372699

Zoledronic Acid Injection I.P.

Zoldonat®

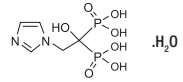
For Intravenous Infusion Sterile, Lyophilized

COMPOSITION

Each vial contains Zoledronic acid I.P. equivalent to Zoledronic acid (Anhydrous) 4 mg and Mannitol I.P. 220 mg

DESCRIPTION

Zoldonat contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as [1-hydroxy-2-(1 H-imidazol-1-yl)ethylidene] diphosphonic acid, monohydrate and its structural formula is:



.H_2O

Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \bullet H_2O$ and its molar mass is 290.1g/Mol. Zoledronic acid 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 2.0.

CLINICAL PARTICULARS

Therapeutic indications

Hypercalcemia of Malignancy

Zoldonat is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of >12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (mid-range of measured albumin in mg/dL).

Multiple Myeloma and Bone Metastases of Solid Tumors

Zoldonat is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.
Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Dose and method of administration

Adults and elderly: The recommended dose in hypercalcaemia (albumin-corrected serum calcium 2: 12.0 mg/dl or 3.0 mmol/l) is 4 mg reconstituted and further diluted Zoledronic acid solution for infusion (diluted with 100 ml 0.9% w/v sodium chloride or 5% w/v glucose solution), given as a single 15 minute intravenous infusion.

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zoldonat. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, overhydration in cardiac failure patients must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia.

Dose adjustments are not necessary for patients having serum creatinine levels <400 µmol/L or <4.5 mg/dL prior to initiation of therapy.

Retreatment with Zoldonat 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zoldonat and serum creatinine must be assessed prior to retreatment.

Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Zoldonat in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over **no less than 15 minutes** every 3-4 weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Zoldonat doses for patients with reduced renal function (mild and moderate renal impairment) are listed in below Table. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula

Reduced Doses for Patients with Baseline CrCl <60 mL/min	
Baseline Creatinine Clearance (mL/min)	**Zoldonat Recommended Dose***
> 60	**4 mg**
50-60	**3.5 mg**
40-49	**3.3 mg**
30-39	**3 mg**
*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl = 75 mL/min)	

During treatment, serum creatinine should be measured before each Zoldonat dose and treatment should be withheld for renal deterioration. Renal deterioration is defined as follows:

For patients with normal baseline creatinine, increase of 0.5 mg/dL
For patients with abnormal baseline creatinine, increase of 1.0 mg/dL
Zoldonat treatment will be resumed only when the creatinine returned to within 10% of the baseline value. Zoldonat should be reinitiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Method of Administration

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zoldonat should not exceed 4 mg and the duration of infusion should be no less than 15 minutes

WARNINGS AND PRECAUTIONS

Drugs with Same Active Ingredient

Patients being treated with Zoldonat should not be treated with drugs having same ingredient.

Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zoldonat. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zoldonat in order to avoid hypocalcemia. Zoldonat should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zoldonat. If hypocalcemia, hypophosphatemia or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Renal Impairment

Zoldonat treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment.

Zoldonat treatment is not recommended in patients with bone metastases with severe renal impairment.

Osteonecrosis of the Jaw

Caution is advised to cancer patients when bisphosphonates intravenous administration due to predominant chances of getting Osteonecrosis of the jaw (ONJ).

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

While on treatment, these patients 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. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment

Pregnancy

Zoldonat should not be used during pregnancy. Zoldonat may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus

Musculoskeletal Pain

Caution should also be exercised when bisphosphonates is used due to risk of getting severe and occasionally incapacitating bone, joint, and/or muscle pain. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop.

Patients with Asthma

Caution is indicated for bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

Contra indications

Zoledronic acid powder for solution for infusion is contraindicated in patients with clinically significant hypersensitivity to Zoledronic acid, other bisphosphonates or any of the excipients in the formulation of Zoledronic acid.

Special warning and special precautions for use

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating Zoledronic acid therapy.

Bisphosphonates have been associated with renal dysfunction. In view of possible serum creatinine level elevations and the lack of data in patients with severe renal impairment (serum creatinine 400 µmol/l or 4.5 mg/dl), the use of Zoledronic acid cannot be recommended in these patients unless the benefits outweigh the risks.

In any patient requiring repeated administration of Zoledronic acid, serum creatinine should be evaluated prior to each dose. Patients with evidence of renal function deterioration should be appropriately evaluated and consideration should be given as to whether the potential benefit outweighs the possible risk.

Interaction with other medicinal products

Aminoglycosides

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods.

Loop Diuretics

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

Nephrotoxic Drugs

Caution is indicated when Zoldonat is used with other potentially nephrotoxic drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Zoldonat should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant

Nursing Mothers

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

Pediatric Use

Zoldonat is not indicated for use in children.

Geriatric Use

Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function while Zoldonat administration to the elder patients.

Overdose

Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically significant hypocalcaemia, reversal may be achieved with an infusion of calcium gluconate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption.

Zoledronic acid belongs to a new highly potent class of bisphosphonates, which act specifically on bone. It is one of the most potent inhibitors of osteoclastic bone resorption known to date. The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long term animal studies, Zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone. In addition to inhibiting osteoclastic bone resorption, Zoledronic acid exerts direct anti-tumor effects on cultured human myeloma and breast cancer cells, inhibiting proliferation and inducing apoptosis.

Pharmacokinetic properties

Distribution

The postinfusion decline of Zoledronic acid concentrations in plasma is known to be consistent with a triphasic process showing a rapid decrease from peak concentrations at end of infusion to <1% of C_{max} 24 hours postinfusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$1.87 hours for the early disposition phases of the drug. The terminal elimination phase of Zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 postinfusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of Zoledronic acid was dose proportional from 2-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

Metabolism

Following an intravenous dose of zoledronic acid, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h. Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance.

Adverse Drug Reactions

The most frequently observed adverse events were fever, nausea, constipation, anemia, and dyspnea

Renal Toxicity

Administration of Zoldonat 4 mg given as a 5-minute intravenous infusion result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zoldonat 4 mg is given as a 15-minute intravenous infusion. Zoldonat should be administered by intravenous infusion over no less than 15 minutes

Acute Phase Reaction-like Events

Symptoms consistent with acute phase reaction (APR) can occur with intravenous isphosphonate use. Fever has been the most commonly associated symptom and occasionally, a flu-like syndrome consisting of fever, chills, flushing, bone pain and/or arthralgias, and myalgias.

Mineral and Electrolyte Abnormalities

Electrolyte abnormalities, most commonly hypocalcemia, hypophosphatemia and hypomagnesemia, can occur with bisphosphonate use.

Injection Site Reactions

Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Ocular Adverse Events

Ocular inflammation such as uveitis and scleritis can occur with bisphosphonate use, including Zoldonat.

Multiple Myeloma and Bone Metastases of Solid Tumors

Blood and Lymphatic

Anemia, Neutropenia, Thrombocytopenia

Gastrointestinal

Nausea, Vomiting, Constipation, Diarrhea, Abdominal Pain, Dyspepsia, Stomatitis, Sore Throat

General Disorders and Administration Site

Fatigue, Pyrexia, Weakness, Edema Lower Limb, Rigors

Infections

Urinary Tract Infection, Upper Respiratory Tract Infection

Metabolism

Anorexia, Weight Decreased, Dehydration, Appetite Decreased

Musculoskeletal

Bone Pain, Myalgia, Arthralgia, Back Pain, Pain in Limb

Neoplasms

Malignant Neoplasm Aggravated

Nervous

Headache, Dizziness (excluding vertigo) , Insomnia, Paresthesia, Hypoesthesia

Psychiatric

Depression, Anxiety, Confusion

Respiratory

Dyspnea, Cough

Skin

Alopecia, Dermatitis

PHARMACEUTICAL PARTICULARS

List of Excipients

Zoledronic acid vial: Mannitol, sodium citrate and sterile water for Injection I.P.

Incompatibilities

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with Zoledronic acid.

To avoid potential incompatibilities, Zoledronic acid reconstituted solution is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Zoledronic acid reconstituted solution must not be mixed with calcium containing solutions such as Ringer's solution.

Special precautions for storage

Store the vial below 30°C. The reconstituted injection should be administered within 24 hours of preparation when stored at 2° to 8°C.

Instructions for use and handling

Note: Zoledronic acid injection should be kept out of the reach of the children.

Zoledronic acid 4mg powder for solution for infusion is for intravenous use only. The powder must first be reconstituted in the vial with 5ml of Sterile Water for Injection I.P. Dissolution must be complete before the solution is withdrawn. The reconstituted solution is then further diluted with 100 ml of calcium -free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution). If refrigerated, the solution must be allowed to reach room temperature before administration. If an 8 mg dose is required (re-treatment), two vials are each to be reconstituted with 5ml water for injection as described above and the resulting 10ml reconstituted solution further diluted with 100 ml 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Do not mix Zoledronic acid reconstituted solution with calcium-containing solutions such as Ringer's solution.

The zoledronic acid infusion solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the care provider and should be in a refrigerator at 2°C - 8°C. Allow the refrigerated solution to reach room temperature before administration. The total time between reconstitution, dilution, storage in the refrigerator and end of administration must not exceed 24 hours. The solution containing Zoledronic acid is given as a single 15-minute intravenous infusion. The hydration status of patients must be assessed prior to administration of zoledronic acid to assure that they are adequately hydrated. Since no data is available on the compatibility of Zoledronic acid with other intravenously administered substances. Zoledronic acid must not be mixed with other medications/substances and should always be given through a separate infusion line.

How Supplied

Each Carton of Zoldonat contains one vial of Zoledronic acid I.P. equivalent to Zoledronic acid (Anhydrous) 4 mg in Lyophilized form and one ampoule of 5 ml Sterile Water for Injection I.P.

Storage

Store below 30°C.

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Manufactured in India by:
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