Zoledronic Acid
Osteomet®

4 mg/5 mL Concentrate Solution for Intravenous Infusion
Bisphosphonate

FORMULATION
Each 5 mL vial of concentrated solution contains:
Zoledronic acid (as monohydrate)...................................... 4 mg

PHARMACOLOGIC CATEGORY

Bisphosphonate

PRODUCT DESCRIPTION

Zoledronic acid is a clear and colorless concentrated solution intended to be diluted prior to intravenous infusion.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Zoledronic acid is an aminobisphosphonate whose main action is to inhibit bone resorption. Although the antiresorptive mechanism is not completely understood, its effects appear to be mediated by several mechanisms. *In vitro,* zoledronic acid directly inhibits osteoclast activity by affecting a variety of intracellular processes necessary for osteoclast function; it induces apoptosis in osteoclasts and reduces the formation and recruitment of osteoclasts into the bone. It blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid also inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Pharmacokinetics
Single and multiple 5- and 15-minute infusions of 2, 4, 8, and 16 mg zoledronic acid in patients with bone metastases yielded the following pharmacokinetic data, which were found to be independent of the dose. After initiating the infusion of zoledronic acid, plasma concentrations of the drug rapidly increased, achieving their peak at the end of the infusion period. This was followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of drug on day 28. There was no dose accumulation of zoledronic acid in plasma after multiple doses given every 28 days.

Zoledronic acid showed no affinity for the cellular components of the blood. Plasma protein binding is low (approximately 56%) and independent of the concentration of zoledronic acid.

Zoledronic acid is not metabolized and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue, zoledronic acid is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 + 2.5 L/hour and is independent of the dose. Zoledronic acid does not inhibit human P450 enzymes *in vitro.*

Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but this had no effect on the area under the plasma concentration versus time curve (AUC).

Renal Impairment
The renal clearance of zoledronic acid was correlated with creatinine clearance (CL_{cr}), renal clearance representing 75 ± 33% of the CL_{cr}, which showed a mean of 84 ± 29 mL/minute (range 22 to 143 mL/minute) in cancer patients studied. Population analysis showed that for a patient with CL_{cr} of 20 mL/minute (severe renal impairment), or 50 mL/minute (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37% or 72%, respectively, of that of a patient showing CL_{cr} of 84 mL/minute. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (CL_{cr} < 30 mL/minute). The use of zoledronic acid is not recommended in patients with severe renal impairment.

Hypercalcemia or Hepatic Insufficiency
No pharmacokinetic data for zoledronic acid are available in patients with hypercalcemia or in patients with hepatic insufficiency

Effect of Gender, Age and Race
Pharmacokinetic studies in patients with bone metastasis showed that gender, race, age (between 38-84 years old), and body weight have no effect on total clearance of zoledronic acid.

INDICATIONS
- For the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in adult patients with advanced malignancies involving bone.
- For the treatment of adult patients with tumor-induced hypercalcemia (TIH).

DOSAGE AND ADMINISTRATION

General Dosing Considerations

Aseptic techniques must be followed during the preparation of the infusion. Visually inspect the solution for particulate matter or discoloration prior to use, whenever the solution and container permit.

This product is for intravenous infusion only.

This product is intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Dosing Recommendations

Prevention of skeletal related events in patients with advanced malignancies involving bone:
4 mg given as an intravenous infusion lasting for no less than 15 minutes every 3 to 4 weeks. The concentrate must be diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution prior to administration.

Hypercalcemia of Malignancy (HCM) (albumin-corrected serum calcium > 12 mg/dL [3 mmol/L]):
4 mg given as a single dose intravenous (IV) infusion over not less than 15 minutes following standard rehydration procedures

- ***Hydration:*** Patients must be maintained in a well hydrated state prior to and following administration of zoledronic acid. Promptly initiate vigorous saline hydration (an integral part of hypercalcemia therapy) and make an attempt to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (e.g., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout treatment but overhydration should be avoided especially in patients who have cardiac failure. Do not employ diuretic therapy prior to correction of hypovolemia.

- ***Retreatment:*** If serum calcium does not return to normal or does not remain normal after initial treatment, retreatment with zoledronic acid 4 mg may be considered. 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 zoledronic acid, and possible deterioration in renal function must be assessed prior to retreatment with zoledronic acid.

  In addition, retreatment should be given only to those patients who can tolerate the standard rehydration procedures (i.e., 3 to 5 liters of fluids per day and more than 400 mEq of sodium chloride per day). Serum BUN and creatinine must be evaluated and possible deterioration in renal function must be assessed prior to each re-administration in any patient requiring repeated administration.

- ***Dosage Adjustment in Patients with Renal Impairment***
  The risks and benefits of treatment with zoledronic acid should be evaluated in patients with HCM who have severe renal impairment. In clinical trials, patients with serum creatinine < 400 micromol/L or < 4.5 mg/dL were excluded. Although no dose adjustment is necessary in HCM patients with mild to moderate renal impairment, i.e., serum creatinine < 400 micromoL/L or < 4.5 mg/dL, zoledronic acid should not be used in patients with severe renal impairment.

Bone Metastases of Solid Tumors and Osteolytic Lesions of Multiple Myeloma (for patients with creatinine clearance > 60 mL/min):

4 mg given as a single dose IV infusion over not less than 15 minutes every 3 to 4 weeks

In patients requiring antineoplastic therapy, zoledronic acid should be administered either before or after this treatment. The optimal duration of therapy is not known.

Patients will be required to take oral supplementation of calcium (500 mg) and vitamin D (at least 400 IU) per day. If a patient has a prior history of hypercalcemia or develops hypercalcemia during therapy, the patient is advised to discontinue taking calcium and Vitamin D.

- ***Dosage Adjustment in Patients with Renal Impairment***
  In patients with mild to moderate renal impairment (defined as creatinine clearance 30 mL/min to 60 mL/min), the dose of zoledronic acid should be reduced (see table below). These doses are based on pharmacokinetic data in order to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CL_{cr}) is calculated using the Cockcroft-Gault formula as follows:

Male: CL_{cr} (mL/min) = $\frac{1.2\,[140\text{-age (years)}] \times [\text{total body weight (kg)}]}{\text{Serum creatinine (micromol/L)}}$

Female: 0.85 x value calculated using the above formula

<table>
<tr><th colspan="2">Reduced Doses for Patients with Baseline $CL_{cr} \leq 60$ mL/min</th></tr>
<tr><th>Baseline Creatinine Clearance (mL/min)</th><th>Recommended Zoledronic Acid Dose (given every 3-4 weeks)</th></tr>
<tr><td>>60</td><td>4 mg</td></tr>
<tr><td>50-60</td><td>3.5 mg</td></tr>
<tr><td>40-49</td><td>3.3 mg</td></tr>
<tr><td>30-39</td><td>3 mg</td></tr>
<tr><td colspan="2">Doses calculated assuming target AUC of 0.66(mg•hr/L) (CL_{cr} = 75 mL/min)</td></tr>
</table>

Serum creatinine should be measured before each zoledronic acid dose and treatment; it should be withheld if renal function has deteriorated. In clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (<1.4 mg/dL), an increase of 0.5 mg/dL;
- For patients with abnormal baseline serum creatinine (>1.4 mg/dL), an increase of 1 mg/dL.

Direction for dilution

Using a sterile syringe, withdraw the contents of zoledronic acid concentrated solution (entire content of 5 mL vial) and dilute immediately in **100 mL of sterile 0.9% sodium chloride or 5% dextrose injection prior to administration.**

Preparation of Reduced Doses of Zoledronic Acid for Patients with Baseline $CL_{cr} \leq 60$ mL/min

Withdraw appropriate amount of concentrate needed as follows:
4.4 mL for 3.5 mg dose
4.1 mL for 3.3 mg dose
3.8 mL for 3 mg dose
The withdrawn amount of concentrate must be diluted immediately in 100 mL of **sterile 0.9% sodium chloride solution or 5% glucose solution.**

Note: *Smaller infusion volumes (e.g., 50 mL) and rapid (over 5 minutes) IV infusion rates have been associated with an increased risk of renal impairment, which may progress to renal failure. Strict adherence to administration recommendations for diluted zoledronic acid concentrate is recommended.*

Incompatibilities:

To avoid potential incompatibilities, zoledronic acid concentrate is to be diluted with 0.9% sodium chloride solution or 5% glucose solution.

Do not mix zoledronic acid with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's Solution, and should be administered as a single intravenous solution separate from all other drugs.

No incompatibilities with zoledronic acid have been detected in studies performed with several types of infusion bags and infusion sets made from polyvinyl chloride, polyethylene and polypropylene (filled with 0.9% sodium chloride solution or 5% glucose solution beforehand) and glass bottles.

Special Precautions for Storage:

Diluted zoledronic acid solution with 100 mL 0.9% sodium chloride or 5% glucose solution is stable for 24 hours at 2 to 8°C.

Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

The diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.

CONTRAINDICATIONS

- Hypersensitivity to zoledronic acid, other bisphosphonates or to any component of this product
- Pregnant or breastfeeding women

WARNINGS AND PRECAUTIONS

General

Patients receiving zoledronic acid should be under the supervision of a physician experienced in the administration of intravenous bisphosphonates.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be monitored after initiating zoledronic acid therapy. Short-term supplemental therapy may be necessary if hypocalcemia occurs.

Serum creatinine concentration must be evaluated prior to administration of each dose of zoledronic acid. Lower doses of zoledronic acid are recommended in patients with bone metastases with mild to moderate renal impairment. Zoledronic acid should be withheld in patients who show evidence of renal deterioration. Treatment should only be resumed (at the same dose as that given prior to treatment interruption) when serum creatinine returns to within 10% of baseline.

Hydration and Electrolyte Monitoring

Prior to administration, patients (including pediatric patients) should be assessed to assure that they are adequately hydrated. The use of loop diuretics is not recommended. Use zoledronic acid with caution with other nephrotoxic drugs. (see ***Dosing Recommendations***)

Renal Impairment

Bisphosphonates, including zoledronic acid, have been associated with renal toxicity (manifested as deterioration of renal function and potential renal failure). Using the usual recommended dose of zoledronic acid may reduce the risk of renal impairment. However, deterioration in renal function may still occur. In some cases, renal deterioration (which progressed to renal failure) occurred after administration of the initial dose of zoledronic acid.

Risk factors predisposing patients to renal deterioration include dehydration, pre-existing renal impairment, chemotherapy, concomitant therapy with other nephrotoxic drugs, dosage, infusion volume and rate, and multiple cycles of treatment.

Transient increases in serum creatinine concentration may be greater in patients with impaired renal function.

Musculoskeletal Pain

Severe and occasionally incapacitating bone, joint and/or muscle pain have been reported infrequently in patients taking bisphosphonates. This may occur from one day to several months after initiation of treatment. Recurrence of symptoms has been observed in some patients when rechallenged with the same medicine or another bisphosphonate.

Osteonecrosis of the Jaw (ONJ)

ONJ has been associated with the use of bisphosphonates. ONJ has been reported mostly in cancer patients treated with intravenous bisphosphonates, including zoledronic acid.

Signs and symptoms (which may occur months to years after commencing bisphosphonate therapy) of ONJ include altered local sensation (hyperesthesia or numbness), maxillofacial pain, "toothaches", denture sore spots, loose teeth, exposed bone in the oral cavity, impaired healing, recurrent or persistent soft tissue infection in the oral cavity and marked oral odor.

Known risk factors for ONJ include: invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (such as chemotherapy, radiotherapy, corticosteroids, immunosuppressive drugs), poor oral hygiene, co-morbid disorders (such as periodontal and/or other pre-existing dental disease, and poorly fitting dentures). Patients should consider a dental examination with appropriate preventive dentistry prior to treatment with bisphosphonates. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms (e.g., dental mobility, pain, swelling) during bisphosphonate treatment.

For patients requiring invasive dental procedures, the risk for ONJ may be reduced by stopping bisphosphonate treatment. The management plan for each patient should be based on the clinical judgment of the physician and on individual risk/benefit assessment.

Patients who develop ONJ while on bisphosphonate therapy should receive appropriate antibiotic therapy and be seen by an oral surgeon. In these patients, extensive dental surgery may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Atypical Fractures of the Femur

In bisphosphonate-treated patients, atypical, low-energy, or low trauma fractures of the femoral shaft have been reported. 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 comminution.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients experience prodromal pain (presenting as dull, aching thigh pain) in the affected area weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral, therefore, the contralateral femur should be examined in zoledronic acid treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.

Evaluate any patient with a history of bisphosphonate exposure who presents with thigh or groin pain to rule out an incomplete femoral fracture. Discontinuation of bisphosphonate therapy should be considered, pending a benefit/risk assessment, on an individual basis.

Patients with Asthma

There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates. However, this effect was not observed in clinical trials of zoledronic acid.

Ophthalmic

Zoledronic acid may cause ocular disturbances (conjunctivitis, uveitis, episcleritis, scleritis, and orbital inflammation). Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. Treatment may need to be discontinued.

Effects on Ability to Drive or Use Machines

Rarely, zoledronic acid causes somnolence and/or dizziness. Patients receiving zoledronic acid should be advised to take precautions while performing activities requiring mental alertness or physical coordination. It should be carefully considered whether it is advisable to drive or operate machinery under these circumstances.

DRUG INTERACTIONS

There have been no specific drug-drug interaction studies conducted with zoledronic acid. Since zoledronic acid is approximately 22% bound to plasma proteins *in vitro* and does not inhibit microsomal CYP450 enzymes, interactions resulting from displacement of highly protein-bound drugs are unlikely. Moreover, zoledronic acid is not metabolized and is excreted into the urine as the intact drug *in vivo*.

Zoledronic acid has been administered concomitantly with the following drugs without clinically apparent interactions: Anticancer agents, diuretics, antibiotics and analgesics.

Loop Diuretics: Concomitant use may result in increased risk of hypocalcemia.

Aminoglycosides: Concomitant administration may result in possible additive effect in lowering serum calcium concentrations for prolonged periods.

Nephrotoxic Drugs (e.g., aminoglycosides, other antineoplastic agents, ASA, NSAIDs) or drugs that significantly impact renal function (e.g., diuretics, ACE inhibitors): Zoledronic acid should be used with caution since concomitant administration may result in increased risk of renal impairment.

Thalidomide: The risk of renal insufficiency may be increased when zoledronic acid is used concomitantly with thalidomide especially in patients with multiple myeloma.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: Category D

Zoledronic acid should not be used during pregnancy. Although no data exists on fetal risk in humans, bisphosphonates are incorporated into the bone matrix and is gradually released over a period of years. This may theoretically cause serious skeletal malformation when a fetus is exposed to zoledronic acid.

Lactation

It is not known whether zoledronic acid is excreted in human milk. Since many drugs are excreted in human milk and because zoledronic acid binds to bone long term, zoledronic acid should not be used by breastfeeding women.

Use in Infants and Children

The safety and efficacy of zoledronic acid in children 1 to 17 years old have not been established.

Use in the Elderly

There are no age-related differences in zoledronic acid's adverse events profile. However, since decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

Hepatic Impairment

The clinical data available for the use of zoledronic acid in patients with hepatic impairment is limited; no dosage recommendations may be given in this group.

ADVERSE EFFECTS

Zoledronic acid is generally well tolerated and adverse effects are usually mild and do not require discontinuance of the drug.

Body as a Whole: Fever and flu-like syndrome (usually at the start of treatment), fatigue, chills, rigors, malaise and flushing, progression of cancer, weakness

Cardiovascular: Hypotension (associated with syncope or circulatory collapse primarily in patients with underlying risk factors), hypertension, bradycardia, atrial fibrillation, edema of lower limb/peripheral edema, chest pain

CNS: Insomnia, sleep disorder/disturbance, somnolence, anxiety, depression, confusion, agitation, headache, dizziness, vertigo, asthenia, paresthesia, taste disturbance, hypoesthesia, hyperesthesia, tremor, hallucination

Gastrointestinal Effects: Abdominal pain, nausea, anorexia, dyspepsia, constipation, diarrhea, vomiting, stomatitis, sore throat, decreased weight, increased weight, dehydration, decreased appetite, dry mouth, thirst, peptic ulceration

Hemic and Lymphatic System: Anemia, neutropenia, granulocytopenia, thrombocytopenia, leukopenia, pancytopenia

Hypersensitivity Reactions: Rare reports of allergic reactions including angioedema; very rare cases of anaphylactic reaction/shock

Infections: Moniliasis

Injection Site Reactions: Local reactions at the infusion site (including redness or swelling, pain, irritation, induration), thrombophlebitis

Laboratory Abnormalities: Hypophosphatemia, hypomagnesemia, hyperkalemia, hypokalemia, hypernatremia, increased blood creatinine and blood urea, hypocalcemia

Musculoskeletal, Connective Tissue and Bone Disorders: Musculoskeletal pain (which may be severe and incapacitating), bone pain, myalgia, arthralgia, back pain, pain in the limb, muscle cramps, generalized pain, joint stiffness, ONJ, atypical subtrochanteric and diaphyseal femoral fractures

Ocular: Uveitis, scleritis, episcleritis, conjunctivitis, blurred vision, iritis, and orbital inflammation

Renal and Urinary Disorders: Renal impairment, acute renal failure, renal deterioration, hematuria, proteinuria, urinary tract infection

Respiratory: Dyspnea, cough, upper respiratory tract infection, bronchoconstriction

Skin and Subcutaneous Tissue Disorders: Alopecia, dermatitis, hyperhidrosis, pruritus, urticaria, rash (including erythematous and macular rash)

OVERDOSAGE AND MANAGEMENT

There is limited information on acute zoledronic acid overdosage. Overdosage would likely result in hypocalcemia, hypophosphatemia and hypomagnesemia which may be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In two patients who received zoledronic acid 32 mg over 5 minutes in clinical trials, neither experienced any clinical or laboratory toxicity.

A female patient received a single 48 mg dose of zoledronic acid in error in an open label study of zoledronic acid. The patient experienced a single episode of hyperthermia (38°C), which resolved after treatment, two days after the overdose. All other evaluations were normal, and the patient was discharged seven days after the overdose.

Carefully monitor patients who have received doses higher than those recommended since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed.

AVAILABILITY

Zoledronic Acid (Osteomet®) 4 mg/5 mL vial **-** 5 mL clear POC plastic vial with white flip-off cap (Box of 1's)

CAUTION

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

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE

Store at temperatures not exceeding 30°C.

Keep out of reach and sight of children.

Store in original packaging.

Manufactured by PharmIdea SIA
4 Rupnicu Str., Olaine, Latvia, LV-2114
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UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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*Reg. IPOPHIL