

Zoledronic acid: Drug information

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(For additional information [see "Zoledronic acid: Patient drug information"](#))

For abbreviations and symbols that may be used in Lexicomp ([show table](#))

Special Alerts

Bisphosphonates Safety Alert November 2016

A Health Canada safety review has concluded that there is a higher risk of osteonecrosis of the jaw (ONJ) with the use of intravenous (IV) bisphosphonate products compared with oral formulations, especially in cancer patients. The review was prompted by a report from the European Medicines Agency, which reviewed adverse events due to zoledronic acid. Health Canada is working with drug manufacturers to update product safety information for IV bisphosphonate formulations to reflect the increased risk of ONJ. Updates will also include recommendations to stop bisphosphonate use if ONJ occurs while on treatment and to delay the start of bisphosphonate use in patients with unhealed open wounds in the mouth, as well as mentioning additional factors that may play a role in ONJ for all bisphosphonate products.

Further information may be found at <http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/bisphosphonates-eng.php>.

Brand Names: US Reclast; Zometa

Brand Names: Canada Aclasta; Taro-Zoledronic Acid; Taro-Zoledronic Acid Concentrate; Zoledronic Acid Injection; Zoledronic Acid for Injection; Zoledronic Acid Z; Zometa Concentrate

Pharmacologic Category Bisphosphonate Derivative

Dosing: Adult **Note:** Acetaminophen administration after the infusion may reduce symptoms of acute-phase reactions. Patients treated for bone metastases from solid tumors, multiple myeloma, and Paget disease should receive a daily calcium and vitamin D supplement, and patients with osteoporosis should receive calcium and vitamin D supplementation if dietary intake is inadequate.

Bone metastases from solid tumors (Zometa): IV: 4 mg once every 3 to 4 weeks

Bone metastases due to breast cancer or prostate cancer (off-label dosing): IV: 4 mg once every 12 weeks; dosing once every 12 weeks (compared to once every 4 weeks) did not result in an increased risk of skeletal events within 2 years in patients with at least 1 site of bone involvement (Himmelstein 2017).

Hypercalcemia of malignancy (albumin-corrected serum calcium ≥ 12 mg/dL) (Zometa): IV: 4 mg (maximum) given as a single dose. Wait at least 7 days before considering re-treatment.

Multiple myeloma osteolytic lesions (Zometa): IV: 4 mg once every 3 to 4 weeks

Multiple myeloma (off-label dosing): IV: 4 mg once every 12 weeks; dosing once every 12 weeks (compared to once every 4 weeks) did not result in an increased risk of skeletal events within 2 years in patients with at least 1 site of bone involvement (Himmelstein 2017).

Osteoporosis, glucocorticoid-induced, treatment and prevention (Reclast, Aclasta [Canadian product]): IV: 5 mg once a year

Osteoporosis, prevention (Reclast): IV: 5 mg once every 2 years

Canadian labeling (Aclasta): 5 mg as a single (one-time) dose

Osteoporosis, treatment (Reclast, Aclasta [Canadian product]): IV: 5 mg once a year; consider discontinuing after 3 to 5 years of use in patients at low risk for fracture

Paget disease (Reclast, Aclasta [Canadian product]): IV: 5 mg as a single dose.

Re-treatment: Data concerning retreatment is not available; retreatment may be considered for relapse (increase in alkaline phosphatase) if appropriate, for inadequate response, or in patients who are symptomatic.

Canadian labeling (Aclasta): Data concerning retreatment is limited; retreatment with 5 mg (single dose) may be considered for relapse after an interval of at least 1 year from initial treatment.

The Endocrine Society guidelines suggest re-treatment is seldom required within 5 years (Singer 2014).

Postrenal transplant bone loss (prevention) (off-label use): IV: 4 mg at week 2 and month 3 after engraftment (Haas 2003; Schwarz 2004). Additional data may be necessary to further define the role of zoledronic acid in this condition.

Bone loss associated with androgen deprivation therapy in prostate cancer, prevention (off-label use): IV: 4 mg once every 3 months for 1 year (Smith, 2003) or 4 mg every 12 months (Michaelson 2007)

Bone loss associated with aromatase inhibitor therapy in women with breast cancer, prevention (off-label use): IV: 4 mg once every 6 months for 5 years (Brufsky 2012)

Dosing: Geriatric Refer to adult dosing.

Dosing: Renal Impairment **Note:** Prior to each dose, obtain serum creatinine and calculate the creatinine clearance using the Cockcroft-Gault formula.

Nononcology uses: Note: Use actual body weight in the Cockcroft-Gault formula when calculating clearance for nononcology uses.

CrCl ≥ 35 mL/minute: No dosage adjustment is necessary.

CrCl < 35 mL/minute: Use is contraindicated.

Oncology uses:

Multiple myeloma and bone metastases:

CrCl >60 mL/minute: 4 mg (no dosage adjustment is necessary)

CrCl 50 to 60 mL/minute: Reduce dose to 3.5 mg

CrCl 40 to 49 mL/minute: Reduce dose to 3.3 mg

CrCl 30 to 39 mL/minute: Reduce dose to 3 mg

CrCl <30 mL/minute: Use is not recommended.

Hypercalcemia of malignancy:

Mild to moderate impairment: No dosage adjustment is necessary.

Severe impairment (serum creatinine >4.5 mg/dL): Evaluate risk versus benefit

Dosage adjustment for renal toxicity (during treatment):

Hypercalcemia of malignancy: Evidence of renal deterioration: Evaluate risk versus benefit.

Multiple myeloma and bone metastases: Evidence of renal deterioration: Withhold dose until renal function returns to within 10% of baseline; renal deterioration defined as follows:

Normal baseline creatinine: Increase of 0.5 mg/dL

Abnormal baseline creatinine: Increase of 1 mg/dL

Reinitiate therapy at the same dose administered prior to treatment interruption.

Multiple myeloma: Albuminuria >500 mg/24 hours (unexplained): Withhold dose until return to baseline, then reevaluate every 3 to 4 weeks; consider reinitiating with a longer infusion time of at least 30 minutes (Kyle 2007).

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, zoledronic acid is not metabolized hepatically.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Concentrate, Intravenous:

Zometa: 4 mg/5 mL (5 mL)

Generic: 4 mg/5 mL (5 mL)

Concentrate, Intravenous [preservative free]:

Generic: 4 mg/5 mL (5 mL)

Solution, Intravenous:

Reclast: 5 mg/100 mL (100 mL)

Zometa: 4 mg/100 mL (100 mL)

Generic: 5 mg/100 mL (100 mL)

Solution, Intravenous [preservative free]:

Generic: 4 mg/100 mL (100 mL); 5 mg/100 mL (100 mL)

Solution Reconstituted, Intravenous:

Generic: 4 mg (1 ea [DSC])

Generic Equivalent Available (US) Yes

Dosage Forms: Canada Information with regard to form, strength, and availability of products uniquely available in Canada but currently not available in the US. Refer also to Dosage forms.

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Concentrate, Intravenous:

Zometa: 4 mg/5 mL (5 mL)

Infusion, Solution [premixed]:

Aclasta: 5 mg/100 mL (100 mL)

Medication Guide and/or Vaccine Information Statement (VIS) An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication:

Reclast: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM241522.pdf>

Administration

If refrigerated, allow solution to reach room temperature before administration. Infuse over at least 15 minutes. Flush IV line with 10 mL NS flush following infusion. Infuse in a line separate from other medications. Patients must be appropriately hydrated prior to treatment. Acetaminophen after administration may reduce the incidence of acute reaction (eg, arthralgia, fever, flu-like symptoms, myalgia).

Multiple myeloma: If treatment is withheld for unexplained albuminuria, consider increasing the infusion time to at least 30 minutes upon reinitiation (Kyle 2007).

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 3]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) if compounding. Double gloving and a gown are required during administration (NIOSH 2016). Premixed solutions may be excluded from some hazardous drug handling requirements; assess risk to determine appropriate containment strategy (USP-NF 2017).

Use

Bone metastases from solid tumors (Zometa): Treatment of documented bone metastases from solid tumors (in conjunction with standard antineoplastic therapy); prostate cancer should have progressed following treatment with at least one hormonal therapy.

Glucocorticoid-induced osteoporosis (Reclast, Aclasta [Canadian product]): Treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are initiating or continuing systemic glucocorticoids in a daily dose equivalent to 7.5 mg or more of prednisone and who are expected to remain on glucocorticoids for at least 12 months.

Hypercalcemia of malignancy (Zometa): Treatment of hypercalcemia (albumin-corrected serum calcium ≥ 12 mg/dL) of malignancy.

Multiple myeloma (Zometa): Treatment of osteolytic lesions of multiple myeloma.

Osteoporosis in men (Reclast, Aclasta [Canadian product]): To increase bone mass in men with osteoporosis.

Paget disease of bone (Reclast, Aclasta [Canadian product]): Treatment of Paget disease of bone in men and women. **Note:** In patients without contraindications, zoledronic acid is recommended as the treatment of choice per Endocrine Society guidelines (Singer 2014).

Postmenopausal osteoporosis (Reclast, Aclasta [Canadian product]): Treatment and prevention of osteoporosis in postmenopausal women.

Limitations of use: Safety and efficacy for treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions have not been established. Safety and efficacy for osteoporosis treatment is based on clinical data of 3 years duration; the optimal duration has not been determined. All patients on bisphosphonate therapy for the treatment of osteoporosis should be re-evaluated periodically for the need to continue therapy; consider discontinuing after 3 to 5 years in patients at low-risk for fracture; re-evaluate fracture risk periodically in patients who discontinue therapy.

Use: Off-Label

Bone loss associated with androgen deprivation therapy in prostate cancer (prevention); Bone loss associated with aromatase inhibitor therapy in women with breast cancer (prevention); Postrenal transplant bone loss (prevention)

Medication Safety Issues

Sound-alike/look-alike issues:

Zometa may be confused with Jevtana, Xgeva, Xofigo, Xtandi, Zofran, Zoladex, Zytiga

Other safety concerns:

Duplicate therapy issues: Reclast and Aclasta contain zoledronic acid, which is the same ingredient contained in Zometa; patients receiving Zometa should not be treated with Reclast or Aclasta

Adverse Reactions

Oncology indications:

>10%:

Cardiovascular: Lower extremity edema (5% to 21%), hypotension (11%)

Central nervous system: Fatigue (39%), headache (5% to 19%), dizziness (18%), insomnia (15% to 16%), depression (14%), anxiety (11% to 14%), agitation (13%), confusion (7% to 13%), hypoesthesia (12%), rigors (11%)

Dermatologic: Alopecia (12%), dermatitis (11%)

Endocrine & metabolic: Dehydration (5% to 14%), hypophosphatemia (13%), hypokalemia (12%), hypomagnesemia (11%)

Gastrointestinal: Nausea (29% to 46%), vomiting (14% to 32%), constipation (27% to 31%), diarrhea (17% to 24%), anorexia (9% to 22%), weight loss (16%), abdominal pain (14% to 16%), decreased appetite (13%)

Genitourinary: Urinary tract infection (12% to 14%)

Hematologic & oncologic: Anemia (22% to 33%), progression of cancer (16% to 20%), neutropenia (12%)

Infection: Candidiasis (12%)

Neuromuscular & skeletal: Ostealgia (55%), weakness (5% to 24%), myalgia (23%), arthralgia (5% to 21%), back pain (15%), paresthesia (15%), limb pain (14%), skeletal pain (12%)

Renal: Renal insufficiency (8% to 17%; up to 40% in patients with abnormal baseline creatinine)

Respiratory: Dyspnea (22% to 27%), cough (12% to 22%)

Miscellaneous: Fever (32% to 44%; most common symptom of acute phase reaction)

1% to 10%:

Cardiovascular: Chest pain (5% to 10%)

Central nervous system: Somnolence (5% to 10%)

Endocrine & metabolic: Hypocalcemia (5% to 10%; grades 3/4: ≤1%), hypermagnesemia (grade 3: 2%)

Gastrointestinal: Dyspepsia (10%), dysphagia (5% to 10%), mucositis (5% to 10%), sore throat (8%), stomatitis (8%)

Hematologic & oncologic: Granulocytopenia (5% to 10%), pancytopenia (5% to 10%), thrombocytopenia (5% to 10%)

Infection: Infection (nonspecific; 5% to 10%)

Renal: Increased serum creatinine (grades 3/4: $\leq 2\%$)

Respiratory: Upper respiratory tract infection (10%)

Nononcology indications:

>10%:

Cardiovascular: Hypertension (5% to 13%)

Central nervous system: Pain (2% to 24%), fever (9% to 22%), headache (4% to 20%), chills (2% to 18%), fatigue (2% to 18%), flank pain ($\leq 2\%$)

Endocrine & metabolic: Hypocalcemia ($\leq 3\%$; Paget's disease 21%), dehydration (3%)

Gastrointestinal: Nausea (5% to 18%), upper abdominal pain (5%), abdominal distension ($\leq 2\%$)

Immunologic: Infusion related reaction (4% to 25%)

Neuromuscular & skeletal: Arthralgia (9% to 27%), myalgia (5% to 23%), back pain (4% to 18%), limb pain (3% to 16%), musculoskeletal pain ($\leq 12\%$), osteoarthritis (6%)

Respiratory: Flu-like symptoms (1% to 11%)

1% to 10%:

Cardiovascular: Chest pain (1% to 8%), peripheral edema (3% to 6%), atrial fibrillation (1% to 3%), palpitations ($\leq 3\%$)

Central nervous system: Dizziness (2% to 9%), rigors (8%), malaise (1% to 7%), hypoesthesia ($\leq 6\%$), lethargy (3% to 5%), vertigo (1% to 4%), paresthesia (2%), hyperthermia ($\leq 2\%$)

Dermatologic: Skin rash (2% to 3%), hyperhidrosis ($\leq 3\%$)

Gastrointestinal: Abdominal pain (1% to 9%), diarrhea (5% to 8%), vomiting (2% to 8%), constipation (6% to 7%), dyspepsia (2% to 7%), abdominal discomfort (1% to 2%), anorexia (1% to 2%)

Hematologic & oncologic: Change in serum protein (C-reactive protein increased; $\leq 5\%$)

Neuromuscular & skeletal: Ostealgia (3% to 9%), arthritis (2% to 9%), neck pain (1% to 7%), shoulder pain ($\leq 7\%$), muscle spasm (2% to 6%), weakness (2% to 6%), stiffness (1% to 5%), jaw pain (2% to 4%), joint swelling ($\leq 3\%$)

Ophthalmic: Eye pain ($\leq 2\%$)

Renal: Increased serum creatinine (2%)

Respiratory: Dyspnea (5% to 7%)

All indications: <1%, postmarketing, and/or case reports: Acute phase reaction-like symptoms (including pyrexia, fatigue, bone pain, arthralgia, myalgia, chills, influenza-like illness; usually resolves within 3 to 4 days of onset, although may take up to 14 days to resolve), acute renal failure (requiring hospitalization/dialysis), acute renal tubular necrosis (toxic), anaphylactic shock, anaphylaxis, angioedema, arthralgia (sometimes severe and/or incapacitating), blurred vision, bradycardia, bronchoconstriction, bronchospasm, cardiac arrhythmia, cerebrovascular accident, conjunctivitis, diaphoresis, drowsiness, dysgeusia, episcleritis, exacerbation of asthma, femur fracture (diaphyseal or subtrochanteric), hematuria, hyperesthesia, hyperkalemia, hypernatremia, hyperparathyroidism, hypersensitivity reaction, hypertension, injection site reaction (eg, itching, pain, redness), interstitial pulmonary disease, iridocyclitis, iritis, muscle cramps, myalgia (sometimes severe and/or incapacitating), numbness, osteonecrosis (primarily of the jaws), periorbital edema, periorbital swelling, prolonged QT interval on ECG, proteinuria, pruritus, renal insufficiency, scleritis, seizure, skin rash, Stevens-Johnson syndrome, tetany, toxic epidermal necrolysis, tremor, urticaria, uveitis, weight gain, xerostomia

Contraindications

US labeling:

Hypersensitivity to zoledronic acid or any component of the formulation; hypocalcemia (Reclast only); CrCl <35 mL/minute and in those with evidence of acute renal impairment (Reclast only).

Canadian labeling:

All indications: Hypersensitivity to zoledronic acid or other bisphosphonates, or any component of the formulation; uncorrected hypocalcemia at the time of infusion; pregnancy, breast-feeding

Nononcology uses: Additional contraindications: Use in patients with CrCl <35 mL/minute and use in patients with evidence of acute renal impairment due to an increased risk of renal failure

Documentation of allergenic cross-reactivity for bisphosphonates is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

Warnings/Precautions

Concerns related to adverse effects:

- Bone fractures: Atypical, low-energy, or low-trauma femur fractures have been reported in patients receiving bisphosphonates. The fractures include subtrochanteric femur (bone just below the hip joint) and diaphyseal femur (long segment of the thigh bone). Some patients experience prodromal pain weeks or months before the fracture occurs. It is unclear if bisphosphonate therapy is the cause for these fractures; atypical femur fractures have also been reported in patients not taking bisphosphonates, and in patients receiving glucocorticoids. Patients receiving long-term (>3 to 5 years) bisphosphonate therapy may be at an increased risk. Patients presenting with thigh or groin pain with a history of receiving bisphosphonates should be evaluated for femur fracture. Consider interrupting bisphosphonate therapy in patients who develop a femoral shaft fracture; assess for fracture in the contralateral limb.
- Hypersensitivity reactions: Rare cases of urticaria and angioedema and very rare cases of

anaphylactic reactions/shock have been reported.

- Hypocalcemia: Hypocalcemia (including severe and life-threatening cases) has been reported with use; patients with Paget disease may be at significant risk for hypocalcemia after treatment with zoledronic acid (because pretreatment rate of bone turnover may be elevated); severe and life-threatening hypocalcemia has also been reported with oncology-related uses. Measure serum calcium prior to treatment initiation. Correct preexisting hypocalcemia before initiation of therapy in patients with Paget disease, osteoporosis, or oncology indications. Use with caution with other medications known to cause hypocalcemia (severe hypocalcemia may develop). Ensure adequate calcium and vitamin D supplementation during therapy. Use caution in patients with disturbances of calcium and mineral metabolism (eg, hypoparathyroidism, thyroid/parathyroid surgery, malabsorption syndromes, excision of small intestine). QTc prolongation, cardiac arrhythmias, and neurologic events (eg, tetany, tonic-clonic seizures, numbness) secondary to severe hypocalcemia have been reported 1 day to several months after initiation of therapy.

- Musculoskeletal pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Consider discontinuing therapy in patients who experience severe symptoms; symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Ocular infection: Conjunctivitis, uveitis, episcleritis, iritis, scleritis, and orbital inflammation have been reported (infrequently) with use; further ophthalmic evaluation (and possibly therapy discontinuation) may be necessary in patients with complicated infection.

- Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ), also referred to as medication-related osteonecrosis of the jaw (MRONJ), has been reported in patients receiving bisphosphonates. Known risk factors for MRONJ include invasive dental procedures (eg, tooth extraction, dental implants, bony surgery), cancer diagnosis, concomitant therapy (eg, chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, ill-fitting dentures, and comorbid disorders (anemia, coagulopathy, infection, preexisting dental disease). Risk may increase with duration of bisphosphonate use and/or may be reported at a greater frequency based on tumor type (eg, advanced breast cancer or multiple myeloma). According to a position paper by the American Association of Maxillofacial Surgeons (AAOMS), MRONJ has been associated with bisphosphonates and other antiresorptive agents (denosumab), and antiangiogenic agents (eg, bevacizumab, sunitinib) used for the treatment of osteoporosis or malignancy; risk is significantly higher in cancer patients receiving antiresorptive therapy compared to patients receiving osteoporosis treatment (regardless of medication used or dosing schedule). MRONJ risk is also increased with monthly IV antiresorptive therapy compared to the minimal risk associated with oral bisphosphonate use, although risk appears to increase with oral bisphosphonates when duration of therapy exceeds 4 years. The manufacturer's labeling states that there are no data to suggest whether discontinuing bisphosphonates in patients requiring invasive dental procedures reduces the risk of ONJ. The manufacturer recommends a dental exam and preventive dentistry be performed prior to placing patients with risk factors on chronic bisphosphonate therapy and that during therapy, invasive dental procedures be avoided, if possible. The AAOMS suggests that if medically permissible, initiation of IV bisphosphonates for cancer therapy should be delayed until optimal dental health is attained (if extractions are required, antiresorptive therapy should be delayed until the extraction site has mucosalized or until after adequate osseous healing). Once IV bisphosphonate therapy is initiated for oncologic disease, procedures that involve direct osseous injury and

placement of dental implants be avoided. Patients developing ONJ during therapy should receive care by an oral surgeon (AAOMS [Ruggiero 2014]).

Disease-related concerns:

- Aspirin-sensitive asthma: Use with caution in patients with aspirin-sensitive asthma; may cause bronchoconstriction.
- Breast cancer (metastatic): The American Society of Clinical Oncology (ASCO) updated guidelines on the role of bone-modifying agents (BMAs) in the prevention and treatment of skeletal-related events for metastatic breast cancer patients (Van Poznak, 2011). The guidelines recommend initiating a BMA (denosumab, pamidronate, zoledronic acid) in patients with metastatic breast cancer to the bone. There is currently no literature indicating the superiority of one particular BMA. Optimal duration is not yet defined; however, the guidelines recommend continuing therapy until substantial decline in patient's performance status. The ASCO guidelines are in alignment with prescribing information for dosing, renal dose adjustments, infusion times, prevention and management of osteonecrosis of the jaw, and monitoring of laboratory parameter recommendations. BMAs are not the first-line therapy for pain. BMAs are to be used as adjunctive therapy for cancer-related bone pain associated with bone metastasis, demonstrating a modest pain control benefit. BMAs should be used in conjunction with agents such as NSAIDs, opioid and nonopioid analgesics, corticosteroids, radiation/surgery, and interventional procedures.
- Multiple myeloma: The American Society of Clinical Oncology (ASCO) has published guidelines on bisphosphonate use for prevention and treatment of bone disease in multiple myeloma (Kyle, 2007). Bisphosphonate (pamidronate or zoledronic acid) use is recommended in multiple myeloma patients with lytic bone destruction or compression spine fracture from osteopenia. Bisphosphonates may also be considered in patients with pain secondary to osteolytic disease, adjunct therapy to stabilize fractures or impending fractures, and for multiple myeloma patients with osteopenia but no radiographic evidence of lytic bone disease. Bisphosphonates are not recommended in patients with solitary plasmacytoma, smoldering (asymptomatic) or indolent myeloma, or monoclonal gammopathy of undetermined significance. The guidelines recommend monthly treatment for a period of 2 years. At that time, consider discontinuing in responsive and stable patients, and reinitiate if a new-onset skeletal-related event occurs. The ASCO guidelines are in alignment with prescribing information for dosing, renal dose adjustments, infusion times, prevention and management of osteonecrosis of the jaw, and monitoring of laboratory parameter recommendations. According to the guidelines, in patients with a serum creatinine >3 mg/dL or CrCl <30 mL/minute or extensive bone disease, an alternative bisphosphonate (pamidronate) should be used. Monitor for albuminuria every 3 to 6 months; in patients with unexplained albuminuria >500 mg/24 hours, withhold the dose until level returns to baseline, then recheck every 3 to 4 weeks. Upon reinitiation, the guidelines recommend considering increasing the zoledronic acid infusion time to at least 30 minutes; however, one study has demonstrated that extending the infusion to 30 minutes did not change the safety profile (Berenson, 2011).
- Renal impairment: Use with caution in mild to moderate renal impairment. Single and multiple infusions in patients with both normal and impaired renal function have been associated with renal deterioration, resulting in renal failure and dialysis (rare). Preexisting renal compromise, severe dehydration, and concurrent use with diuretics or other nephrotoxic drugs may increase the risk for renal impairment. Adequate hydration is required during treatment (urine output ~2 L/day); avoid overhydration, especially in patients with heart failure.

Nononcology indications: Use is contraindicated in patients with CrCl <35 mL/minute and in patients with evidence of acute renal impairment. Do not use single doses >5 mg and do not infuse over less than 15 minutes. Patients with underlying moderate to severe renal impairment, increased age, concurrent use of nephrotoxic or diuretic medications, or severe dehydration prior to or after zoledronic acid administration may have an increased risk of acute renal impairment or renal failure. Others with increased risk include patients with renal impairment or dehydration secondary to fever, sepsis, gastrointestinal losses, or diuretic use. If history or physical exam suggests dehydration, treatment should not be given until the patient is normovolemic. Obtain serum creatinine and calculate creatinine clearance (using actual body weight) with the Cockcroft-Gault formula prior to each administration. Transient increases in serum creatinine may be more pronounced in patients with impaired renal function; monitoring creatinine clearance in at-risk patients taking other renally eliminated drugs is recommended.

Oncology indications: Dosage adjustment required with renal impairment. Use is not recommended in patients with severe renal impairment (serum creatinine >3 mg/dL or CrCl <30 mL/minute) and bone metastases (limited data); use in patients with hypercalcemia of malignancy and severe renal impairment (serum creatinine >4.5 mg/dL for hypercalcemia of malignancy) should only be done if the benefits outweigh the risks. In cancer patients, do not use single doses >4 mg and do not infuse over less than 15 minutes (renal toxicity has been reported with doses >4 mg or infusions administered over less than 15 minutes). Risk factors for renal deterioration include preexisting renal insufficiency and repeated doses and other bisphosphonates therapy. Dehydration and the use of other nephrotoxic drugs which may contribute to renal deterioration should be identified and managed. Diuretics should not be used before correcting hypovolemia. Assess renal function (eg, serum creatinine) prior to each dose and withhold for renal deterioration (increase in serum creatinine of 0.5 mg/dL [if baseline level normal] or increase of 1 mg/dL [if baseline level abnormal]); treatment should be withheld until renal function returns to within 10% of baseline.

Special populations:

- Elderly: Because decreased renal function occurs more commonly in elderly patients, take special care to monitor renal function.

Other warnings/precautions:

- Duplicate therapy: Do not administer Zometa and Reclast (Aclasta [Canadian product]) to the same patient for different indications.
- Duration of therapy: In the management of osteoporosis, reevaluate the need for continued therapy periodically; the optimal duration of treatment has not yet been determined. Consider discontinuing after 3 to 5 years of use in patients at low risk for fracture; following discontinuation, reevaluate fracture risk periodically.

Metabolism/Transport Effects None known.

Drug Interactions

(For additional information: [Launch drug interactions program](#)) Lexicomp®

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Calcitonin: May enhance the hypocalcemic effect of Zoledronic Acid. *Risk C: Monitor therapy*

Deferasirox: Bisphosphonate Derivatives may enhance the adverse/toxic effect of Deferasirox. Specifically, the risk for GI ulceration/irritation or GI bleeding may be increased. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May diminish the therapeutic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Systemic Angiogenesis Inhibitors: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

Thalidomide: May enhance the adverse/toxic effect of Zoledronic Acid. *Risk C: Monitor therapy*

Pregnancy Risk Factor D ([show table](#))

Pregnancy Implications Adverse events were observed in animal reproduction studies. It is not known if bisphosphonates cross the placenta, but fetal exposure is expected (Djokanovic, 2008; Stathopoulos, 2011). Bisphosphonates are incorporated into the bone matrix and gradually released over time. The amount available in the systemic circulation varies by dose and duration of therapy. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy; however, available data have not shown that exposure to bisphosphonates during pregnancy significantly increases the risk of adverse fetal events (Djokanovic, 2008; Levy, 2009; Stathopoulos, 2011). Until additional data is available, most sources recommend discontinuing bisphosphonate therapy in women of reproductive potential as early as possible prior to a planned pregnancy; use in premenopausal women should be reserved for special circumstances when rapid bone loss is occurring (Bhalla, 2010; Pereira, 2012; Stathopoulos, 2011). Because hypocalcemia has been described following *in utero* bisphosphonate exposure, exposed infants should be monitored for hypocalcemia after birth (Djokanovic, 2008; Stathopoulos, 2011).

Breast-Feeding Considerations It is not known if zoledronic acid is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.

Dietary Considerations

Multiple myeloma or metastatic bone lesions from solid tumors: Take daily calcium supplement (500 mg) and daily multivitamin (with 400 units vitamin D).

Osteoporosis: Ensure adequate calcium and vitamin D intake; if dietary intake is inadequate, dietary supplementation is recommended. Women and men should consume:

Calcium: 1,000 mg/day (men: 50 to 70 years) **or** 1200 mg/day (women \geq 51 years and men \geq 71 years) (IOM 2011; NOF [Cosman 2014])

Vitamin D: 800 to 1,000 int. units/day (men and women \geq 50 years) (NOF 2014). Recommended Dietary Allowance (RDA): 600 int. units/day (men and women \leq 70 years) **or** 800 int. units/day (men and women \geq 71 years) (IOM 2011).

Paget disease: Take elemental calcium 1500 mg/day (750 mg twice daily or 500 mg 3 times/day) and vitamin D 800 units/day, particularly during the first 2 weeks after administration.

Monitoring Parameters Prior to initiation of therapy, dental exam and preventive dentistry for patients at risk for osteonecrosis, including all cancer patients

Nononcology uses: Serum creatinine prior to each dose, especially in patients with risk factors, calculate creatinine clearance before each treatment (consider interim monitoring in patients at risk for acute renal failure), evaluate fluid status and adequately hydrate patients prior to and following administration.

Osteoporosis: Bone mineral density (BMD) should be evaluated 1 to 2 years after initiating therapy and every 2 years thereafter (NOF [Cosman 2014]); in patients with combined zoledronic acid and glucocorticoid treatment, BMD should be made at initiation of therapy and repeated after 6 to 12 months; serum calcium and 25(OH)D; annual measurements of height and weight, assessment of chronic back pain; serum calcium and 25(OH)D; phosphorus and magnesium; may consider monitoring biochemical markers of bone turnover

Paget disease: Alkaline phosphatase at 6 to 12 weeks for initial response to treatment (when bone turnover will have shown a substantial decline) and potentially at 6 months (maximal suppression of high bone turnover); following treatment completion, monitor at ~1- to 2-year intervals (Singer, 2014); monitoring more specific biochemical markers of bone turnover (eg, serum P1NP, NTX, serum beta-CTx) is generally only warranted in patients with Paget disease who have abnormal liver or biliary tract function or when early assessment of response to treatment is needed (eg, spinal compression, very active disease) (Singer, 2014); serum calcium and 25(OH)D; phosphorus and magnesium; symptoms of hypocalcemia, pain

Oncology uses: Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment. In patients with multiple myeloma, monitor urine every 3 to 6 months for albuminuria.

Reference Range

Calcium (total): Adults: 9 to 11 mg/dL (2.05 to 2.54 mmol/L), may slightly decrease with aging

Phosphorus: 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L)

Vitamin D: There is no clear consensus on a reference range for total serum 25(OH)D concentrations or the validity of this level as it relates clinically to bone health. In addition, there is significant variability in the reporting of serum 25(OH)D levels as a result of different assay types in use; however, the following ranges have been suggested:

Adults (IOM 2011): Sufficient levels in practically all persons: ≥ 20 ng/mL (50 nmol/L); concern for risk of toxicity: > 50 ng/mL (125 nmol/L)

Osteoporosis patients (NOF [Cosman 2014]): Recommended level to reach and maintain: ~ 30 ng/mL (75 nmol/L)

Mechanism of Action A bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; inhibits osteoclastic activity and skeletal calcium release induced by tumors.

Decreases serum calcium and phosphorus, and increases their elimination. In osteoporosis, zoledronic acid inhibits osteoclast-mediated resorption, therefore reducing bone turnover.

Pharmacodynamics/Kinetics

Distribution: Binds to bone

Protein binding: 23% to 53%

Metabolism: Primarily eliminated intact via the kidney; metabolism not likely

Half-life elimination: Triphasic; Terminal: 146 hours

Excretion: Urine (39% ± 16% as unchanged drug) within 24 hours; feces (<3%)

Pricing: US

Concentrate (Zoledronic Acid Intravenous)

4 mg/5 mL (5 mL): \$294.00

Concentrate (Zometa Intravenous)

4 mg/5 mL (5 mL): \$1106.98

Solution (Reclast Intravenous)

5 mg/100 mL (100 mL): \$1300.60

Solution (Zoledronic Acid Intravenous)

4 mg/100 mL (100 mL): \$72.00

5 mg/100 mL (100 mL): \$420.00

Solution (Zometa Intravenous)

4 mg/100 mL (100 mL): \$1106.98

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Aclasta (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IE, IL, IS, IT, KR, KW, LB, LK, LT, LU, LV, MT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, QA, RO, RU, SA, SE, SG, SI, SK, SV, TH, TR, TW, UY, VN, ZA); Ai Lang (CN); Aklasta (UA); Amonzitra (SG); Blaztere (IN, VN); Bolenic (TW); Bonizol (BD); Drometa (BD); Leuzotev (TH); Osteomet (LK); Reclast (JP); Sinresor (VN); Vexonib-4 (PH); Xoleron (BD); Zidronic (EC); Zinvel (TH); Zobonic (TW); Zofaden (MX); Zoffec (ID); Zoldonat (SG); Zoldron-4 (PH); Zoled (PH); Zoledran (SG); Zolennic (TH); Zoletalis (PH, VN); Zoltero (BD); Zomegoal (MX); Zomera (IL); Zometa (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CL, CN, CY, CZ, DE, DK, EC, EE, FI, FR, GB, GR, HK, HR, HU, ID, IE, IT, JO, JP, KR, KW, LB, LK, LT, LU, MT, MX, MY, NL, NO, NZ, PE, PH, PK, PL, PR, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, TH, TR, TW, UY, VE, VN, ZA); Zova (SG)

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