Zoledronic acid is a white, crystalline powder. Its chemical formula is \( \text{C}_{17}\text{H}_{15}\text{NO}_{5}\text{P}_{2} \) and its molecular weight is 341.22. It is almost completely absorbed after IV administration and is not metabolized. Elimination occurs mainly by renal excretion, and minimal amounts are excreted in the feces. It is indicated for the treatment of hypercalcemia of malignancy and for the management of bone metastases associated with prostate cancer and breast cancer.

Zoledronic acid should be administered intravenously over a minimum of 15 minutes. It is available in a vial containing 4 mg of zoledronic acid per ml of diluent. Each mL contains: 1 mg of sodium citrate, 0.9 mg of sodium bisulfite, and 25.7 mg of mannitol.

**INDICATIONS AND USAGE**

- **Hypercalcemia of Malignancy**
  - Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy in patients who have not responded adequately to prior calcium antagonist therapy or when such therapy is not feasible.

- **Bone Metastases in Patients with Prostate Cancer**
  - Zoledronic acid is indicated for the treatment of bone metastases associated with prostate cancer.

- **Bone Metastases in Patients with Breast Cancer**
  - Zoledronic acid is indicated for the treatment of bone metastases associated with breast cancer.

**CONTRAINDICATIONS**

- Hypersensitivity to zoledronic acid or any of its excipients.
- Impaired renal function, single doses of Zometa should not exceed 4 mg and the total dose and duration of bisphosphonate use should be considered when Zometa is used with other potentially nephrotoxic drugs.

**WARNINGS AND PRECAUTIONS**

- **Bone Marrow Suppression**
- **Hypocalcemia**
- **Seizures**
- **Fetal Toxicity**

**ADVERSE REACTIONS**

- The most common adverse reactions associated with zoledronic acid include hypocalcemia, nausea, vomiting, constipation, and headache.

**DOSE AND ADMINISTRATION**

- The recommended dosage for the treatment of hypercalcemia of malignancy is 4 mg given as a single 15-minute intravenous infusion.

**CLINICAL PHARMACOLOGY**

- Zoledronic acid is a non-biologically active mimic of pyrophosphate. It is a potent non-competitive inhibitor of farnesyl diphosphate synthase, an enzyme that catalyzes the conversion of farnesyl pyrophosphate to geranylgeranyl pyrophosphate. This inhibitory action reduces the availability of these compounds, which are essential for the post-translational modification of some GTPases, including Ras, Rap1, and Rho.

- Zoledronic acid is rapidly cleared from the plasma following IV administration. The mean plasma terminal elimination half-life is approximately 1.87 hours for the early disposition phases of the drug. The terminal elimination half-life in patients with impaired renal function is approximately 10 hours.

- Zoledronic acid is not metabolized and is excreted unchanged in the urine.

**PHARMACOKINETICS**

- Zoledronic acid is eliminated almost entirely by urine, with less than 5% of the administered dose excreted in the feces. The mean area under the plasma concentration versus time curve (AUC0-24h) of zoledronic acid was dose proportional over the range of 0.5 to 10 mg given as a single 15-minute IV infusion. The mean plasma clearance of zoledronic acid was 3.7 ± 2.0 L/h.

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**CLINICAL STUDIES**

- In a placebo-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in breast cancer, a placebo-controlled study in multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma.

**EFFECTS OF RENAL IMPAIRMENT ON CLINICAL EFFICACY AND SAFETY**

- Limited pharmacokinetic data are available for patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 43%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 15%, whereas patients with severe renal impairment (N=4) showed an average increase in plasma AUC of 86% compared to patients with normal renal function.

- The formulae CL (L/h)=6.5(CLcr/90)0.4 can be used to predict the Zometa AUC in patients with renal impairment. The terminal elimination half-life increases in patients with renal impairment, but the area under the plasma concentration versus time curve (AUC0-24h) remains unchanged.

**RECOMMENDATIONS**

- Limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with impaired renal function and these data do not adequately support good clinical practice with regard to the use of Zometa in these patients.

**Pregnancy and lactation**

- Zoledronic acid is not known to be teratogenic in animals. It is not known to be teratogenic or embryotoxic in humans.

**REFERENCES**

- The information contained in this package insert should be used in conjunction with the most current Summary of Product Characteristics and the Summary of Product Characteristics should be consulted when Zometa is used with other potentially nephrotoxic drugs.

**ADDITIONAL INFORMATION**

- Limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with impaired renal function and these data do not adequately support good clinical practice with regard to the use of Zometa in these patients.

**Pregnancy and lactation**

- Zoledronic acid is not known to be teratogenic in animals. It is not known to be teratogenic or embryotoxic in humans.
Hypomagnesemia

Beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and dermatologic effects. This appears to be a bisphosphonate-class specific treatment and the symptoms subside after 24-48 hours.

Adverse reactions to Zometa® (zoledronic acid) Injection are usually mild and transient and similar in nature to those observed with other intravenous bisphosphonates. The most frequently occurring adverse events of Zometa (zoledronic acid) Injection in clinical trials are listed in Table 8. The events were generally reported as mild, transient, and self-limiting and did not significantly affect daily activities or interfere with treatment.

Table 8: Adverse Events of Zometa® (zoledronic acid) Injection

<table>
<thead>
<tr>
<th>Event</th>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (N)</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>55 (13)</td>
<td>31 (10)</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (4)</td>
<td>5 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Flushing</td>
<td>2 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rigors</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Temperature increase</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leg edema</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Metastases</td>
<td>1 (0.25)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

In male rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of offspring was decreased. The studies were performed at the non-teratogenic dose levels of zoledronic acid where no evidence of embryotoxicity or teratogenicity was observed in the high-dose group. Additional studies were performed at lower dose levels and a decrease in body weight and fetal body weight, uterine weight, and fetal dry weight was observed in the high-dose group and the control group. This decrease in body weight and fetal body weight was the only effect observed in the control group. There were no effects in the low-dose or mid-dose groups. These studies were performed in rats at a maternal dose of zoledronic acid of 0.1 mg/kg/day.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of offspring was decreased. The studies were performed at the non-teratogenic dose levels of zoledronic acid where no evidence of embryotoxicity or teratogenicity was observed in the high-dose group. Additional studies were performed at lower dose levels and a decrease in body weight and fetal body weight, uterine weight, and fetal dry weight was observed in the high-dose group and the control group. This decrease in body weight and fetal body weight was the only effect observed in the control group. There were no effects in the low-dose or mid-dose groups. These studies were performed in rats at a maternal dose of zoledronic acid of 0.1 mg/kg/day.

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