Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidney.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D [see WARNINGS AND PRECAUTIONS].

Zoledronic acid SHOULD NOT BE USED DURING PREGNANCY. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Zoledronic acid.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception space, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

Nursing Mothers

It is not known whether Zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because Zoledronic acid binds to bone long-term, Zoledronic acid should not be administered to a nursing woman.

Geriatric Use

Because of decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

Renal Impairment

Zoledronic acid is contraindicated in patients with creatinine clearance < 35 mL/min and in those with evidence of acute renal impairment. There is no safety or efficacy data to support the adjustment of the Zoledronic acid dose based on baseline renal function. Therefore, no dosage adjustment is required in patients with a creatinine clearance of ⩾ 35 mL/min. Risk of acute renal failure may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, advanced age, etc.

Effects on ability to drive and operate machines

Adverse reactions, such as dizziness, may affect the ability to drive or use machines, though no studies on this effect with Zoledronic acid have been performed.

COMMON ADVERSE EFFECTS

Osteoporosis Treatment in Postmenopausal Women: Arthralgia, fever, headache, hypertension, myalgia, extremity pain, flu-like illness, dizziness, shoulder pain, diarrhea, bone pain. fatigue, chills, asthenia.

Osteoporosis Prevention in Postmenopausal women: Headache, dizziness, hypoesthesia, hypertension, nausea, diarrhea, vomiting. dyspepsia, abdominal pain, constipation, arthralgia, myalgia, back pain, extremity pain. muscle spasms, musculoskeletal pain, bone pain, neck pain, generalized pain, pyrexia. Chills, fatigue, asthenia, peripheral edema, non-cardiac chest pain.

Osteoporosis Treatment in Men: Myalgia, fatigue, headache, musculoskeletal pain, pain (unspecified), chills, flu - like illness, abdominal pain, malaise, dyspnea.

Corticosteroid-induced Osteoporosis: Adverse effects are generally similar to those reported in the postmenopausal osteoporosis population. Common adverse effects that were either nor observed in the. postmenopausal osteoporosis treatment trial or reported more frequently in the corticosteroid Induced osteoporosis trial included abdominal pain, musculoskeletal pain, back pain, bone pain, extremity pain, nausea, and dyspepsia.

Pagets Disease of Bone: Headache, nausea, dizziness, arthralgia, bone pain, influenza/flu-like illness, fever, fatigue, rigors, myalgia, diarrhea, constipation, lethargy, dypsnea, dyspepsia, pain

OVERDOSAGE

Clinical experience with acute overdosage of zoledronic acid solution for intravenous infusion is limited. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant renal impairment, hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

Single doses should not exceed 5 mg and the duration of the intravenous infusion should be no less than 15 minutes

STORAGE

- Keep out of reach of children.
- Protect from light and moisture.
- Store at temperatures not exceeding 30°C
- Do not freeze.

AVAILABILITY

USP Type 1 Clear Glass Vial with Grey Bromobutyl Rubber Stopper and Red Aluminum Flip Off Seal x 100 mL (Box of 1's)

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

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I-Z802-M25-00-01

ZOLEDRONIC ACID

ZORUXA

5mg/100mL
Solution for
Intravenous Infusion
Bisphosphonate

℞

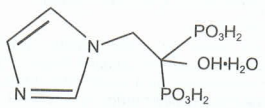
FORMULATION:

Each 100mL contains:

Zoledronic acid Monohydrate Equivalent to Zoledronic acid	5mg
Mannitol USP	4950mg
Water for Injection USP	q.s. to 100mL

DESCRIPTION

Zoruxa contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (l-Hydroxy-2-imidazol-l-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is:



Zoledronic acid monohydrate is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and a molar mass of 290.1 g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of Zoledronic acid in water is approximately 2.

Zoledronic Acid Injection is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 100 mL vial contains 5.330 mg of Zoledronic Acid monohydrate, corresponding to 5 mg Zoledronic acid on an anhydrous basis.

Inactive Ingredients: Mannitol USP, Sodium Citrate Dihydrate USP and Water for Injection USP.

MECHANISM OF ACTION

Zoledronic acid is a potent inhibitor of bone resorption. It inhibits osteoclast proliferation and induces osteoclast apoptotic cell death. Its potency results from its high affinity for mineralized bone and especially for sites of high bone turnover. Zoledronic acid inhibits farnesyldiphosphate (FPP) synthase and in addition the cellular biosynthetic, FPP synthase-mediated mevalonate pathway .

In the absence of FPP synthase, FPP and geranyl diphosphate are not produced, which results in the inhibition of the GTP-binding proteins prenylation in osteoclasts. Low levels of prenylated GTP-binding proteins inhibit osteoclast activity and induce osteoclast apoptosis. Furthermore, zoledronic acid may boost osteoblast differentiation and increase bone mineralization.

PHARMACOKINETICS

Zoledronic acid is not metabolized in humans and is excreted intact in the urine. It has minor or no effects on the cytochrome P450 enzyme system and therefore has no interaction with the drugs metabolized via cytochrome P450. Zoledronic acid binding to plasma proteins is 22%. Zoledronic acid concentration in plasma after the infusion decreases rapidly due to the increased absorption of the drug by the bone. However, small amounts of zoledronic acid can be detected in plasma several days after the infusion, representing the drug released gradually from the bone during bone turn-over.

The excretion of zoledronic acid by the kidney does not depend on the dose or the infusion time. The drug can be detected in urine in trace amounts up to 28 days after the infusion, although adequate amounts are present in urine only in the first 24 hours. The amount found in the urine in the first 24 hours post dose, however, represents just the one- or two-thirds of the total dose as a result of the increased binding of the drug to the bone.

SPECIFIC POPULATIONS

Pediatrics: Zoledronic acid is not indicated for use in children.

Geriatrics: No overall differences in safety and efficacy of zoledronic acid relative to younger adults; however, the incidence of acute-phase inflammatory reactions was less in geriatric patients with osteoporosis or Paget's disease of bone than in younger adult's. Because of the greater frequency of impaired renal function in geriatric patients, the renal function should be monitored with particular care in this age group.

Hepatic Impairment: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Impairment: No dosage adjustment is required in patients with a creatinine clearance of ⩾ 35 mL/min. Zoledronic acid is contraindicated in patients with creatinine clearance < 35 mL/min and in those with evidence of acute renal impairment due to an increased risk of renal failure.

INDICATIONS & USAGE:

Treatment of Osteoporosis in Postmenopausal Women

Zoruxa is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Zoledronic acid reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Zoledronic acid reduces the incidence of new clinical fractures.

Prevention of Osteoporosis in Postmenopausal Women

Zoruxa is indicated for prevention of osteoporosis in postmenopausal women.

Osteoporosis in Men

Zoruxa is indicated for treatment to increase bone mass in men with osteoporosis.

Glucocorticoid-Induced Osteoporosis

Zoruxa is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months.

Paget's disease of Bone

Zoruxa is indicated for treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease.

Important Limitations of Use

The safety and effectiveness of Zoledronic acid for the treatment of osteoporosis is based on clinical data of three

years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

DOSAGE AND ADMINISTRATION

Important Administration Instructions

Zoledronic acid injection must be administered as an intravenous infusion over no less than 15 minutes.

Patients must be appropriately hydrated prior to administration of Zoledronic acid.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Intravenous infusion should be followed by a 10 mL normal saline flush of the intravenous line.

Administration of acetaminophen following Zoledronic acid administration may reduce the incidence of acute-phase reaction symptoms.

Treatment of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes.

Prevention of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion given once every 2 years intravenously over no less than 15 minutes.

Osteoporosis in Men

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes.

Treatment of Paget's Disease of Bone

The recommended dose is a 5 mg infusion. The infusion time must not be less than 15 minutes given over a constant infusion rate.

Re-treatment of Paget's Disease

After a single treatment with Zoledronic acid in Paget's disease an extended remission period is observed. Specific re-treatment data are not available. However, re-treatment with Zoledronic acid may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

Laboratory Testing and Oral Examination Prior to Administration

Prior to administration of each dose of Zoledronic acid, obtain a serum creatinine and creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each Zoledronic acid dose. Zoledronic acid is contraindicated in patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment. A 5 mg dose of Zoledronic acid administered intravenously is recommended for patients with creatinine clearance greater than 35 mL/min. There are no safety or efficacy data to support the adjustment of the Zoledronic acid dose based on baseline renal function. Therefore, no dose adjustment is required in patients with CrCl greater than 35 mL/min.

A routine oral examination should be performed by the prescriber prior to initiation of Zoledronic acid treatment.

Calcium and Vitamin D Supplementation

Instruct patients being treated for Paget's disease of bone on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia. All patients should take 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 international units vitamin D daily, particularly in the 2 weeks following Zoledronic acid administration.

Instruct patients being treated for osteoporosis to take supplemental calcium and vitamin D if their dietary intake is inadequate. An average of at least 1200 mg calcium and 800-1000 international units vitamin D daily is recommended.

METHOD OF ADMINISTRATION

The Zoledronic acid infusion time must not be less than 15 minutes given over a constant infusion rate. The I.V. infusion should be followed by a 10 mL normal saline flush of the intravenous line.

Zoledronic acid solution for infusion must not be allowed to come in contact with any calcium or other divalent cation-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line.

If refrigerated, allow the refrigerated solution to reach room temperature before administration. After opening, the solution is stable for 24 hours at 2°C-8°C (36°F - 46°F).

For single use only.

Must not be mixed with other divalent cation-containing infusion solutions, such as Lactated Ringer's Solution, and should be administered as a single intravenous solution in a line separate from all other drugs. It is ready-to use solution infusion and may be administered without further dilution.

CONTRAINDICATIONS

Known hypersensitivity to Zoledronic Acid, any other bisphosphonate or any components of Zoruxa Hypocalcemia.

Renal Failure

Zoledronic acid is contraindicated in patients with creatinine clearance < 35 ml/min and in those with evidence of acute renal impairment.

WARNINGS

Included as part of the PRECAUTIONS section.

PRECAUTIONS

Drug Products with Same Active Ingredient

Zoledronic acid contains the same active ingredient found in Zoledronic acid, used for oncology indications, and a patient being treated with Zoledronic acid should not be treated with Zoledronic acid.

Hypocalcemia and Mineral Metabolism

Pre-existing hypocalcemia and disturbances of mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery; malabsorption syndromes, excision of small intestine) must be effectively treated before initiating therapy with Zoledronic acid. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended for these patients.

Hypocalcemia following Zoruxa administration is a significant risk in Paget's disease. All patients should be instructed about the symptoms of hypocalcemia and the importance of calcium and vitamin D supplementation in maintaining serum calcium levels.

All osteoporosis patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels.

Renal Impairment

A single dose of Zoledronic acid should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.

Zoledronic acid is contraindicated in patients with creatinine clearance < 35 mL/min and in those with evidence of acute renal impairment. If history or physical signs suggest dehydration, Zoledronic acid therapy should be withheld until normovolemic status has been achieved.

Zoledronic acid should be used with caution in patients with chronic renal impairment. Acute renal impairment, including renal failure, has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise, advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Zoledronic acid administration. Acute renal failure (ARF) has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis or fatal outcome occurred in patients with underlying moderate to severe renal impairment or with any of the risk factors described in this section. Renal impairment may lead to increased exposure of concomitant medications and/or their metabolites that are primarily renally excreted.

Creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each Zoledronic acid dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; interim monitoring of creatinine clearance should be performed in at-risk patients. Elderly patients and those receiving diuretic therapy are at increased risk of acute renal failure. These patients should have their fluid status assessed and be appropriately hydrated prior to administration of Zoledronic acid. Zoledronic acid should be used with caution with other nephrotoxic drugs. Consider monitoring creatinine clearance in patients at-risk for ARF who are taking concomitant medications that are primarily excreted by the kidney.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including zoledronic acid. Most cases have been in cancer patients treated with intravenous bisphosphonates undergoing dental procedures. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy).

While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of commination. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Pregnancy

IT SHOULD NOT BE USED DURING PREGNANCY. Zoledronic acid may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while on Zoruxa therapy [see Use In Specific Populations].

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including zoledronic acid. The time to onset of symptoms varied from one day to several months after starting the drug. Consider withholding future zoledronic acid treatment if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Respiratory effects

While not observed in clinical trials with zoledronic acid, there have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates. Use zoledronic acid with caution in aspirin-sensitive patients.

DRUG INTERACTIONS

No in vivo drug interaction studies have been performed for zoledronic acid. In vitro and ex vivo studies showed low affinity of zoledronic acid for the cellular components of human blood. In vitro mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL. In vivo studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

Aminoglycosides

Caution is advised when bisphosphonates, including zoledronic acid, are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in zoledronic acid clinical trials.

Loop Diuretics

Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcemia.

Nephrotoxic Drugs

Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.

Drugs Primarily Excreted by the Kidney

Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise or other risk factors. In patients with renal impairment, the exposure to concomitant medications that are primarily renally excreted (e.g., digoxin) may increase.