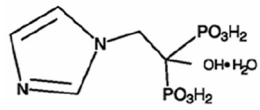
Composition :

Each vial contains Zoledronic acid Monohydrate IP equivalent to anhydrous

Zoledronic acid 4 mg.

DESCRIPTION:

Zoledronic acid contains a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1Hydroxy-2-imidazol-1-yl-phoshoneothyl) phosphonic acid monohydrate Zoledronic acid is a white crystalline powder. Its molecular formula is C3H10N2O1P2H2O and its molecular weight is 290.1



Zoledronic acid injection is available in vials as a sterile lyophilized powder or intravenous infusion. Each vials contains Zoledronic acid monohydrate equivalent to anhydrous Zoledronic acid 4 mg.

Inactive Ingredients: Mannitol, IP, Trisodium Citrate dehydrate.

Clinical Pharmacology:

The principal pharmacology action of Zoledronic acid is inhibition of bone reception. It is one of the most potent inhibitors of osteoclast bone resorption. Although the antiresoptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro. Zoledronic acid inhibits osteoclastic activity and and induces osteoclast apotopsis. Also blocks the osteoclastic activity and skeletal calcium release included by various stimulatory factors released by tumors. In addition to inhibiting osteoclast bone resorption, Zoledronic acid exerts direct antitumor effects on human myeloma and breast cancer cells, inhibiting their proliferation and including apotosis. Zoledronic acid is antiangiogenic in animal tumor model. This antitumor efficacy may be enhanced when used in combination with other anticancer drugs.

Pharmacodynamics :

Clinical studies in patients with hyoercalcemia of malignancy (HCM) showed that single dose infusions of Zoledronic acid are associated with decrease in serum calcium and phosphorus and increase in urinary calcium and phosphorous excretion, Normalisation of serum calcium by day 4 mg was greater for Zoledronic acid and 8 mg doses than pamidronate.

Hypocalcaemia of Malignancy :

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcamia of malignancy (HCM), tumor-induced hypercalcamia) and metastatic bone diseases. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This is turn results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcaemia. Reducing excessive bone resorption and adequate fluid administration are, therefore, essential

to the management of hypocalcemia.

Clinical Pharmacokinetics

Single or multiple (q 28 days) 5 minute infusion or 2, 48, or 16mg Zoledronic acid were given to patients with cancer and bone metastases. The post infusion decline of Zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% C max hours and t ½ beta 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of Zoledronic acid was 146 hours. There are under the plasma concentration versus time curve (AUCO-24h) of Zoledronic acid measured over three cycles was low, with mean AUCO-24h rations for cycles 2 and 3 versus 1 of 1.13 + 0.30 and 1.16 + 0.36, respectively.

In vitro and ex vivo studies showed low affinity of Zoledronic acid for the cellular, components of human blood, binding to human plasma proteins was approximately 22% and was independent of the concentration of Zoledronic acid.

Metabolism:

Zoledronic acid does not inhibit human P450 enzymes in vitro, Zoledronic acid dose not undergo biotransformation in vivo In animal studies <3% of the administered intravenous does was found in the feces, with the balance either recovered in the urine or taken up by bone, indication that the drug is eliminated intact via the kidney.

Excretion:

In patients with cancer and bone metastases on average (±s.d.) 39±16% of the administration Zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post day 2. 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 days 2 to 20 post dose. The 0-24 hours renal clearance 3.7 + 2.0L/h.

Zoledronic acid clearance was reasonably independent of dose and demographic variables, with effect of bodyweight gender and race, on clearance was dependent or creatinine clearance.

Special Populations:

No pharmacokinetics data in patients with hypercalcemia.

Pediatrics: No pharmacokinetics data in pediatric patients.

Geratrics: the pharmacokinetics of Zoledronic acid were not affected by age in patients with cancer and bone metastases aged 38 years to 84 years.

Race: The pharmacokinetics of Zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic Insufficiency: There are no pharmacokinetic data in patients with impaired

liver functions : Zoledronic acid is not cleared by liver therefore impaired liver function may no affect the pharmacokinetic of Zoledronic acid.

Renal Insufficiency: Patients with mild to moderate (creatinine 50-80 ml / min) renal impairment showed an increase in plasma AUC of 26-27 % whereas patients with moderate to severe renal impairment (creatinine clearance 30-50ml/min) showed an increase I plasma AUC 27-41% Limited pharmacokinetic data are available for Zoledronic acid in patients with severe renal impairment (creatinine clearance <30 ml/min). Based on population PK/PD modeling the risk of renal deterioration appears to increase with AUC which is doubled at a creatinine clearance of 10 ml/min.

INDICATIONS AND USAGE :

Hypercalcemia of Malignany

Zoldric (Zoledronic acid) injection is indicated for the treatment of hypercalcaemia of; malignancy following adequate saline rehydration.

Vigorous saline hydration, and integral part of hypercalcemia therapy, should be intiated promptly and an attempt should be made to restore the urine output to about 2 L/throughful treatment.

The safety and efficacy of Zoledronic acid in the treatment of hypercalcamia associated with hyperparathyroidism or with other non-tumor-related conditions have not been established.

DOSAGE AND ADMINISTRATION

Hypercalcaemia of Malignancy

The recommended dose of Zoledronic acid in hypercalcaemia (albumin corrected serum calcium – 12mg/dl) is 4 mg. The 4 mg is given as a single dose i.v. infusion over 15 minutes. Patients should be adequately rehydrated prior to administration of Zoledronic acid. Retreatment with Zoledronic acid 4mg, may be considered it serum calcium does no 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.

Preparation of Solution:

Zoledronic Lyophilized powder of infusion is reconstituted by adding 5ml of sterile water for injection to each vial. The resulting concentration allows for withdrawal. The content of the reconstituted vials are withdrawn and further diluted in 100ml of sterile 0.9% sodium chloride or 5% Dextrose injection. Do not

store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single intravenous solution infusion over no less than than 15 minutes.

If not used immediately after dilution with infusion media, for microbiological integrity the solution should be refrigerated at 2°C-8° (36° F- 46° F). Zoledronic acid must not be mixed with calcium – containing infusion solutions such as Lactated Ringers Solution, and should administered as a single intravenous solution in a line separate from all other drugs.

WARNINGS :

Due to the risk of clinical significant deterioration in renal function. which may progress to renal failure, single doses of Zoledronic acid should not exceed 4 mg and the duration of infusion should be not less then 15 minutes.

Because safety and pharmacokinetics data are limited in patients with severe renal impairment (Serum creatinine>4.5 mg/ml). Zoledronic acid treatment is not recommended in patients with bone metatases with severe renal impairment.

Concomitant use if potentially nephrotoxic drugs (Aspirin, NSAIDs, diuretics, ACE inhibitors) may increase the potential for renal impairment. Zoledronic acid should not be mixed with calcium containing I.V. infusion.

Pregnancy : Zoledronic acid should not be used during pregnancy Zoledronic acid may cause fetal harm when administered to pregnant woman, Women of childbearing potential should be advised to avoid becoming pregnant during treatment with Zoledronic acid.

PRECAUTIONS :

GENERAL

Standard hypocalcaemia-related metabolic parameters, such as seum levels of calcium, phosponate and magnesium as well as serum creatinine should be carefully monitored following initation of therapy with Zoledronic acid injection. If hypocalcaemia, hypophoshatemia or hypomagnesemia occur, short - term supplement therapy may be necessary

Patients with hypercalcemia of malignancy must be adequately dehydrated prior to administration of Zoledronic acid. Loop diurectics should not be used until the patients us adequately dehydrated and should be used with caution in combination with

Zoledronic in order to avoid hypocalcaemia. Zoledronic acid should be used with caution with other nephrotoxic drugs.

Renal Insufficiency : Zoledronic acid excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Serum creatinine should be monitored in all patients treated with Zoledronic acid prior to each dose. Zoledronic acid has not been tasted in patients with serve renal impairment (serum cretinine>4.5 mg/ml). Therefore, its use is not recommended in this patient population.

Hepatic Insufficiency : Only limited clinical data are available for use of Zoledronic acid to treat hypercalcaemia if malignancy in patients with hepatic insufficiency, therefore dosage recommendation cannot be given for the group.

Patient With Asthma : While not observed in clinical trains with Zoledronic acid, administration of other biophosphonates has been associated with brouchoconstruction in aspirin-sensitive asthma.

LABORATORY TESTS :

Serum creatinine should be monitored prior to each dose of Zoledronic acid, serum calcium, electrolytes, phosphate, magnesium and hematoccrit / hemoglobin must be monitored closely in patients treated with Zoledronic acid.

Adverse Reactions:

Hypocalcaemia of malignancy

Adverse reactions to Zoledronic acid injection are usually mild an transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with fever. Occasionally patients experience a flu like syndrome consisting of fever, chills, bone pain and/prarthralgias, and myalgias. Gastrointestinal reactions such as nausea and vomiting have been reported following intravenous infusion of Zoledronic acid. Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and symptoms subside after 24-28 hours.

Rare cases of rash, pruritus and chest pain have been reported following treatment with Zoledronic acid.

As with other bisphonates, cases of conjusctivies and hypomagnesemia have been reported following treatment with Zoledronic acid.

Body as a Whole : Asthenia, Chest Pain, leg edema, mucositis, metastases

Digestive System : Dysphapia

Hemic and Lymphic System: Granulocytopenia, Thrombocytopenia, pancytopenia

Infection : non-specific infection

Laboratory Abnormalities: Hypocalcaemia

Metabolic and Nutritional : Dehydration

Musculoskeletal : Arthralgias

Nervous System : Headache, somnolence

Respiratory System: Pleural effusion.

Adverse events are listed regardless of presumed causality to study drug, among the less frequently occurring adverse events (<15% of patients), rigors, hypokalemia, influenza, like illness and hypocalcaemia showed a trend for more events with bisphosphonate administration compared to place bo group.

Less common adverse events reported more often with Zoledronic acid 4 mg than pamidronate included decreased weight, which was reported in 13.0% of patients in the Zoledronic acid 4mg compared with 7.1% in the pamidronate group. The incidence of decreased weight, however was similar for the place bo group (12.5%) and Zoledronic acid, Decreased appetite was reported in slightly are patients in the Zoledronic acid 4mg (10.08%) compared with pamidornate (7.3%) and placebo (8.6%) groups, but the clinical significance or these small differences are not clear.

Single doses of Zoledronic acid should not exceed 4mg and the duration of the intravenous infusion should be no less then 15 minutes.

DRUG INTERACTIONS:

No clinically apparent interactions occurred when Zoledronic acid was administered

concomitantly with commonly used anticancer drugs, diuretics antibiotics and analgesics,

Zoledronic acid shows no apperaciable binding in vitro to plasma protein and a human

P450 enzymes, indicating a low likelihood of pharmackinetic drug interactions, However,

no formal clinical interactions studies have been performed.

Caution is advised when biophosphonates are administered with amino glycoside,

since these agents may have a additive effect to lower serum calcium level of prolonged

periods. This has not been reported in Zoledronic acid clinical trials. Caution is adviseed when

Zoledronic acid is used with potentially nephrotoxic drugs. (Renal functions be monitored) in

multiple myeloma patients the risk of renal daysfunction may be increased when Zoledronic

acid used in combination with thaldio

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis : Zoledronic acid was administered orally (gavage) to rats and mice for a least 104 weeks without evidence of carcinogenic potential.

Chronic parenteral administration was not feasible given the potential of the compound to cause serve loyal irritation.

Mutagenesis : Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster over cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the vivo rat micronucleus assay.

Impairment of Fertility : Female rats were given subcutaneous doses of Zoledronic acid of 0.01,0.03 or 01 mg / kg / day beginning of 15 days before mating and continuing through gestation Effects observed in the high-dose group (with systemic exposure of 1.2 time the human systemic exposure following an intravenous dose of 4 mg, based AUC comparision) included inhibition if ovulation and a decrease in the number of pregnant rats.

Pregnancy : Category D. There is no clinical evidence to support the use of Zoledronic acid in pregnant women Therefore, Zoledronic acid should no be administered during pregnancy except for life threating hypocalcaemia.

NURSING MOTHERS :

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

Predatric Use :

The safely and effectiveness of Zoledronic acid in pediatric patients have not been established. Because of long term retention in bone. Zoledronic acid should only be used in children if the potential risk.

Geriatric Use :

No significant differences in response rate of adverse reactions were seen in geriatric patients receiving Zoledronic acid as compared to younger patients.

Overdose :

There is no experience of acute overdose with Zoledronic acid. Two patients received Zoledronic acid 32mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity, Over dosage may cause clinically significant hypocalcaemia, hypophoshatemia, and hypomagnesaemia. 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, repectively.

CONTRAINDICATIONS :

Zoledronic acid injection is contraindicated in patients with clinically significant hypersenstivity to Zoledronic acid or other bisphosphonates or any of the excipients

Storage : Store Below 30°C

Presentation:

Each vial of Zoledronic contains Zoledronic acid monohydrate equivalent to anhydrous Zoledronic acid 4mg.

Inactive Ingredients: Mannitol, IP, Trisodium citrate dehydrate.

Carton of 1 vial.

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in