporosis associated with paralysis (immobilization) other than situations noted above; or
Reduction of fracture risk in men undergoing androgen deprivation therapy for prostate cancer; or
Treatment of acute back pain associated with vertebral crush fracture; or
Treatment of avascular necrosis; or
Treatment of bacterial osteomyelitis; or
Treatment of Charcot arthropathy; or
Treatment of chondrodystrophy; or
Treatment of chronic inflammatory joint disease not treated by glucocorticoids; or
Treatment of Fanconi Bickel syndrome; or
Treatment of fibrous dysplasia; or
Treatment of Gaucher's disease; or
Treatment of glucocorticoid-induced osteoporosis; or
Treatment of hypercalcemia associated with hyperparathyroidism or other nontumor-related conditions other than immobilization; or
Treatment of lumbar spinal stenosis; or
Treatment of osteoarthropathy; or
Treatment of osteoblastic lesions in prostate cancer; or
Treatment of osteoporosis or osteopenia associated with androgen deprivation therapy for prostate cancer; or
Treatment of osteoporosis associated with cystic fibrosis; or
Treatment of post-menopausal osteoporosis; or
Treatment of reflex sympathetic dystrophy or
Treatment of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis); or
Treatment of spondyloarthropathy; or
Treatment of stiff man/still person syndrome; or
Treatment of thalassemia-associated osteoporosis.

See also CPB 0524 - Zoledronic Acid and CPB 0666 - Teriparatide (Forteo).

Background

This policy is based on the Food and Drug Administration (FDA)-approved indications for pamidronate, the conclusions of the U.S. Pharmacopeial Convention (USPDI, 2003), and the National Comprehensive Cancer Network Drugs and Biologics Compendium (2008).

Bisphosphonates have been shown to be effective in the treatment of osteoporosis. Alendronate (Fosamax) and risedronate (Actonel) have been the most extensively studied bisphosphonates under clinical trials conditions. Both drugs can lower the risk of vertebral and hip fractures by 25 to 50 %. However, oral bisphosphonates exhibit gastro-intestinal toxicity and strict adherence to constraining therapeutic schemes is mandatory. Pamidronate (Aredia), an intravenous (IV) bisphosphonate, is a much more potent inhibitor of bone resorption than etidronate. Pamidronate is a bisphosphonate that is administered by injection because it is poorly tolerated orally. Pamidronate is approved by the FDA for use in hypercalcemia of malignancy, Paget's disease of the bone, osteolytic bone metastases from breast cancer and osteolytic lesions of multiple myeloma. Newer more potent bisphosphonates, such as oral ibandronate and intravenous zoledronic acid (Zometa), which will allow much less frequent administration, are currently being investigated (Reid et al, 2002). Moreover, bone
-forming agents (e.g., teriparatide) provide another therapeutic option for the treatment of severe osteoporosis.

Hypercalcemia of malignancy is a potentially life-threatening complication of cancer resulting from increased bone resorption by osteoclasts. Management of patients with cancer-related hypercalcemia primarily consists of rehydration therapy as well as the use of a variety of available drugs that inhibit bone resorption. One of the drugs used for this purpose is IV bisphosphonate, which has been demonstrated to lower serum calcium levels by interfering with osteoclast activity and stimulating osteoclast apoptosis. In fact, bisphosphonates are now considered the standard treatment for cancer-related hypercalcemia (Berenson, 2002; Hurtado and Esbrit, 2002; Body and Mancini, 2002).

Paget's disease of bone, also known as osteitis deformans, is a non-malignant metabolic disease of unknown etiology, with the spine being involved in over 50% of cases. It is one of the most common diseases to affect bone, yet it is rare before the age of 50. Moreover, Paget's disease of bone affects up to 2 to 3% of the population over the age of 60 years. This metabolic bone disorder is characterized by abnormalities of bone turnover, structure and architecture. Bisphosphonates are the first-choice treatment option for patients with active disease (Schneider et al, 2002; Keen, 2003).

The American Society of Clinical Oncology (ASCO) convened an expert multi-disciplinary panel to determine clinical practice guidelines for the use of bisphosphonates in the prevention and treatment of bone metastases in breast cancer and their role relative to other therapies for this condition. The panel recommended IV pamidronate for patients with metastatic breast cancer who have imaging evidence of lytic destruction of bone and who are concurrently receiving systemic therapy with hormonal therapy or chemotherapy (Hillner et al, 2000). A Cochrane evidence review of randomized controlled clinical trials of bisphosphonates in breast cancer concluded that IV pamidronate has been demonstrated to be effective in improving metastatic bone pain (Pavlakis et al, 2005).

The ASCO also convened an expert multi-disciplinary panel to determine clinical practice guidelines for the use of bisphosphonates in the prevention and treatment of lytic bone disease in multiple myeloma (MM) and to determine their respective role relative to other conventional therapies for this condition (Berenson et al, 2002). The available evidence indicates that oral clodronate, IV pamidronate, and IV zoledronic acid are superior to placebo in reducing skeletal complications. A reduction in vertebral fractures has consistently been observed across all studies. No agent has shown a definitive survival benefit. Intravenous zoledronic acid has recently been shown to be as effective as IV pamidronate. Because there are no direct comparisons between clodronate and pamidronate or zoledronic acid, the superiority of one agent cannot be definitively established. However, the panel recommended only IV pamidronate or zoledronic acid in light of the use of the time to first skeletal event as the primary end point and more complete assessment of bony complications in studies evaluating it. Additionally, clodronate is not available in the United States. The choice between pamidronate and zoledronic acid will depend on choosing between the higher drug cost of zoledronic acid, with its shorter, more convenient infusion time (15 mins), versus the less expensive
drug, pamidronate, with its longer infusion time (2 hrs). The panel concluded that bisphosphonates provide a meaningful supportive benefit to MM patients with lytic bone disease.

A Cochrane evidence review of clinical trials concluded that adding bisphosphonates to the treatment of myeloma reduces pathological vertebral fractures and pain but -- from the published evidence -- not mortality (Djulbegovic et al, 2002). The review stated that, based upon current evidence, clodronate or pamidronate may be the preferred agents for this indication.

Mayo Clinic's consensus statement on the use of bisphosphonates (e.g., pamidronate and zoledronic acid) in MM (Lacy et al, 2006) recommended discontinuing bisphosphonates after 2 years of therapy for patients who achieve complete response and/or plateau phase. For patients whose disease is active, who have not achieved a response, or who have threatening bone disease beyond 2 years, therapy can be decreased to every 3 months.

Both pamidronate and zoledronic acid have been shown to reduce bone loss in men undergoing androgen deprivation therapy in prostate cancer. However, zoledronic acid has also been shown to increase bone mineral density in these patients (Smith, 2003). In addition, zoledronic acid has been shown in randomized controlled clinical studies to reduce the incidence of skeletal-related events in men undergoing androgen-deprivation therapy. In addition, zoledronic acid has been shown in clinical trials to reduce the incidence of skeletal events in men with osteoblastic bone metastases from prostate cancer. By contrast, a clinical study comparing pamidronate to placebo control in men with bone metastases due to prostate cancer found no significant differences in incidence of skeletal events between the 2 groups (Lipton et al, 2002).

Although there is evidence that pamidronate increases bone mass, there are no clinical trials demonstrating that intravenous pamidronate decreases fracture rate in post-menopausal osteoporosis or glucocorticoid-induced osteoporosis. As the experience with etidronate has shown, increases in bone mass may not translate into a reduction in fracture incidence; the quality of the bone that is formed is also important. Solomon (2002) suggested that the notion that an IV dose of a bisphosphonates once-yearly or even less often can be used for the treatment of post-menopausal osteoporosis is encouraging. However, before this treatment can be recommended for routine use, more research is needed to ascertain if the risk of fractures is actually lowered and to determine the safety of long-term use of this treatment. This is in accordance with the report by Crandall (2002) who stated that the combination of bisphosphonates (alendronate) with estrogen can increase bone mass density (BMD) more so than each medication given singly in post-menopausal osteoporotic women; however, the utility of these combinations rests on whether bone density changes will translate into decreased fracture rates.

Guidelines on treatment of glucocorticoid-induced osteoporosis from the American College of Rheumatology state that “[b]oth alendronate and risedronate are recommended for the prevention and treatment of glucocorticoid-induced bone loss” and to “[c]onsider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy.” An evidence-based assessment conducted by the Royal College of Physicians (2002) noted that while pamidronate and a number of other bisphosphonates have been shown
in clinical studies to reduce glucocorticoid-induced bone loss, only the
bisphosphonates risedronate, alendronate, and etidronate have been shown to
reduce the incidence of fractures.

Rapid bone loss following organ transplantation has been attributed to numerous
factors, including hypogonadism, cyclosporine, and glucocorticoids. Clinical
studies have demonstrated the effectiveness of intravenous pamidronate in
reducing the rate of bone loss following organ transplantation (ICSI, 2002). In
addition, there is limited evidence that pamidronate reduces the incidence of
fractures following organ transplantation (Hodsman, 2001; Cahill et al, 2001; Aris

Orcel and Beaudreuil (2002) noted that the available evidence does not support
the use of bisphosphonates in the management of patients with reflex sympathetic
dystrophy, acute back pain after a vertebral crush fracture, and chronic
inflammatory joint disease not treated by glucocorticoids. Although pamidronate
has been shown to increase bone mass in post-menopausal osteoporosis and
glucocorticoid-induced osteoporosis, there are no published prospective
randomized controlled clinical trials of the effectiveness of IV pamidronate in
reducing fracture risk in these conditions.

Saad and Schulman (2004) recently reviewed the evidence regarding the role of
bisphosphonates in prostate cancer. These investigators concluded that
pamidronate has been shown to prevent bone loss, whereas zoledronic acid has
been shown to increase bone mass in men undergoing androgen deprivation
therapy. Finally, zoledronic acid is the only bisphosphonate that has
demonstrated efficacy in reducing objectively measurable skeletal complications in
patients with bone metastases secondary to prostate cancer. This is in agreement
with the findings of Small et al (2003) as well as Rosen (2004). Rosen stated that
clinical trials addressing the treatment of bone metastases related to prostate
cancer have shown zoledronic acid to be the only bisphosphonate to have a
significant positive effect on skeletal-related events.

Small and colleagues (2003) performed a combined analysis of 2 multi-center,
randomized, placebo-controlled studies of pamidronate for men with metastatic
prostate cancer. The authors concluded that pamidronate failed to demonstrate a
significant overall treatment benefit compared with placebo in the palliation of bone
pain or reduction of skeletal-related events (defined as pathologic fracture,
radiation or surgery to bone, spinal cord compression, or hypercalcemia). In an
editorial that accompanied the article by Small et al, Kelly and Steineck (2003)
stated that “the cumulative data on bisphosphonates in patients with castrate
metastatic prostate cancer to date have not shown substantial clinical benefits to
patients .... until this evidence is provided, routine administration of
bisphosphonates in castrate metastatic prostate cancer can not be
recommended”.

A review of the evidence for the use of pamidronate for ankylosing spondylitis and
spondyloarthropathies concluded that results of preliminary studies have yielded
promising results, but that “[f]urther studies are required to confirm these
preliminary data and to better determine the optimal regimen (dosage and rhythm)
of administration” (Toussirot and Wendling, 2005).
There is limited evidence from case reports and uncontrolled case series of the effectiveness of pamidronate in the treatment of hypercalcemia associated with immobilization. Massagli and Cardenas (1999) reported on the results of pamidronate treatment of patients with acute spinal cord injury (SCI) who developed immobilization hypercalcemia. A total of 9 patients (7 men, 2 women), aged 15 to 41 years, with SCI (8 tetraplegia, 1 paraplegia) were treated using pamidronate between 1994 and 1998. A single dose of 60 mg of pamidronate resolved the hypercalcemia or its symptoms in 7 (78 %) patients within days. One patient required a 2nd dose (90 mg) and 1 patient required 3 additional doses (the 4th at 90 mg) to achieve resolution of the hypercalcemia or symptoms. These investigators reported that side effects were mild, and included drug-related fever in 1 patient and transient asymptomatic hypocalcemia in 4 patients. They reported that pamidronate was effective in treating immobilization hypercalcemia caused by SCI. These investigators commented that the advantages of pamidronate include its effectiveness, the duration of treatment, ease of administration, and elimination of the need for long-term intravenous saline or daily medications.

There is, however, insufficient evidence of the effectiveness of pamidronate in preventing bone loss from immobility. In a prospective placebo-controlled study (n = 11), Bauman et al (2005) examined the effectiveness of pamidronate in reducing bone loss in persons with acute SCI. Pamidronate (treatment) or normal saline (placebo) was administered intravenously at baseline (22 to 65 days after injury) and sequentially over 12 months, with follow-up at 18 and 24 months. Regional BMD was lost over time, regardless of group. In the treatment group compared with the placebo group, these investigators noted a mild early reduction in loss of total leg BMD. Significant bone loss from baseline occurred earlier in the placebo group at the regional sites than in the treatment group. However, by the end of the treatment and follow-up phases, both groups demonstrated a similar percent bone loss from baseline. The authors concluded that despite an early reduction in bone loss, pamidronate failed to prevent major, long-term bone loss in persons with acute neurologically complete SCI.

Chronic nonbacterial osteomyelitis (CNO) is a sterile inflammatory bone disorder of unknown etiology. CNO is currently thought to be in the spectrum of autoimmune and autoinflammatory disorders. Non-infectious inflammatory lesions of the mandible occur in chronic recurrent multi-focal osteomyelitis (CRMO). Diffuse sclerosing osteomyelitis of the mandible (DSOM) is a condition thought to be a localized form of CRMO. Treatment of CNO has been directed at reducing pain and inflammation, with the intent of halting bone destruction and disease progression. Bisphosphonate therapy, especially intravenous pamidronate, has been proposed as a treatment for patients with both CRMO and DSOM who do not improve with non-steroidal anti-inflammatory drug (NSAID) treatment. A review of CNO published in Pediatrics (Borzutzky, et al., 2012) states that, due to the low prevalence of this disease, most treatment reports involve small series or individual cases. The review article explains that NSAIDS are generally used as first-line therapy, but frequently patients require additional treatments. The review states that small series have reported successful treatment of CNO with bisphosphonates. The article cites several studies involving use of pamidronate for this indication.
Yamazaki and colleagues (2007) reported a juvenile case of DSOM that showed a favorable response to pamidronate. Although conventional treatments had been ineffective for 5 years, pamidronate administration resulted in conspicuous improvement both clinically and radiographically. Severe adverse reaction was not found except for low-grade fever and lassitude on the day following administration. During the course of the treatment, however, non-suppurative osteomyelitis of the right humerus also occurred, leading to the established diagnosis of chronic recurrent multi-focal osteomyelitis. Pamidronate therapy was again performed successfully with near disappearance of clinical symptoms. Both bone-specific alkaline phosphatase (bone formation marker) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (bone resorption marker) showed a marked decrease with pamidronate therapy, suggesting that pamidronate is useful for the treatment of chronic recurrent multi-focal osteomyelitis with inhibitory effect on bone turnover.

Olivieri et al (2006) stated that the SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome (SaS) includes different skeletal manifestations such as recurrent multi-focal osteomyelitis, osteitis and arthritis, which are frequently associated with different forms of skin pustulosis (palmoplantar pustulosis, pustular psoriasis and severe acne). This syndrome is strictly related to the spondyloarthopathies (particularly to psoriatic arthritis) and many SaS cases fulfill the classification criteria for the spondyloarthopathies. Because SaS is an uncommon disease, current knowledge regarding its therapy is based on limited experiences gained by treating mainly small groups of patients. As a consequence, its treatment is still empiric. Several drugs (including NSAIDs, corticosteroids, sulfasalazine, methotrexate, cyclosporine, leflunomide, and calcitonin) have been administered and obtained conflicting results. The use of antibiotics, due to the isolation of Propionibacterium acnes from the bone biopsies of several subjects with SaS, has not represented a turning point in therapy, although some patients are responsive to this treatment. Initial reports concerning the administration of bisphosphonates (pamidronate and zoledronic acid) and of an anti-TNF-alpha agent (infliximab) are very promising for the future. In any case, larger, multi-center, controlled, double-blind studies are needed to emerge from the present pioneering phase.

Kerrison et al (2004) reported their clinical experience with pamidronate in childhood SAPHO syndrome. The standard dosing regimen for pamidronate was 1 mg/kg to a maximum of 30 mg, administered daily for 3 consecutive days, repeated thrice-monthly as required. Response to treatment was determined by clinical observation, patient subjective response and reduction in other treatments. A total of 7 girls were treated, with a median (range) age at diagnosis of 11 years (9 to 15 years). All patients demonstrated a beneficial clinical response, with relief of pain, increased activity and improved well-being. Subsequent courses of pamidronate were used in all patients. Other medications including corticosteroids and methotrexate could subsequently be stopped. Transient symptoms were associated with the initial course of pamidronate in some patients. No serious adverse events were reported. The authors concluded that pamidronate was associated with a marked improvement in function and well-being, and a reduction of pain and use of other medications in all patients, with no significant adverse effects. However, this study represented preliminary clinical
data. The authors stated that a prospective multi-center study is needed to evaluate the role and long-term safety of pamidronate in the management of childhood SAPHO syndrome.

Gaucher's disease, the most prevalent lysosomal storage disorder, is characterized by an autosomal recessive inheritance of a deficiency of lysosomal acid glucocerebrosidase. Three clinical phenotypes are recognized: (i) type 1 (non-neuronopathic), (ii) type 2 (acute neuronopathic), and (iii) type 3 (subacute neuronopathic). Bone lesions are associated with type 1 and type 3 Gaucher's disease. Skeletal involvement is secondary to the progressive accumulation of histiocytes and macrophages laden with glucosylceramide in bone marrow. Pamidronate has been employed in treating patients with Gaucher's disease; however, there is insufficient evidence to support the effectiveness of this approach.

Ciana et al (1997) reported their findings of 5 patients (3 women and 2 men; age range of 24 to 60 years) who had type 1 Gaucher's disease and severe skeletal involvement (as defined by a combination of osteopenia, osteonecrosis-osteosclerosis, and severe chronic bone pain) who were treated with pamidronate. The drug was given intravenously (45 mg once every 3 weeks for 3 to 5 months); patients were also given 500 mg of elemental calcium daily. The bone pain decreased rapidly in each patient. The treatment was accompanied by decreases in markers of both bone resorption (urinary hydroxyproline and total deoxypyridinoline [p = 0.08 for both] and urinary calcium [p = 0.04]) and bone formation (serum osteocalcin, p = 0.04). At the end of the treatment period, the mean (+/- SD) BMD of the lumbar spine, as determined by dual-energy x-ray absorptiometry, increased from 0.79 +/- 0.07 to 0.84 +/- 0.05 g per square centimeter (p = 0.04).

Fibrous dysplasia (FD) of bone, a rare disease caused by osteoblastic lineage differentiation defects, is associated with bone pain, fracture, and bone deformity, but few therapeutic options are available. Chapurlat (2006) stated that in open studies, bisphosphonate therapy (pamidronate, alendronate) reduced bone pain associated with FD of bone and was associated to some radiological improvement. Calcium, vitamin D, and phosphorus supplements may be useful in patients with deficiency. The author reviewed published data on the treatment of FD with bisphosphonates, calcium, vitamin D, and phosphorus; and presented new results on FD therapy with a more potent bisphosphonate, zoledronic acid, given intravenously at the dose of 4 mg every 6 months. Pamidronate therapy, given intravenously every 6 months at a dose of 180 mg in adults, relieved bone pain, decreased bone resorption, and improved the radiological aspect (filling of lytic lesions and/or thickening of cortices) in approximately 50 % of patients. Bone mass density in affected sites was also significantly increased after pamidronate treatment. Those results have been obtained only in open studies, without controls, by several research groups. In a series of 9 patients on long-term pamidronate treatment, but resisting to this medication and switched to IV zoledronic acid, no substantial improvement was observed. There is some biological rationale supporting the use of calcium and vitamin D in patients with deficiency to improve FD lesions by limiting secondary hyper-parathyroidism. Phosphorus supplementation may prevent mineralization defects in those patients who have both FD and renal phosphate wasting. However, there is a lack of
clinical evidence for the effectiveness of such supplements. The author concluded that bisphosphonate treatment reduces increased osteoclastic activity in FD and probably improves bone pain, but their use should be better studied in randomized controlled trials.

Plotkin et al (2003) described the effects of pamidronate therapy in 18 children and adolescents (age at start of therapy, 6.2 to 17.5 years; 8 girls and 10 boys) with polyostotic FD, who received pamidronate for 1.2 to 9.1 years (median of 3.8 years). Treatment cycles with pamidronate (1 to 1.5 mg/kg/day on 3 consecutive days) were given every 4 months. Levels of serum alkaline phosphatase and urinary collagen type I N-telopeptide were elevated at baseline and decreased continuously during the first 3 years of therapy. There was no radiographical evidence of filling of lytic lesions or thickening of the bone cortex surrounding the lesions in any patient. Histo-morphometrical results in dysplastic bone tissue of patients receiving pamidronate (n = 7; time of therapy, 1.4 to 4.8 years) were similar to those of patients without medical therapy (n = 9). No serious side effects were noted. The authors concluded that pamidronate therapy appears to be safe in children and adolescents with polyostotic FD. However, these researchers found no clear evidence that pamidronate has an effect on dysplastic lesions in such patients.

Chan and Zacharin (2006) did not find bisphosphonate treatment to be effective in treating children with McCune-Albright syndrome (MAS); one of the main features of MAS is FD. These investigators examined outcomes of pamidronate treatment on FD in 3 children with MAS. Radiological evidence of FD progress was reviewed in these patients who were treated with pamidronate from age 2.5 to 5 years, for 8 to 10.5 years. Despite minimal pain and a low fracture rate in long bones, except where gross deformity exists, all dysplastic lesions present in long bones continued to undergo uncontrolled expansion. In contrast, there were no major new changes in facial configuration, no clinically obvious expansion of sphenoid wing lesions and no encroachment on optic foramina or visual field restriction in any patient. The authors concluded that despite previous reports of limitation or reduction in size of FD lesions in adults and children, it is the authors’ experience that bisphosphonate treatment of polyostotic FD in children with MAS does not arrest the expanding nature of these lesions. Furthermore, Chapurlat and Orcel (2008) stated that bisphosphonates have been used in the treatment of FD to relieve bone pain and improve lytic lesions, but they are still under clinical evaluation.

Patients with chronic kidney disease have significant abnormalities of bone remodeling and mineral homeostasis and are at increased risk of fracture. The fracture risk for kidney transplant recipients is 4 times that of the general population and higher than for patients on dialysis. Ebeling (2007) noted that organ transplant candidates should be assessed and pre-transplantation bone disease should be treated. Preventive therapy initiated in the immediate post-transplantation period is indicated in patients with osteopenia or osteoporosis, as further bone loss will occur in the first several months following transplantation. Long-term organ transplant recipients should also have bone mass measurement and treatment of osteoporosis. Bisphosphonates are the most promising approach for the management of transplantation osteoporosis. Active vitamin D metabolites may have additional benefits in reducing hyperparathyroidism,
particularly after kidney transplantation. The author stated that large, multi-center treatment trials with oral or parenteral bisphosphonates and calcitriol are needed.

In a Cochrane review, Palmer et al (2007) assessed the use of interventions for treating bone disease following kidney transplantation. Randomized controlled trials (RCTs) and quasi-RCTs comparing different treatments for kidney transplant recipients of any age were selected. All other transplant recipients, including kidney-pancreas transplant recipients were excluded. Two authors independently evaluated trial quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as relative risk (RR) with 95 % confidence intervals (CI) for dichotomous variables and mean difference (MD) for continuous outcomes. A total of 24 trials (n = 1,299) were included. No individual intervention (bisphosphonates, vitamin D sterol or calcitonin) was associated with a reduction in fracture risk compared with placebo. Combining results for all active interventions against placebo demonstrated any treatment of bone disease was associated with a reduction in the RR of fracture (RR 0.51, 95 % CI: 0.27 to 0.99). Bisphosphonates (any route), vitamin D sterol, and calcitonin all had a beneficial effect on the BMD at the lumbar spine. Bisphosphonates and vitamin D sterol also had a beneficial effect on the BMD at the femoral neck. Bisphosphonates were more effective in preventing BMD loss when compared head-to-head with vitamin D sterols. Few or no data were available for combined hormone replacement, testosterone, selective estrogen receptor modulators, fluoride or anabolic steroids. Other outcomes including all-cause mortality and drug-related toxicity were reported infrequently. The authors concluded that treatment with bisphosphonates, vitamin D sterol or calcitonin after kidney transplantation may protect against immunosuppression-induced reductions in BMD and prevent fracture. However, they stated that adequately powered clinical studies are needed to ascertain if bisphosphonates are better than vitamin D sterols for fracture prevention in this population. Moreover, the optimal route, timing, and duration of administration of these interventions remains unknown.

Walsh et al (2009) examined the effect of pamidronate on bone loss following kidney transplantation. Patients were randomly assigned to treatment (n = 46) or control (no treatment; n = 47) groups. They were stratified according to parathyroid hormone (PTH) level and sex. Those with PTH level less than 150 pg/ml were excluded. The treatment and control groups received pamidronate, 1 mg/kg, peri-operatively and then at 1, 4, 8, and 12 months or no treatment, respectively. All received calcium (500 mg) and vitamin D (400 units) daily. Immunosuppression was cyclosporine and prednisolone, with no difference in dosing between the 2 groups. Bone mineral density was evaluated by means of dual-energy x-ray absorptiometry of the lumbar spine and hip at baseline and 3, 6, 12, and 24 months, with the primary end point at 1 year of percentage of change in BMD from baseline. Clinical fractures were recorded and also evaluated by means of spinal radiographs at baseline and 1 and 2 years. Pamidronate protected BMD at the lumbar spine; BMD increased by 2.1 % in the treatment group and decreased by 5.7 % in the control group at 12 months (p = 0.001). Protection was also seen in Ward's area of the hip (p = 0.002) and the total hip (p = 0.004). There was no difference in femoral neck BMD loss between the 2 groups. Fracture rates in the treatment and control groups were 3.3 % and 6.4 % per annum, respectively. The authors concluded that pamidronate protects against post-transplantation bone loss at the lumbar spine and Ward's area of the
hip. The major limitation of this study was that it was not powered to detect differences in fracture rates.

It is also interesting to note that in a RCT of pamidronate in the prevention of bone loss following liver transplantation, Monegal et al (2009) reported that 90 mg of IV pamidronate within the first 2 weeks and at 3 months following liver transplantation preserve lumbar bone mass during the first year, without significant adverse events. However, pamidronate does not reduce bone loss at the femoral neck; and furthermore it does not reduce skeletal fractures.

Osteonecrosis of the jaws is a recently described adverse effect in patients treated with bisphosphonates and, in particular, potent aminobisphosphonates. Most of the reported cases have been in patients with multiple myeloma or metastatic cancer, though cases have also been identified in patients with osteoporosis. In a systematic review, Woo et al (2006) found that, in almost all reported cases, patients received pamidronate or zoledronic acid. These investigators conducted a systematic review of reported cases of osteonecrosis of the jaws following treatment with bisphosphonates. A total of 29 papers (n = 368) were included: 10 case series of 10 or more individuals and 19 series or case reports of fewer than 10 patients. There were 368 reported cases of bisphosphonate-associated osteonecrosis of the jaw. The mandible alone was affected in 65 % of cases, the maxilla alone in 26 %, and both sites in 9 %. The most important risk factors were, according to the reviewers, type and total dose of bisphosphonate, history of trauma, dental surgery or dental infection. Ninety-four per cent of patients received pamidronate or zoledronic acid. Osteonecrosis occurred after having a tooth removed or other dentoalveolar surgery in 60 % of cases; the remaining cases occurred spontaneously.

Moreover, in a population-based analysis, Wilkinson et al (2007) reported that users of IV bisphosphonates (pamidronate and/or zoledronic acid) had an increased risk of inflammatory conditions, osteomyelitis, and surgical procedures of the jaw and facial bones. The increased risk may reflect an increased risk for osteonecrosis of the jaw.

In an open, pilot study, Feld and colleagues (2009) stated that degenerative lumbar spinal stenosis, manifesting as chronic low back pain and neurogenic claudication, is an increasing chronic problem in an aging population, with limited effective conservative treatment options. Based on previous reports on the utility of subcutaneous calcitonin and 2 anectodal cases, these researchers launched an open trial of intravenous monthly pamidronate infusions, over a course of 3 to 6 months in this condition. Of 24 patients, 75 % reported pain improvement, with the mean visual analog scale score improved by 40 %; while composite functional improvement in walking time, activities of daily living, and sense of wellbeing was reported by 66 %, with a mean improvement of 50 %. The authors concluded that these findings suggested the usefulness of this modality and warrant examination in a RCT.

In a systematic review, Cardozo and colleagues (2008) examined the use of bisphosphonates in the treatment of avascular necrosis (AN). Studies in which bisphosphonate was used for the treatment of AN were researched through the Medline databases (from 1966 to 2007) and the Cochrane Central Register of Controlled Trials and using the following terms: "vascular necrosis," "aseptic
necrosis," "bisphosphonates," "alendronate," "pamidronate," "zoledronate," and "risedronate". Only 7 articles that met the previously established criteria were obtained from MedlineE, and none was obtained from the Cochrane Central Register of Controlled Trials. Of these 7 articles, 2 were RCTs and 5 were prospective comparative studies; 1 of them corresponded to an extension of a previous study. The review demonstrated that there are no controlled and double-blind studies about the efficacy of bisphosphonates in the treatment of AN. Thus, the data are still insufficient for justifying its use for this indication. On the other hand, non-controlled studies appear to demonstrate favorable results, particularly in diminishing pain, improving mobility, and lowering the incidence of articular collapse, which justifies new studies being developed in this area.

Voskaridou and Terpos (2008) noted that osteopenia and osteoporosis cause severe problems in patients with thalassemia major (TM). The delay in sexual maturation, the presence of diabetes and hypothyroidism, the parathyroid gland dysfunction, the accelerated hemopoiesis with progressive marrow expansion, the direct iron toxicity on osteoblasts, the iron chelators, the deficiency of growth hormone or insulin growth factors, all have been identified as major causes of osteoporosis in patients with TM. However, despite the normalization of hemoglobin levels, adequate hormone replacement and effective iron chelation, patients continue to show an unbalanced bone turnover with an increased resorptive phase resulting in seriously diminished BMD. During the last decade, bisphosphonates have been used for the management of osteoporosis in TM. Alendronate, pamidronate, and zoledronic acid have shown efficacy in increasing BMD in patients with TM. However, further trials must be conducted in order to clarify the exact role of each bisphosphonate, the long-term benefit and side-effects as well as the effects of the combination of bisphosphonates with other effective agents, such as hormonal replacement, on thalassemia-associated osteoporosis.

Gaudio and colleagues (2008) stated that TM is a common cause of skeletal morbidity, as shown by the increased fracture risk in thalassemic patients. The pathogenesis of this bone disease is multi-factorial and culminates in a state of increased bone turnover with excessive bone resorption and remodeling. Despite hormonal replacement therapy, calcium and vitamin D administration, effective iron chelation, and normalization of hemoglobin levels, patients with TM continue to lose bone mass. The increased bone turnover rate observed in patients with TM justifies the use of powerful anti-resorption drugs, such as bisphosphonates. To date, alendronate, pamidronate, and zoledronate seem to be effective in increasing BMD and normalizing bone turnover, but more trials are needed to evaluate their efficacy in reducing fracture risks in larger thalassemic populations.

Skordis et al (2008) examined the effect of 2 bisphosphonate drugs, alendronate and pamidronate on bone mass in patients of both genders with TM. A total of 53 (22 males and 31 females) TM patients of Greek Cypriot origin were randomly divided into 2 groups; (i) 29 patients in group A with a mean age of 33 years were treated with alendronate and (ii) 24 patients in group B with a mean age of 34 years received pamidronate for a period of 2 years. The effectiveness of both drugs was estimated based on the change of BMD values of lumbar spine and femoral neck. Bone mineral density of lumbar spine and femoral neck was
measured by dual-energy X-ray absorptiometry. All patients were on the standard treatment protocol of Thalassaemia. Statistical analysis was performed with the SPSS program. Following completion of treatment with pamidronate, the mean lumbar spine BMD has improved from -2.813 to -2.174 (p < 0.001) and the mean hip BMD from -2.138 to -2.078 (p = 0.018). The change of spine BMD in patients who received alendronate was from -2.720 to -2.602 (p = 0.059) and the changes in BMD at the femoral neck from -2.035 to -2.007 (p = 0.829). The authors concluded that these findings demonstrated the effectiveness of 2 bisphosphonate drugs in improving BMD values in patients with TM and osteoporosis. Since the origin of bone disease in TM is multi-factorial and some of the underlying pathogenic mechanisms are still unclear, further research in this field is needed, which will allow the design of optimal therapeutic measures.

Slobodin et al (2009) reviewed the available published data regarding the potential use of pamidronate in rheumatology practice. Methods include the review of relevant articles retrieved by a PubMed search utilizing the index term "pamidronate". All available RCTs, open trials, and case series as well as properly reported case studies evaluating usage of pamidronate in rheumatic disorders were included in the literature review. The efficacy of pamidronate in patients with spondyloarthropathies; SAPHO syndrome; hypertrophic osteoarthropathy; osteoporotic vertebral fractures; chronic back pain due to disk disease or spinal stenosis; Charcot arthropathy; transient osteoporosis; and complex regional pain syndrome-type 1, has been demonstrated in more than 40 reports, the majority of which, however, were not controlled studies. In some of reviewed conditions, aside from providing analgesic relief, pamidronate may also have disease-modifying properties. While used in different doses in a variety of rheumatic disorders, pamidronate was generally reported to be well-tolerated with an overall good safety profile. Pamidronate may represent an effective and safe choice for a spectrum of rheumatic patients, suffering from intractable musculoskeletal pain, unresponsive to traditionally recommended therapies. The authors stated that large RCTs examining the efficacy of pamidronate in the rheumatic conditions are urgently needed.

De La Mata and co-workers (2011) examined the effectiveness of available drugs in undifferentiated spondyloarthritis (u-SpA). Systematic review of studies were retrieved from Medline (1961 to July 2009), Embase (1961 to July 2009), and Cochrane Library (up to July 2009). A complementary hand search was also performed. The selection criteria were as follows: (population) u-SpA patients; (intervention) non-steroidal anti-inflammatory agents, disease-modifying anti-rheumatic drugs, anti-tumor necrosis factor-alpha, anakinra, abatacept, biphosphonates, or thalidomide; (outcome) pain, function, structural damage and quality of life; (study design) RCT, cohort studies, and case reports; (level of evidence) according to The Oxford Centre for Evidence-based Medicine (update 2009). An additional narrative review was performed to analyze the effects of drug therapies in patients with spondyloarthritis according new Assessment of Spondyloarthritis International Society criteria. A total of 7 studies were included in this review: 2 RCTs, 1 cohort study, and 4 case reports, which included 117 patients with u-SpA (mostly young men). No evidence related to the effect of non-steroidal anti-inflammatory agents or disease-modifying anti-rheumatic drugs on u-SpA patients was found. Infliximab and etanercept showed some benefit regarding clinical outcomes, function, and quality of life. Two RCTs reported
Important benefit of infliximab and adalimumab also in patients with predominantly axial spondyloarthritis. Rifampicin plus doxycycline improved some clinical outcomes but ciprofloxacin had no benefit. Anecdotal positive evidence was reported with pamidronate. No serious adverse events were reported in the retrieved studies. The authors concluded that low-quality evidence suggested a benefit of tumor necrosis factor-alpha blockers in u-SpA and good-quality evidence in predominantly axial spondyloarthritis. The use of antibiotics remains controversial. High-quality trials are needed to definitively assess the effect of available drugs in these patients.

Soriano and colleagues (2012) stated that little data are available for the use of disease-modifying anti-rheumatic drugs in ankylosing spondylitis. Sulfasalazine has been the best studied. These researchers examined efficacy data for individual agents (including pamidronate) and combinations of agents. Intriguingly, these agents continue to be used with some frequency, even in the absence of efficacy data. To answer these questions, additional systematic studies of these agents in ankylosing spondylitis are needed and will likely need to be done by interested collaborative groups such as SPARTAN.

The ASCO executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer (Van Poznak et al, 2011) stated that bone-modifying agent therapy is only recommended for patients with breast cancer with evidence of bone metastases; subcutaneous denosumab 120 mg every 4 weeks, IV pamidronate 90 mg over no less than 2 hours, or IV zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence to show greater efficacy of one bone-modifying agent over another. In patients with a calculated serum creatinine clearance of more than 60 mg/min, no change in dosage, infusion time, or interval of bisphosphonate administration is required. Serum creatinine should be monitored before each dose. All patients should receive a dental examination and appropriate preventive dentistry before bone-modifying agent therapy and maintain optimal oral health. Furthermore, the guideline noted that the use of biochemical markers to monitor bone-modifying agent use is not recommended.

In a Cochrane review, Conwell and Chang (2012) evaluated the effects of bisphosphonates on the frequency of fractures, BMD, quality of life, adverse events, trial withdrawals, and survival in people with cystic fibrosis (CF). These investigators searched the Cystic Fibrosis and Genetic Disorders Group Trials Register of references (identified from electronic database searches and handsearches of journals and abstract books) on February 15, 2012. Additional searches of PubMed were performed on May 14 2011. Randomized controlled trials of at least 6 months duration studying bisphosphonates in people with cystic fibrosis were included. Two authors independently selected trials and extracted data. Trial investigators were contacted to obtain missing data. A total of 9 trials were identified and 7 (with a total of 237 adult participants) were included. Data were combined (when available) from 6 included studies in participants without a lung transplant. Data showed that there was no significant reduction in fractures between treatment and control groups at 12 months, odds ratio 0.72 (95% CI: 0.13 to 3.80). No fractures were reported in studies with follow-up at 24 months. However, in patients taking bisphosphonates after 6 months the percentage change in BMD increased at the lumbar spine, mean difference 4.61 (95% CI:
Pamidronate (Aredia)  

3.90 to 5.32) and at the hip or femur, mean difference 3.35 (95 % CI: 1.63 to 5.07); but did not significantly change at the distal forearm, mean difference -0.49 (95 % CI: -2.42 to 1.45). In patients taking bisphosphonates, at 12 months the percentage change in BMD increased at the lumbar spine, mean difference 6.10 (95 % CI: 5.10 to 7.10) and at the hip or femur, mean difference 4.35 (95 % CI: 2.99 to 5.70). At 24 months, in patients treated with bisphosphonates the percentage change in BMD also increased at the lumbar spine, mean difference 5.49 (95 % CI: 4.38 to 6.60) and at the hip or femur, mean difference 6.05 (95 % CI: 3.74 to 8.36). There was clinical heterogeneity between studies and not all studies reported all outcomes. Bone pain was the most common adverse event with intravenous agents. Flu-like symptoms were also increased in those taking bisphosphonates. In participants with a lung transplant (1 study), intravenous pamidronate did not change the number of new fractures. At axial sites, BMD increased with treatment compared to controls: percentage change in BMD at lumbar spine, mean difference 6.20 (95 % CI: 4.28 to 8.12); and femur mean difference 7.90 (95 % CI: 5.78 to 10.02). The authors concluded that oral and intravenous bisphosphonates increase BMD in people with CF. Severe bone pain and flu-like symptoms may occur with intravenous agents. They stated that additional trials are needed to determine if bone pain is more common or severe (or both) with the more potent zoledronate and if corticosteroids ameliorate or prevent these adverse events. Furthermore, they noted that additional trials are also required to further assess gastro-intestinal adverse effects associated with oral bisphosphonates. Trials in larger populations are needed to determine effects on fracture rate and survival.

Ward and colleagues (2007) stated that children with chronic illnesses are at increased risk for reductions in bone strength and subsequent fractures (osteoporosis), either due to the impact of the underlying condition on skeletal development or due to the osteotoxic effect of medications (e.g., glucocorticoids) used to treat the chronic illness. Bisphosphonates are being administered with increasing frequency to children with secondary osteoporosis; however, the efficacy and harm of these agents remains unclear. In a Cochrane review, these investigators examined the effectiveness and harm of bisphosphonate therapy in the treatment and prevention of secondary osteoporosis in children and adolescents. They searched the Cochrane Central Register of Controlled Trials (Issue 4, 2006), MEDLINE, EMBASE, CINAHL and ISI Web of Science (inception to December 2006). Further literature was identified through expert contact, key author searches, scanning reference lists of included studies, and contacting bisphosphonate manufacturers. Randomized, quasi-randomized, controlled clinical trials, cohort, and case controls of bisphosphonate(s) in children 0 to 18 years of age with at least 1 low-trauma fracture event or reductions BMD in the context of secondary osteoporosis were selected for analysis. Two reviewers independently extracted data and assessed quality. Case series were used for supplemental harms-related data. A total of 6 RCTs, 2 controlled clinical trials (CCTs), and 1 prospective cohort (n = 281 children) were included and classified into osteoporosis due to: (i) neuromuscular conditions (1 RCT) and (ii) chronic illness (5 RCTs, 2 CCTs, 1 cohort). Bisphosphonates examined were oral alendronate, clodronate, and IV pamidronate. Study quality varied. Harms data from 23 case series (n = 241 children) were used. Heterogeneity precluded statistically combining the results. Percent change or Z-score change in lumbar
spine areal BMD from baseline were consistently reported. Two studies carried out between-group analyses; 1 showed no significant difference (using oral alendronate in anorexia nervosa) while the other demonstrated a treatment effect on lumbar spine with IV pamidronate in burn patients. Frequently reported harms included the acute phase reaction, followed by gastro-intestinal complaints, and bone/muscle pain. The authors concluded that the findings of this study justified further evaluation of bisphosphonates among children with secondary osteoporosis. However, the evidence does not support bisphosphonates as standard therapy. Short-term (3 years or less) bisphosphonate use appears to be well-tolerated. An accepted criterion for osteoporosis in children, a standardized approach to BMD reporting, and examining functional bone health outcomes (e.g., fracture rates) will allow for appropriate comparisons across studies.

Bryant et al (2009) evaluated the safety and effectiveness of various treatment options for osteopenia and osteoporosis secondary to cancer treatment in pediatric patients undergoing cancer therapy. A systematic search of PubMed (1949 to November 2008) and International Pharmaceutical Abstracts (to November 2008) was conducted using the following search terms: osteoporosis, osteopenia, pediatrics, cancer, neoplasms, chemotherapy, bisphosphonates, calcium, vitamin D, calcitonin, and physical therapy. All prospective studies that evaluated various osteoporosis treatment options in pediatric patients undergoing chemotherapy were included. Results from studies evaluating bisphosphonates and other treatments in children with osteoporosis due to other causes were also included if important safety and effectiveness data were provided. Most commonly reported primary effectiveness end-points included comparisons of bone density parameters measured before and after treatment. A total of 4 clinical studies and 2 case reports describing treatment with bisphosphonates, specifically alendronate and pamidronate, for osteoporosis or osteopenia in pediatric cancer patients were identified. Results from the trials showed that these medications were effective in reducing BMD loss during cancer therapy and were well-tolerated in this special population. Primary effectiveness end-points included improvements in Z-scores measured by dual-energy X-ray absorptiometry scans. The most commonly reported adverse effects included hypocalcemia, mild stomach upset, and infusion-related hyperpyrexia. Four additional clinical trials involving the treatment of osteoporosis or osteopenia in children and adolescents who developed bone degeneration after chronic steroid therapy were also included. In these trials, treatment options such as calcitonin, and calcium and vitamin D supplementation were also shown to be beneficial. The authors concluded that the clinical trials published to date were limited to only a few conducted in small populations of patients diagnosed with lymphoblastic leukemia or non-Hodgkin's lymphoma. However, alendronate and pamidronate both appeared to be effective options in improving BMD scores with minimal adverse effects.

Lee and associates (2013) stated that reduced BMD is a significant sequelae in children receiving chemotherapy for acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Reduced BMD is associated with an increased risk for fractures. Pamidronate has been used to treat osteoporosis in children. This study evaluated the safety and effectiveness of pamidronate in children with low BMD during and after chemotherapy for ALL and NHL. Between April 2007 and October 2011, a total of 24 children with ALL and NHL were treated with pamidronate. The indication was a decreased BMD Z-score less than -2.0 or bone
pain with a BMD Z-score less than 0. Pamidronate was infused at 1 mg/kg/day for 3 days at 1- to 4-month intervals (pamidronate group, cases). The BMD Z-scores of the cases were compared with those of 10 untreated patients (control group). Lumbar spine BMDs were measured every 6 cycles using dual energy X-ray absorptiometry and Z-scores were calculated. Bone turnover parameters (25-hydroxyvitamin D, alkaline phosphatase, parathyroid hormone, osteocalcin, and type I collagen c-terminal telopeptide) were analyzed. The median cycle of pamidronate treatment was 12. Increases in BMD Z-scores were significantly higher in the pamidronate group than in the control group (p < 0.001). Bone mineral density (mg/cm(2)) increased in all pamidronate-treated cases; 20 patients who complained of bone pain reported pain relief after therapy. The treatment was well-tolerated. The authors concluded that pamidronate appears to be safe and effective for the treatment of children with low BMD during and after chemotherapy for ALL and NHL.

Baroncelli et al (2013) noted that although spontaneous remission occurs in patients with idiopathic juvenile osteoporosis (IJO), permanent bone deformities may occur. These researchers examined the effects of long-term pamidronate treatment on clinical findings, bone mineral status, and fracture rate in patients with IJO. A total of 9 subjects (age 9.8 ± 1.1 years, 7 males) were randomized to IV pamidronate (0.8 ± 0.1 mg/kg per day for 3 days; cycles per year 2.0 ± 0.1; duration 7.3 ± 1.1 years; n = 5) or no treatment (n = 4). Fracture rate, phalangeal quantitative ultrasound, and lumbar BMD by dual energy X-ray absorptiometry at entry and during follow-up (range of 6.3 to 9.4 years) were assessed. Bone pain improved in treated patients. Difficulty walking continued for 3 to 5 years in untreated patients, and vertebral collapses occurred in 3 of them. During follow-up, phalangeal amplitude-dependent speed of sound (AD-SoS), bone transmission time (BTT), and lumbar BMD area and BMD volume progressively increased in treated patients (p < 0.05 to p < 0.0001). In untreated patients AD-SoS and BTT decreased during the first 2 to 4 years of follow-up (p < 0.05 to p < 0.01); lumbar BMD area increased after 6 years (p < 0.001) whereas BTT and lumbar BMD volume increased after 7 years of follow-up (p < 0.05 and p < 0.001, respectively). At the end of follow-up, AD-SoS, BTT, lumbar BMD area, and BMD volume Z-scores were lower in untreated patients than in treated patients (-2.2 ± 0.3 and -0.5 ± 0.2; -1.9 ± 0.2 and -0.6 ± 0.2; -2.3 ± 0.3 and -0.7 ± 0.3; -2.4 ± 0.2 and -0.7 ± 0.3, p < 0.0001, respectively). Fracture rate was higher in untreated patients than in treated patients during the first 3 years of follow-up (p < 0.02). The authors concluded that the findings of this study showed that spontaneous recovery of bone mineral status is unsatisfactory in patients with IJO. Pamidronate treatment stimulated the onset of recovery phase reducing fracture rate and permanent disabilities without evidence of side-effects.

Makitie et al (2013) stated that osteoporosis is an important pediatric disorder that involves almost all pediatric subspecialties. Osteogenesis imperfecta is the most common form of childhood-onset primary osteoporosis, but several other forms are also known. Secondary osteoporosis is caused by an underlying chronic illness or its treatment. The most common causes of secondary osteoporosis include chronic systemic inflammation, glucocorticoid use and neuromuscular disabilities. The skeletal sequelae can present in childhood as low-energy peripheral and vertebral fractures, or become evident in adulthood as low bone mass and an increased propensity to develop osteoporosis. Management should
aim at prevention, as interventions to treat symptomatic osteoporosis in the pediatric age group are scarce. Bisphosphonates are the principal pharmacological agents that can be used in this setting, but data on their safety and effectiveness in pediatric populations remain inadequate, especially in patients with secondary osteoporosis. Consequently, it is important to understand the potential skeletal effects of pediatric illnesses and their therapies in order to institute effective and timely prevention of skeletal complications.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:
96360 -
96368
96374 -
96379

HCPCS codes covered if selection criteria are met:
J2430 Injection, pamidronate disodium, per 30 mg

ICD-9 codes covered if selection criteria are met:
140.0 - 188.9, Malignant neoplasm
189.1 -
209.30, 230.0
- 234.9
198.5 Secondary malignant neoplasm of bone and bone marrow
203.00 - Multiple myeloma
203.02
275.42 Hypercalcemia [of malignancy or immobilization]
337.20 * Reflex sympathetic dystrophy
337.29
343.2 Quadriplegia [quadriplegic cerebral palsy]
731.0 Osteitis deformans w/o mention of bone tumor [symptomatic Paget's disease]
730.10 - Chronic osteomyelitis [nonbacterial]
730.19
756.51 Osteogenesis imperfecta [severe]
V42.0 - Organ or tissue replaced by transplant [with low bone mass or osteoporotic fractures]
V42.89
ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

003.24 Salmonella osteomyelitis

185 Malignant neoplasm of prostate [treatment of osteoblastic lesions in prostate cancer]

189.0 Malignant neoplasm of kidney, except pelvis

198.82 Secondary malignant neoplasm of genital organs [treatment of osteoblastic lesions in prostate cancer]

233.4 Carcinoma in situ of prostate [treatment of osteoblastic lesions in prostate cancer]

252.00 - 252.9 Disorders of parathyroid gland

270.0 Disturbances of amino-acid transport [Fanconi Bickel syndrome]

272.7 Lipidoses [Gaucher's disease]

277.01 - 277.09 Cystic fibrosis

282.41 - 282.49 Thalassemias [thalassemia-associated osteoporosis]

333.91 Stiff-man syndrome

526.4 Inflammatory conditions

526.5 Alveolitis of jaw

526.89 Other specified diseases of the jaws [fibrous dysplasia of jaw (s)]

588.81 Secondary hyperparathyroidism (of renal origin)

706.0 Acne varioliformis

706.1 Other acne

711.00 - 716.99 Arthropathy associated with infections, crystal arthropathies, arthropathy associated with other disorders classified elsewhere, rheumatoid arthritis and other inflammatory polyarthropathies, osteoarthritis and allied disorders, and other and unspecified arthropathies

719.20 - 719.29 Villonodular synovitis
720.0 - Ankylosing spondylitis and other inflammatory spondylopathies and spondylosis and allied disorders
721.91
724.02 Spinal stenosis of lumbar region
724.2 Lumbago
724.5 Backache, unspecified
727.00 Synovitis and tenosynovitis, unspecified
730.00 - Osteomyelitis, periostitis, and other infections involving bone
730.09, 730.20 - 730.99
733.00 - Osteoporosis
733.09
733.01 Senile osteoporosis
733.09 Osteoporosis, other [glucocorticoid-induced]
733.29 Other cyst of bone [fibrous dysplasia]
733.3 Hyperostosis of skull
733.40 - Aseptic necrosis of bone [avascular]
733.49
733.5 Osteitis condensans
733.90 Disorder of bone and cartilage, unspecified [osteopenia]
733.99 Other disorders of bone and cartilage [hyperostosis]
756.4 Chondrodystrophy
756.54 Polyostotic fibrous dysplasia of bone
805.00 - Fracture of vertebral column
806.9
905.1 Late effect of fracture of spine and trunk without mention of spinal cord lesion
907.2 Late effect of spinal cord injury

Other ICD-9 codes related to the CPB:
015.00 - Tuberculosis of bones and joints
015.96
041.02 Streptococcus infection in conditions classified elsewhere and of unspecified site, Group B
041.11  Methicillin susceptible Staphylococcus aureus
041.12  Methicillin resistant Staphylococcus aureus
342.0 - 342.9  Hemiplegia and hemiparesis
343.0 - 343.1, 343.3 – 343.9  Infantile cerebral palsy
344.00 - 344.9  Other paralytic syndromes
728.3  Other specific muscle disorders [immobility syndrome (paraplegic)]
733.10 - 733.19  Pathological fracture
V49.84  Bed confinement status

The above policy is based on the following references:


