zoledronic acid is 4 mg, given as a single-dose intravenous infusion over a minimum of 15 minutes. Adequate rehydration of patient should precede the administration of zoledronic acid. Patient may be retreated with zoledronic acid 4 mg if serum calcium does not return to or remain with in normal limits after initial treatment. It is recommended that a minimum of 7 days allowed to pass between treatment, in order to allow for a full initial response. If patients with a normal serum creatinine prior to treatment have an increase of 1mg/dL from baseline with in 2 weeks of their next dose, zoledronic acid should be withheld untill the serum creatinine is with in 10% of baseline.

**For the treatment of bone metastases:**
For the treatment of bone lesions associated with multiple myeloma and bone metastases from solid tumor, the recommended dose is 4 mg intravenously over 15 minutes every 3 or 4, in conjunction with standard antineoplastic therapy. Concomitant oral calcium (500 mg) and vitamin D supplementation (400 international units) is also recommended. Patients with prostate cancer should have disease that has progressed after treatment with at least one hormonal therapy.

## DOSE MODIFICATIONS

Serum creatinine (Scr) should be measured prior to each zoledronic acid dose. Patients with hypercalcemia of malignancy and deterioration of renal function should be evaluated regarding risk versus benefit for continued zoledronic acid therapy. Patients with bone metastases and deterioration of renal function should have zoledronic acid therapy withheld untill serul creatinine (Scr) values return to with in 10% to baseline.

## RECONSTITUTION

Reconstitute the contents of the vial with 5 ml of sterile water for injection IP and shake gently to dissolve it completely. The reconstituted solution should immediately be diluted in 100 ml of sterile 0.9% w/v sodium chloride injection IP or 5% w/v dextrose injection IP. The dose must be given as a single intravenous infusion over no less than 15 minutes. Reconstitute and diluted solution should be used immediately or with in 24 hours if stored under refrigeration at 2-8 °C. The refrigerated solution should then be equilibrated to room temperature prior to administration. Do not mix with calcium containing infusion solution viz., Ringer's solution and should be administered as a single intravenous solution in a line separate from all other drugs. Inspect the reconstituted solution visually for particulate matter and discolouration prior to administration.

## STORAGE

Store at a temperature below 25 °C. Protect from light.

## PRESENTATION

ZOLDRON™ 4 mg is available as a sterile lyophilized powder for injection in a 5 ml vial containing 4 mg of anhydrous zoledronic acid along with a 5 ml ampoule of sterile water for injection IP as diluent for reconstitution.

## REFERENCES


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**Marketed by:**
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**Manufactured by:**
Getwell Pharmaceuticals
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0700DZW




GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

# Zoledronic Acid Injection IP

**ZOLDRON™**

**LYOPHILIZED**

**FOR I.V INFUSION ONLY**

**Rx only**

**WARNING**

- Renal impairment (renally eliminated; posibility of enhanced toxicity)
- History of hypoparathyroidism, risk of hypocalcemia.
- Concomitant administration of loop diuretics, aminoglycosides, or other nephrotoxic drugs.
- History of aspirin-sensitive asthma.
- Doses greater than 4 milligrams and infusion times less than 15 minutes have increased risk for renal toxicity. Due to risk of renal toxicity, including renal failure, avoid intravenous administration over less than 15 minutes or doses greater than 4 mg.
- Monitor renal function prior to and during treatment, especially in patients with pre-existing renal impairment. Re-treatment should be delayed in patients who develop increased serum creatinine following the initial dose. Risk of zoledronic acid treatment must be carefully considered in patients with renal failure or impairment.
- Caution is recommended when zoledronic acid is administered to elderly patients. Since these patients have greater frequency of decreased renal function and concomitant disease states or other drug therapy.
- Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, as well as serum creatinine, should be carefully monitored during treatment with zoledronic acid.
- Zoledronic acid should not be used in patients with pre-existing hypocalcemia If electrolyte imbalance (i.e., hyphocalcemia, hypomagnesemia, or hypophosphatemia) occurs during therapy, short-term supplementation may be necessary .
- Dehydration or hypovolemia should be corrected during treatment of hypercalcemia and prior to begining zoledronic acid therapy, maintain urine output of 2L/day during treatment of hypercalcemia.

## DESCRIPTION

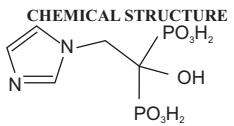
ZOLDRON™ contains Zoledronic acid (also known zoledronate), a potent third-generation bisphosphonate, an intravenous, heterocyclic nitrogen-containing bisphosphonate and a inhibitor of osteoclastic bone resorption.

## COMPOSITION

Each combipack contains:

| | |
|---|---|
| A. One vial containing | |
| Zoledronic Acid monohydrate | |
| Equiv. to Zoledronic acid anhydrous | 4 mg |
| Mannitol IP | 220 mg |
| B. One ampoule containing | |
| Sterile Water For Injection IP | 5 ml |

**CHEMICAL STRUCTURE**




The chemical name of Zoledronic acid is [1-Hydroxy 2- (1H-imidazol-1-yl) ethylidene]-biphosphonic acid. Zoledronic acid has a molecular formula of $C_2H_{10}N_2O_7P_2$ and a molecular weight of 272.1. It is a white crystalline powder highly soluble in 0.1N sodium hydroxide solution. sparingly soluble in water and. 0.1N hydrochloride acid and practically insoluble in organic solvents.

## CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

Zoledronic acid inhibits bone resorption by altering osteoclast activity and by inhibiting normal endogenous, as well as tumor induced, mediators of bone degradation. Like other bisphosphonates, zoledronic acid binds to hydroxyapatite crystals in mineralized bone matrix. The binding to calcium phosphate slows the dissolution of hydroxyapatite crystals, as well as inhibiting the formation and aggregation of these crystals. Zoledronic acid is incorporated into osteoclastic bone surfaces, where is inhibits bone resorption by inhibiting osteoclastic activity and inducing osteoclastic apoptosis. The presence of bisphosphonates in the bone structure appears to prevent acid extrusion, an important step stimulated by osteoclastic during

Folowing subsequent resorption, bone tissue surrounding the bisphophonate containing bone tends to lack ruffled borders and has fewer vacuoles, which are changed consistent with lower resorptive capacity. Therefore, osteoclasts may be inhibited not only when bishposphonates are directly incorporated into the bone matrix, but after they engulf bisphosphonate-containg mineral during bone resorption, as well.

Zoledronic acid affects chemical and hormonal mediators of bone degradation. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. This may be due to the mediation of release of interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF) by monocytes. These cytokines are involved in osteoclast recruitment and activation. Zoledronic acid appears to have direct anti-tumor effects in specific types of cancer cells. Although the exact mechanism is unknown, Zoledronic acid has been demonstrated to inhibit cell growth and induce apoptosis in human myeloma, breast cancer and prostate cancer cell lines.

## PHARMACOKINETICS & PHARMACODYNAMICS

Zoledronic acid is administered by intravenous infusion. Human oral absorption data for zoledronic acid unavailable. Other bisphosphonates are poorly absorbed (eg. less than 5% of a dose for alendronate, tiludronate, etidronate), and absorption is further retarded by administration with food or calcium or other divalent cations. After intravenous infusion. Zoledronic acid distributes primarily to the bone in a triphasic process. Zoledronic acid does not undergo biotransformation. Zoledronic acid does not inhibit P450 enzymes in vitro. Zoledronic acid plasma concentrations are dose proportional. plasma protein binding is approximately 22% and independent of zoledronic acid concentrations. More than 95% of Zoledronic acid is excreted unchanged, via the kidney. The elimination is triphasic, with an alpha early distribution half-life of 0.23 hours, beta half-life of 1.75 hours, and terminal elimination half-life of 167 hours, with low plasma concentrations observed up to 28 days post dose.

**Drug Interactions:**

Loop diuretics should be used with caution in combination with zoledronic acid in order to avoid hypocalcemia.

The initial treatment of hypercalcemia typically includes the use of loop diuretics, in combination with saline hydration; however, diuretic therapy should not be employed prior to correction of hypovolemia and dehydration.

Caution is recommended when bisphosphonates are administered with aminoglycosides since these agents may have an additive effect to lower serum calcium levels for prolonged period

## CLINICAL STUDIES

***Clinical Trials in Hypercalcemia of Malignancy***

Major P et al has reported two identical, concurrent, parallel, Multicenter, randomized, double-blind, double-dummy trials to compare the efficacy and safety of zoledronic acid and pamidronate for treating hypercalcemia of malignancy (HCM). Patients with moderate to severe HCM (corrected serum calcium [CSC]>3.00mmol/L[12.0 mg/dL]) were treated with a single dose of zoledronic acid (4 or 8 mg) via 5-minute infusion or pamidronate (90 mg) via 2-hours infusion. Two hundred eighty-seven patients were randomized and evaluated for safety;275 were evaluated for efficacy. Both doses of zoledronic acid were superior to pamidronate in the treatment of HCM. The complete response rates by day 10 where 88.4% (P=.002), 86.7% (P=.015), and 69.7% for zoledronic acid 4 mg and 8 mg and pramidronate 90 mg respectively normalization of corrected serum calcium occured by day4 in approximately 50% of patients treated with zoledronic acid and in only 33.3% of the pamidronate-treated patients. The median duration of complete response favored zoledronic acid 4 and 8 mg over pamidronate 90 mg with response durations of 32, 43 and 18 days, respectively. This study concluded that zoledronic acid is superior to pamidronate; 4mg is the dose recommended for initial treatment of HCM and 8 mg for relapsed or refractory hypercalcemia.

***Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors***

Rosen LS reported a pamidronate- controlled study in breast cancer and multiple myeloma patients. A total of 1,648 patients with either Durie-Salmon stage III multiple myeloma or advanced breast cancer and at least on bone lesion were randomly assigned to treatment with either 4 to 8 mg of zoledronic acid via 15-minute intravenous infusion or 90 mg of pamidronate via 2-hour intravenous infusion every 3 to 4 weeks for 12 months. Median time to the first skeletal-related event was approximately 1 year in each treatment group. The skeletal morbidity rate was slightly lower in patients treated with zoledronic acid than in those treated with pamidronate. Overall, the number of patients having SRE's requiring radiation therapy to bone was significantly less in the zoledronic acid group. Similar results were seen in the breast cancer patients receiving hormonal therapy. Pain scores decreased in all treatment groups in the presence of stable of decreased analgesic use.



Zoledronic acid (4 mg) and pamidronate were equally well tolerated. This study concludes that zoledronic acid (4 mg) via 15- minute intravenous infusion was as effective and well tolerated as 90 mg of pamidronate in the treatment of osteolytic and mixed bone metastases/lesions in patients with advanced breast cancer or multiple myeloma.

Saad F reported a placebo-controlled study in prostate cancer. Patients with hormone-refractory prostate cancer and a history of bone metastases were randomly assigned to a double-blind treatment regimen of intravenous zoledronic acid at 4 mg (N = 214), zoledronic acid at 8 mg (subsequently reduced to 4 mg;8/4) (N= 221), or placebo (N= 208) every 3 weeks for 15 months. Approximately 38% of patients who received zoledronic acid at 4 mg, 28% who received zoledronic acid at 8/4 mg, and 31% who received placebo completed the study. A greater proportion of patients who received placebo had skeletal-related events than those who received zoledronic acid at 4 mg (44.2% versus 33.2%;difference=-11.0%, 95% CI =-20.3% to 1.8%; P =.021) or those who received zoledronic acid at 8/4 mg (38.5%; difference versus placebo = 5.8%, 95% CI =-15.1 to3.6%; P=.222). Median time to first skeletal-related event was 321 days for patients who received placebo, was not reached for patients who received zoledronic acid at 4 mg (P=.011 versus placebo), and was 363 day for those who received zoledronic acid at 8/4 mg (P=.491 versus placebo). Thus zoledronic acid at 4 mg given as a 15-minute infusion was well tolerated, but the 8 mg dose was associated with renal function deterioration

## INDICATION(S)

Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy and for treatment of bone metastases in patients with multiple myeloma and solid tumors in conjunction with antineoplastic therapy. Patient with prostate cancer should have progressed after therapy with at least one hormonal agent.

## CONTRA INDICATION(S)

Prior hypersensitivity to zoledronic acid, its excipients, or other bisphosphonates

Patients with bone metastases and severe renal impairment; serum creatinine greater than 3 milligrams/deciliter

Pregnancy

## ADVERSE REACTION(S)

Adverse effects include bone pain, nausea, constipation, fatigue, confusion, hallucination, anemia, muscle pain, vomiting, weakness, anorexia, fever, dyspnea, eye irritation, hypocalcemia, headache, diarrhea, and hypophosphatemia.

Administration is most commonly associated with fever (44.2%). Occasionally, patients experience a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias (10%) and myalgia.

Gastrointestinal reactions such as nausea/vomiting (29%/14%) and anorexia (9%) have been reported following administration. Injection site reactions, such as erythema, redness or swelling, were observed infrequently and resolved in most cases without treatment within 24-48 hours.

Azotemia (2%) has been reported during therapy with zoledronic acid; serum creatinine should be monitored.

Electrolyte imbalances may occur during treatment with zoledronic acid. Hypocalcemia (1.2%), hypomagnesemia (10%) and hypophosphatemia (52%) have been reported. Monitor serum calcium, phosphate and magnesium during therapy, short-term supplementation of these electrolytes may be necessary.

Rare cases of rash (unspecified), pruritus, and chest pain (unspecified) have been reported. As with other bisphophonates, cases of conjunctivitis and bronchospasm have been reported following treatment with zoledronic acid.

Other adverse events that have been reported in >1% of patients include abdominal pain, agitation, anemia anxiety, confusion, constipation, cough, diarrhea, dyspnea, hypotension, insomnia, condidiasis and urinary tract infection.

## USE IN PREGNANCY AND LACTATION

Zoledronic acid is classified as FDA pregnancy risk category D. In animal studies, administration of zoledronic acid was associated with increased pre-and post- implantation losses and stillbirths; decreased neonatal survival; skeletal, visceral, and external malformations; and adverse maternal effects including periparturient mortality. Because no adequate and well -controlled studies of zoledronic acid have been conducted in pregnant women, the drug should be avoided during pregnancy whenever possible.

## DOSAGE AND ADMINISTRATION

**For the treatment of hypercalcemia of malignancy:**

For hypercalcemia of malignancy(albumin-corrected serum calcium equal to or greater than 12 mg/dL), the maximum recommended dose of