Zoletrust
Injection

DRUG INTERNATIONAL LTD.

Composition: Each vial contains Zoledronic Acid 4mg/5ml as Zoledronic Acid Monohydrate INN concentrate solution for IV infusion.

Pharmacology: **Mechanism of Action:** Zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. The principal pharmacologic action of Zoledronic Acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro, Zoledronic Acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic Acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic Acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. **Pharmacokinetics:** Pharmacokinetic data in patients with hypercalcemia are not available. Distribution: In vitro and ex vivo studies showed low affinity of Zoledronic Acid for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/mL to 5000 ng/mL. In vitro, the plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2000 ng/mL of Zoledronic Acid. **Metabolism:** Zoledronic acid does not inhibit human P450 enzymes in vitro. Zoledronic Acid does not undergo biotransformation in vivo. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi 14C- Zoledronic Acid in a patient with cancer and bone metastases, 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:** In 64 patients with cancer and bone metastases, on average (± SD) 39 ± 16% of the administered 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. The 0-24 hour renal clearance of Zoledronic Acid was 3.7 ± 2.0 L/h.

Indications: **Hypercalcemia of Malignancy:** Zoledronic Acid is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of greater than or equal to 12mg/dL [3.0mmol/L] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (4.0 g/dL -patient albumin [g/dL]). **Multiple Myeloma and Bone Metastases of Solid Tumors:** Zoledronic Acid 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. **Important Limitation of Use:** The safety and efficacy of Zoledronic Acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions have not been established.

Dosage and Administration: **Hypercalcemia of Malignancy:** The maximum recommended dose of Zoledronic Acid in hypercalcemia of malignancy (albumin-corrected serum calcium greater than or equal to 12mg/dL [3.0mmol/L]) is 4 mg. The 4mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes. Patients who receive Zoledronic Acid should have serum creatinine assessed prior to each treatment. Dose adjustments of Zoledronic Acid are not necessary in treating patients for hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine less than 400pmol/L or less than 4.5mg/dL). Retreatment with Zoledronic Acid 4mg 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 Zoledronic Acid and serum creatinine must be assessed prior to retreatment with Zoledronic Acid. **Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors:** The recommended dose of Zoledronic Acid in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance (CrCl) greater than 60mL/min is 4mg infused over no less than 15 minutes every 3 to 4 weeks. The optimal duration of therapy is not known. Patients should also be administered an oral calcium supplement of 500mg and a multiple vitamin containing 400 international units of vitamin D daily. **Patients with Renal Impairment:** The use of Zoledronic Acid is not recommended in patients with severe renal impairment (Creatinine clearance < 30ml/min).No dose adjustment is necessary in patients with Creatinine clearance 60ml/min. Based on Creatinine clearance the following dose is recoomended for the patients with impaired renal function:

Reduced Doses for Patients Mith Baseline Creatinine Clearance < 60ml/min	
Baseline Creatinine Clearance (ml/min)	**Recommended Dose of Zoledronic Acid**
> 60	3mg (5ml)
50-60	3.5mg (4.4ml)
40-49	3.3mg (4.1ml)
30-39	3mg (3.8ml)

Preparation of Solution and Method of Administration: Prior to administration, the required amount of concentrate from one vial must be further diluted with 100ml of Calcium-free solution (0.9% w/v Sodium chloride solution or 5% w/v Glucose solution). The duration of infusion must not be less than 15 minutes. After addition of the solution to the infusion media, the infusion solution should be used as soon as possible. If storage of the infusion solution is necessary, hold at 20-80C for not more than 24 hours. If refrigerated, the solution must be allowed to reach room temperature before administration. Zoledronic Acid must not be mixed with Calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution and should be administered as a single IV solution in a line separate from all other drugs. Or, as directed by the registered physicians.

Contraindications: Hypersensitivity reactions including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.

Precautions: **Hydration and Electrolyte Monitoring:** Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zoledronic Acid. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zoledronic Acid in order to avoid hypocalcemia. Adequate hydration can be achieved by the patient drinking two glasses of fluid (such as water) before and after the infusion. Serum levels of calcium, phosphate, magnesium, and potassium, as well as serum creatinine, should be carefully monitored after initiating Zoledronic Acid therapy. If hypocalcemia, hypophosphatemia, or hypomagnesemia occurs, short-term supplemental therapy may be necessary. Moreover, careful renal function monitoring should be considered. **Renal Impairment:** Zoledronic Acid is 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. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased. Preexisting renal insufficiency and multiple cycles of Zoledronic Acid and other bisphosphonates are risk factors for subsequent renal deterioration with Zoledronic Acid. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible. **Osteonecrosis of the Jaw:** Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zoledronic Acid. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. The risk of ONJ may increase with duration of exposure to bisphosphonates. **Atypical Subtrochanteric and Diaphyseal Femoral Fractures:** Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including Zoledronic Acid. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to just above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. These fractures occur after minimal or no trauma. Patients may experience thigh or groin pain weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. A number of case reports noted that patients were also receiving treatment with glucocorticoids (such as Prednisone or Dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Side Effects: The post-dose side effects are headache, nausea, anorexia, fatigue, osteonecrosis of jaw, anemia, bone pain, constipation, fever, vomiting, flu-like syndrome, hypocalcemia, hypophosphataemia, myalgia, arthralgia.

Use in Pregnancy and Lactation: Pregnancy Category D. There are no adequate and well-controlled studies of Zoledronic Acid in pregnant women. Zoledronic Acid may cause fetal harm when administered to a pregnant woman. **Nursing Mothers:** It is not known whether Zoledronic Acid is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Zoledronic Acid, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: It is not indicated for use in children. **Geriatric Use:** No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zoledronic Acid as compared to younger patients.

Drug Interactions: **Aminoglycosides and Calcitonin:** Caution is advised when bisphosphonates are administered with aminoglycosides or calcitonin, 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. **Thalidomide:** No dose adjustment for Zoledronic Acid 4 mg is needed when coadministered with thalidomide.

Overdose: Clinical experience with acute overdosage of Zoledronic Acid is limited. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. In such cases, 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.

Storage: Store below 30°C, prior to opening. After dilution, keep the solution at 2°-8°C not more than 24 hours. Do not freeze or shake. Protect from light and moisture, keep out of reach of children.

Packaging: Each box contains one vial of Zoledronic Acid INN 4mg/5ml concentrate solution for IV infusion.