Help protect your patients with bone metastases* from skeletal complications with **THE ZOMETA EXPERIENCE**

*ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.*

Please see Important Safety Information on pages 18 and 19.

Please see accompanying full Prescribing Information.

**Daily life is precious**  
**HANDLE with ZOMETA**

*More than 8 YEARS of real-world experience*
ZOMETA is indicated for the treatment of hypercalcemia of malignancy (HCM) and patients with multiple myeloma and 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. Safe and efficacious use of ZOMETA has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.

**Important Safety Information**

- Hypersensitivity reactions, including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.
- Patients being treated with ZOMETA should not be treated with Reclast® (zoledronic acid).
- Patients treated for hypercalcemia of malignancy should be adequately rehydrated prior to administration of ZOMETA and have their electrolytes monitored during treatment.

**Skeletal-related events (SREs) that are associated with bone metastases include**

- Spinal cord compression, a result of vertebral collapse, which may lead to paralysis
- Fractures of the hip, long bones, or vertebrae that impair mobility and functioning, and often require orthopedic surgery
- Pain associated with bone metastases that may require palliative radiotherapy

SREs are serious events that, in clinical trials, may include pathologic fracture, spinal cord compression, hypercalcemia of malignancy, and the need for radiation or surgery to bone.

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**Without treatment, 1 in 2 patients with bone metastases is at risk for these potentially debilitating SREs**
Untreated bone metastases can increase frequency of serious SREs

As SREs appear with great frequency...

<table>
<thead>
<tr>
<th>Malignancy type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic breast cancer^2</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>Metastatic lung cancer^3</td>
<td>Every 4 months</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma^7</td>
<td>Every 4 months</td>
</tr>
<tr>
<td>Multiple myeloma^4</td>
<td>Every 5 months</td>
</tr>
<tr>
<td>Metastatic prostate cancer^5*</td>
<td>Every 8 months</td>
</tr>
</tbody>
</table>

*Hormone-refractory prostate cancer.

...IV bisphosphonate treatment may be critical

The National Comprehensive Cancer Network (NCCN) guidelines state that bone health and maintenance of bone integrity are important components of comprehensive cancer care^8

The threat of SREs

More than 8 years of real-world experience

ZOMETA® (zoledronic acid) Injection
With patients living longer, their likelihood of experiencing an SRE increases

- 22% to 52% of patients with bone metastases or osteolytic lesions will experience a pathologic fracture within 9 to 24 months without treatment\(^2\,^4\,^9\,^{10}\)

Now, more than ever, a dependable choice against SREs is required

Median survival has been extended well beyond median time to first SRE in clinical trials*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Median Survival</th>
<th>Median Time to First SRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>5.2*</td>
<td>12.3†</td>
</tr>
<tr>
<td>Prostate</td>
<td>10.7*</td>
<td>18.9†</td>
</tr>
<tr>
<td>Renal</td>
<td>2.4*</td>
<td>26.4*†</td>
</tr>
<tr>
<td>Breast</td>
<td>7*</td>
<td>29‡</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>9**</td>
<td>72§</td>
</tr>
</tbody>
</table>

* SRE data from placebo arms of IV bisphosphonate clinical trials. Survival data from multiple studies with different cancer treatments.
† Median survival for patients treated with paclitaxel+carboplatin+bevacizumab.
‡ Hormone-refractory prostate cancer.
§ Median survival for men with hormone-refractory metastatic prostate cancer treated with docetaxel+prednisone.
¶ Based on 381 consecutive patients diagnosed with stage IV breast cancer from 1994 to 2000 and treated at 3 French cancer centers.
# Approximate values.
In 2008, 24% to 63% of patients newly diagnosed with bone metastases in the United States did not receive IV bisphosphonate treatment**

Patients who did not receive IV bisphosphonate treatment

**As seen in claims database research.
††n=~58,905.
‡‡Hormone-refractory prostate cancer.
ZOMETA is the #1 prescribed IV bisphosphonate\textsuperscript{17}

- More than 3.5 million patients treated worldwide\textsuperscript{17*}
- Supported by safety data from more than 140 completed or active studies in a variety of oncology settings\textsuperscript{18}

*Recognized by the NCCN and American Society of Clinical Oncology (ASCO) as standard therapy across a wide range of solid tumors\textsuperscript{8,19,20} and multiple myeloma.

ZOMETA may break the devastating cycle of bone destruction by

- Inhibiting the mevalonate pathway—an important mediator of osteoclast function and survival\textsuperscript{21}
- Providing consistent protection of bone health by reducing osteoclast activity and inducing osteoclast apoptosis\textsuperscript{21}

ZOMETA may break the cycle of bone destruction\textsuperscript{21}

ZOMETA works in the bone to inhibit tumor cell adhesion to bone matrix. ZOMETA blocks bone resorption by reducing osteoclast activity. ZOMETA induces osteoclast apoptosis.

\textsuperscript{*}Calculated based on average yearly dose.
\textsuperscript{1}ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.
Only ZOMETA has a proven track record across this broad range of malignancy types

- ZOMETA is indicated in more malignancies than any other bone-targeted agent—and is the most potent commercially available bisphosphonate—*in vitro* studies show ZOMETA to be 100 to 1000 times more potent than pamidronate.\(^ {22}\)

<table>
<thead>
<tr>
<th>FDA-approved indications(^ {3,23-29})</th>
<th>ZOMETA</th>
<th>Pamidronate</th>
<th>Oral bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone metastases from breast cancer</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Bone metastases from prostate cancer(^ i)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone metastases from lung cancer</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone metastases from renal cell carcinoma</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone metastases from other solid tumors</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma(^ \S)</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia of malignancy</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>

\(^i\)ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.

\(^\S\)Pamidronate is indicated for the treatment of osteolytic lesions in multiple myeloma.
**ZOMETA may help reduce and delay SREs in more malignancies than any other bone-targeted agent**

**ZOMETA has a breadth of data across malignancies**

<table>
<thead>
<tr>
<th>Relative reduction in percentage of patients experiencing an SRE(^7,23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic hormone-refractory prostate cancer</strong>(^23)*</td>
</tr>
<tr>
<td><strong>Metastatic lung cancer and other solid tumors</strong>(^23)^†</td>
</tr>
<tr>
<td><strong>Metastatic renal cell carcinoma (subset analysis)</strong>(^7)</td>
</tr>
<tr>
<td><strong>Metastatic breast cancer and multiple myeloma</strong>(^23)</td>
</tr>
</tbody>
</table>

**Real-world health outcomes data**\(^8\) in bone metastases patients with breast, prostate, or lung cancer further support ZOMETA efficacy demonstrated in clinical trials\(^30\)

- **ZOMETA doubles the time to first skeletal complication vs no treatment in those without prior skeletal complications** (\(P<0.0001\))\(^30\)
- **Patients receiving ZOMETA had a delayed time to second skeletal complication vs no treatment** (\(P<0.05\))\(^30\)
- **As with most retrospective analyses using claims data, there were limitations to this study, such as the date of drug administration was based on the date of the claim, which may or may not have coincided with the actual date of the prescription or drug administration**

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\(*\) ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.

\(^{†}\) Patients with bone metastases from malignancies other than breast cancer and prostate cancer, including nonsmall cell lung cancer, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer/GI/genitourinary cancer, head and neck cancer, and others (\(N=773\)).

\(^{‡}\) A retrospective subset analysis of patients with RCC who were included in the metastatic lung cancer and other tumors study (\(n=74\)).

\(^{§}\) Results from a retrospective claims database analysis.
Your patients benefit every day that they maintain good skeletal health—ZOMETA may help you extend this time to first SRE

### Difference in median time to SREs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic hormone-refractory prostate cancer</td>
<td>Not reached vs 10.7 months with placebo ($P=0.01$)</td>
</tr>
<tr>
<td>Metastatic lung cancer and other solid tumors</td>
<td>7.7 vs 5.4 months with placebo ($P=0.023$)</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma (subset analysis)</td>
<td>Not reached vs 2.4 months with placebo ($P=0.006$)</td>
</tr>
<tr>
<td>Metastatic breast cancer and multiple myeloma</td>
<td>Proven comparable to pamidronate</td>
</tr>
</tbody>
</table>

*Results of a phase III Japanese study of patients with metastatic breast cancer further support ZOMETA efficacy in clinical trials (N=228)*

- ZOMETA reduced the relative risk of SREs vs placebo by 41% ($P=0.019$) in a multiple event analysis
- ZOMETA significantly reduced median time to first SRE (not reached vs 12 months with placebo; $P=0.007$)

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1. ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.
2. Patients with bone metastases from malignancies other than breast cancer and prostate cancer, including nonsmall cell lung cancer, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer/GI/genitourinary cancer, head and neck cancer, and others (N=773).
3. A retrospective subset analysis of patients with RCC who were included in the metastatic lung cancer and other tumors study (n=74).
The effect of ZOMETA may lessen after 3 to 4 weeks, which makes regular q3-q4 wk treatment a necessity for continued suppression

- The efficacy of the 4 mg q3-q4 wk schedule of ZOMETA has been demonstrated in numerous phase III trials in multiple myeloma and a variety of solid tumor types\textsuperscript{23,31,32}
- No other dosing schedule has demonstrated efficacy in this broad range of malignancies

\textbf{Change from baseline in bone resorption marker\textsuperscript{33}*}\n\textbf{(after single 4 mg dose of ZOMETA; N=12)}

*Urinary N-telopeptide (NTX)/creatinine ratio was chosen as the surrogate marker for bone resorption.

\textit{ASCO guidelines support q3-q4 wk dosing of ZOMETA\textsuperscript{19,20}}
A retrospective analysis supports the approved q3-q4 wk dosing of ZOMETA$^{30+}$

Rate of SREs for ZOMETA 4 mg q3-q4 wk vs other schedules or no treatment$^{30+}$

![Graph showing rate of SREs for ZOMETA 4 mg q3-q4 wk vs other schedules or no treatment.]

- Treatment with ZOMETA 4 mg q3-q4 wk significantly reduced the rate of skeletal morbidity (measured as number of events per month) vs no treatment$^{30}$
- Real-world health outcomes data$^4$ in patients with solid tumors (breast, lung, or prostate$^{II}$ cancer) show that discontinuing ZOMETA therapy increased the rate of skeletal complications$^{30}$
- Patients receiving ZOMETA had a delayed time to second skeletal complication compared with untreated patients ($P<0.05$)$^{30}$

**Clinical guidelines further support the use of ZOMETA therapy**

- *In breast cancer, ASCO guidelines recommend continuing to treat with ZOMETA until evidence of substantial decline in a patient’s performance status$^{19}$*
- *In multiple myeloma, ASCO guidelines recommend the use of ZOMETA$^{20}$*

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$^1$Results from a retrospective claims database analysis.

$^2$ANOVA test, $P<0.001$; post hoc test, with mean difference significant for all paired comparisons, $P<0.05$. Results may be reflective of ZOMETA prescribing patterns and solid tumor cancer type. Sample size did not allow quantification of direct outcomes based on specific solid tumor cancer type. Results are based on 6-month data.

$^3$Results from a retrospective claims database analysis.

$^4$ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.
Almost all patients with metastatic cancer receive q3-q4 wk chemotherapy regimens*

- 85% of patients with advanced hormone-refractory prostate cancer
- 91% of patients with advanced breast cancer
- 93% of patients with multiple myeloma
- 95% of patients with advanced lung cancer

ZOMETA can be infused in as little as 15 minutes, making it convenient to administer along with chemotherapy.

*According to additional claims database research, the majority of patients with advanced cancer are treated with a q3-q4 wk regimen.
†ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.
With more than 8 years of experience, ZOMETA offers a well-understood and predictable safety profile

ZOMETA safety data are based on real-world and clinical experience

- ZOMETA safety has been demonstrated in more than 140 completed or active studies—more than any other bone-targeted agent—in a variety of oncology settings.

ZOMETA has a well-established renal safety profile

- Renal toxicity may be managed by monitoring serum creatinine levels throughout therapy with ZOMETA.
- In multiple clinical trials, the renal safety profile of ZOMETA has been shown to be comparable with pamidronate.

Grade 3/4 abnormalities in serum creatinine

- Grade 3 defined as >3x upper limit of normal (ULN); grade 4 defined as >6x ULN.
### Starting dose of ZOMETA by baseline creatinine clearance

<table>
<thead>
<tr>
<th>Baseline creatinine clearance (mL/min)</th>
<th>ZOMETA dose</th>
<th>Volume to withdraw*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>4.0 mg</td>
<td>5.0 mL</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5 mg</td>
<td>4.4 mL</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3 mg</td>
<td>4.1 mL</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0 mg</td>
<td>3.8 mL</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

*The recommended volume of ZOMETA concentrate that should be withdrawn from the vial for each dose. Doses calculated assuming target AUC of 0.66 (mg×hr/L) (creatinine clearance=75 mL/min).

- Reducing the starting dose for patients with impaired renal function at baseline may reduce the risk of renal toxicity
  - Continue to treat with the reduced dose for the duration of therapy

### Therapy with ZOMETA should be temporarily interrupted if a patient experiences serum creatinine increases as described below

- For patients with normal baseline serum creatinine (<1.4 mg/dL)
  - Withhold ZOMETA if serum creatinine increases by ≥0.5 mg/dL

- For patients with abnormal baseline serum creatinine (≥1.4 mg/dL)
  - Withhold ZOMETA if serum creatinine increases by ≥1.0 mg/dL

### Resume the same dose when serum creatinine returns to within 10% of baseline value
Osteonecrosis of the jaw (ONJ) is uncommon, may be prevented, and can be managed

- <1% of patients receiving ZOMETA have been reported to experience ONJ in a retrospective review17
- There have been uncommon reports of ONJ in advanced cancer patients receiving complex treatment regimens, including chemotherapy, corticosteroids, and bisphosphonates, including ZOMETA23
- Currently, the causes of ONJ are not well understood, but with appropriate measures, ONJ may be prevented and/or managed23

ONJ may be prevented

- Dental examination with appropriate preventive dentistry should be performed prior to treatment with ZOMETA34
- Routine dental exams, including prophylaxis, should be continued throughout treatment with ZOMETA34
- Invasive dental procedures should be avoided during ZOMETA therapy
  - Dental surgery may exacerbate ONJ34

ONJ can be managed if it occurs

- Steps can be taken for conservative management of ONJ, including34
  - Antibiotics
  - Oral rinses
  - Pain control
  - Limited debridement
  - Quarterly clinical follow-up
For your practice

- The ZOMETA Hotline (1-866-4-ZOMETA), which offers help with insurance verification, denials, appeals, and other reimbursement issues
  — Please visit www.us.zometa.com/hcp

- InterventionZ provides a wide array of programs to help nurses improve therapeutic outcomes for patients with metastatic bone disease
  — Please visit www.interventionz.com

For your patients

- ZOMETACares—available at no additional charge—provides your patients with
  — Resources and support
  — Phone calls to remind them of their next infusion

- The Compass patient support web program
  — Gives patients and caregivers the opportunity to learn more about bone metastases and ZOMETA through online communications
  — Please visit www.us.zometa.com
ZOMETA claims reimbursed rapidly in 2009\textsuperscript{17}*

*Includes claims that were received by payer between 1/1/09 and 9/30/09. Results limited to claims submitted to primary payers.
Indication
ZOMETA is indicated for the treatment of hypercalcemia of malignancy (HCM) and patients with multiple myeloma and 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. Safe and efficacious use of ZOMETA has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.

Safety Information
ZOMETA is contraindicated in patients with hypersensitivity to zoledronic acid or any components of ZOMETA. Hypersensitivity reactions, including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock, have been reported. Patients being treated with ZOMETA should not be treated with Reclast® (zoledronic acid) as they contain the same active ingredient.

Patients with HCM must be adequately rehydrated prior to use of ZOMETA and loop diuretics (if applicable). Loop diuretics should be used with caution in combination with ZOMETA to avoid hypocalcemia. ZOMETA should be used with caution with other nephrotoxic drugs. Carefully monitor serum calcium, phosphate, magnesium, and serum creatinine following initiation of ZOMETA. Short-term supplemental therapy may be necessary.

In patients with impaired renal function, the risk of adverse reactions (especially renal adverse reactions) may be greater. Consider individual patient risk/benefit profile before starting ZOMETA therapy in HCM patients with severe renal impairment. ZOMETA treatment is not recommended in patients with bone metastases with severe renal impairment. Preexisting renal insufficiency and multiple cycles of ZOMETA and other bisphosphonates are risk factors for subsequent renal deterioration with ZOMETA. Do not use doses greater than 4 mg. ZOMETA should be administered by IV infusion over no less than 15 minutes. Monitor serum creatinine before each dose.

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including ZOMETA. Many of these patients were also receiving chemotherapy and corticosteroids, which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma) and dental status (dental extraction, periodontal disease, local trauma, including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection, including osteomyelitis. 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, as recovery may be prolonged. 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. A causal relationship between bisphosphonate use and ONJ has not been established. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

ZOMETA should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant. If the patient becomes pregnant or plans to breast-feed while taking this drug, the patient should be apprised of the potential harm to the fetus or baby.

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates including ZOMETA. Discontinue use if severe symptoms develop, and a subset of patients had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. There have been reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates. Insufficient data exist on how to safely use ZOMETA in HCM patients with hepatic impairment.

Acute-phase reaction symptoms can occur in HCM patients, with fever most commonly reported (44% with ZOMETA vs. 33% with pamidronate). Patients may occasionally experience flu-like syndrome (fever, chills, flushing, bone pain and/or arthralgias and myalgias). The most common adverse events (≥10%) in HCM clinical trials, regardless of causality, with ZOMETA 4 mg (n=86) were as follows: fever (44%), nausea (29%), constipation (27%), anemia (22%), dyspnea (22%), diarrhea (17%), abdominal pain (16%), progression of cancer (16%), insomnia (15%), vomiting (14%), anxiety
• Please see full Prescribing Information.


Fosamax Prescribing Information. Merck & Co.


American Society of Clinical Oncology 2003 clinical practice guideline update on the role of bisphosphonates in multiple myeloma.血


Please see Important Safety Information on pages 18 and 19. Please see accompanying full Prescribing Information.
ZOMETA is indicated for the treatment of hypercalcemia of malignancy (HCM) and patients with multiple myeloma and 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. Safe and efficacious use of ZOMETA has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.

Important Safety Information

• Hypersensitivity reactions, including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.
• Patients being treated with ZOMETA should not be treated with Reclast® (zoledronic acid).
• Patients treated for hypercalcemia of malignancy should be adequately rehydrated prior to administration of ZOMETA and have their electrolytes monitored during treatment.
• There have been reports of renal toxicity with ZOMETA. Renal toxicity may be greater in patients with renal impairment. Treatment in patients with severe renal impairment is not recommended. Do not use doses greater than 4 mg and monitor serum creatinine before each dose.
• Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting ZOMETA and invasive dental procedures should be avoided.
• Because ZOMETA can cause fetal harm, women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
• Severe and occasionally incapacitating bone, joint, and/or muscle pain may occur. Discontinue ZOMETA if severe symptoms occur.
• Please see full Important Safety Information on pages 18 and 19.

The ZOMETA experience helps provide...

Help protect your patients with bone metastases∗ from skeletal complications with the ZOMETA experience helps provide...

Extensive experience A favorable risk-benefit profile for more than 8 years17
Proven efficacy Protection from SREs in more solid tumors* and multiple myeloma than any other bone-targeted agent23-29
Effective dosing A dosing regimen to help maintain skeletal health
Established tolerability A well-understood and predictable safety profile
Reliable reimbursement Convenient, dependable, and rapid reimbursement support
Supportive experience Flavored 4 mg oral solution for more than one year

∗ ZOMETA should be used in prostate patients with bone metastases that have progressed after treatment with at least one hormonal therapy.
ZOMETA is indicated for the treatment of hypercalcemia of malignancy (HCM) and patients with multiple myeloma and 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. Safe and efficacious use of ZOMETA has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.

Important Safety Information

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

• Patients being treated with ZOMETA should not be treated with Reclast® (zoledronic acid)

• Patients treated for hypercalcemia of malignancy should be adequately rehydrated prior to administration of ZOMETA and have their electrolytes monitored during treatment

• There have been reports of renal toxicity with ZOMETA. Renal toxicity may be greater in patients with renal impairment. Treatment in patients with severe renal impairment is not recommended. Do not use doses greater than 4 mg and monitor serum creatinine before each dose

• Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting ZOMETA and invasive dental procedures should be avoided

• Because ZOMETA can cause fetal harm, women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant

• Severe and occasionally incapacitating bone, joint, and/or muscle pain may occur. Discontinue ZOMETA if severe symptoms occur

Please see important safety information on pages 18 and 19. Please see accompanying full prescribing information.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Zometa safely and effectively. See full prescribing information for Zometa.

ZOMETA® (zoledronic acid) Injection
Concentrate for Intravenous Infusion

Initial U.S. Approval: 2001

INDICATIONS AND USAGE
Zometa is a bisphosphonate indicated for the treatment of:
• Hypercalcemia of malignancy (1.1)
• 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 (1.2)

Important limitation of use: The safety and efficacy of Zometa has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia (1.3)

DOSE AND ADMINISTRATION
Hypercalcemia of malignancy (2.1)
• 4 mg as a single-dose intravenous infusion over no less than 15 minutes
• 4 mg as retreatment after a minimum of 7 days
Multiple myeloma and bone metastasis from solid tumors (2.2)
• 4 mg as a single-dose intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of >60 mL/min
• Reduce the dose for patients with renal impairment
• Concomitantly administer oral calcium supplements of 500 mg and a multiple vitamin containing 400 IU of vitamin D daily.

Administer through a separate vented infusion line and do not allow to come in contact with any calcium or divalent cation-containing solutions (2.3)

Dosage Forms and Strengths
4 mg/5 mL single dose vials (3)

CONTRAINDICATIONS
Hypersensitivity to any component of Zometa (4)

WARNINGS AND PRECAUTIONS
• Patients being treated with Zometa should not be treated with Reclast® (5.1)

• Adequately rehydrate patients with hypercalcemia of malignancy prior to administration of Zometa and monitor electrolytes during treatment (5.2)
• Renal toxicity may be greater in patients with renal impairment. Do not use doses greater than 4 mg. Treatment in patients with severe renal impairment is not recommended. Monitor serum creatinine before each dose (5.3)
• Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting Zometa. Avoid invasive dental procedures (5.4)
• Zometa can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant (5.5, 8.1)
• Severe incapacitating bone, joint, muscle pain may occur. Discontinue Zometa if severe symptoms occur (5.6)

ADVERSE REACTIONS
The most common adverse events (>25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
• Aminoglycosides: May have an additive effect to lower serum calcium for prolonged periods (7.1)
• Loop diuretics: Concomitant use with Zometa may increase risk of hypocalcemia (7.2)
• Nephrotoxic drugs: Use with caution (7.3)
• Thalidomide: Combination use in patients with multiple myeloma may increase the risk of renal dysfunction (7.4)

USE IN SPECIFIC POPULATIONS
• Nursing Mothers: Zometa should not be given to nursing women (8.2)
• Pediatric Use: Not indicated for use in pediatric patients (8.4)
• Geriatric Use: Special care to monitor renal function (8.5)

See 17 for PATIENT COUNSELING INFORMATION

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Revised: 10/2009
1 INDICATIONS AND USAGE
1.1 Hypercalcemia of Malignancy
Zometa is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected serum calcium (Ca) of >12 mg/dL [3.0 mmol/L] using the formula: Ca in mg/dL = Ca in mg/dL + 0.8 (mid-range of measured albumin in mg/dL).

1.2 Multiple Myeloma and Bone Metastases of Solid Tumors
Zometa 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.

1.3 Important Limitation of Use
The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Hypercalcemia of Malignancy
The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium ≥12 mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes. Patients who receive Zometa should have serum creatinine assessed prior to each treatment.

Dose adjustments of Zometa are not necessary in treating patients for hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <400 µmol/L or <4.5 mg/dL).

Patients should be adequately rehydrated prior to administration of Zometa [see Warnings And Precautions (5.2)].

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa. 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, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia.

Retreatment with Zometa 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 Zometa and serum creatinine must be assessed prior to retreatment with Zometa [see Warnings And Precautions (5.2)].

2.2. Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors
The recommended dose of Zometa 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 Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are listed in Table 1. 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 [see Warnings And Precautions (5.2)].

Table 1. Reduced Doses for Patients with Baseline CrCl <60 mL/min

<table>
<thead>
<tr>
<th>Baseline Creatinine Clearance (mL/min)</th>
<th>Zometa Recommended Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;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>
</tbody>
</table>

*Doses calculated assuming target AUC of 0.56/(mg·hr/L) (CrCl = 75 mL/min)

During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was 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.

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be reintiated 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.

2.3. Preparation of Solution
4 mg Dose
Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

Preparing Reduced Doses for Patients with Baseline CrCl <60 mL/min
Withdraw the appropriate volume of the Zometa concentrate from the vial for the dose required (see Table 2).

Table 2. Preparation of Reduced Doses

<table>
<thead>
<tr>
<th>Zometa Volume (mL)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>3.5</td>
</tr>
<tr>
<td>4.1</td>
<td>3.3</td>
</tr>
<tr>
<td>3.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP.

For All Prepared Doses
If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C-8°C (36°F-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

Zometa 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 intravenous solution in a line separate from all other drugs.

2.4. Method of Administration
Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa should not exceed 4 mg and the duration of infusion should be no less than 15 minutes [see Warnings And Precautions (5.2)]. In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.

3 DOSAGE FORMS AND STRENGTHS
4 mg/5 mL single-dose vial

4 CONTRAINDICATIONS
4.1 Hypersensitivity to Zoledronic Acid or Any Components of Zometa
Hypersensitivity reactions including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS
5.1 Drugs with Same Active Ingredient
Zometa contains the same active ingredient as found in Reclast® (zoledronic acid). Patients being treated with Zometa should not be treated with Reclast.

5.2 Hydration and Electrolyte Monitoring
Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia. Zometa 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 Zometa. If hypocalcemia, hypophosphatemia, or hypegmagnesemia occur, short-term supplemental therapy may be necessary.

5.3 Renal Impairment
Zometa 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 [ see Adverse Reactions (6.1)]. Preexisting renal insufficiency and multiple cycles of Zometa and other bisphosphonates are risk factors for subsequent renal deterioration with Zometa. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zometa treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine >400 µmol/L or >4.5 mg/dL were excluded.

Zometa treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine >265 µmol/L or >3.0 mg/dL were excluded and there were only 8 of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline creatinine >2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance <30 mL/min [see Clinical Pharmacology (12.3)].
5.4 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection including osteomyelitis.

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 [see Adverse Reactions (6.2)].

5.5 Pregnancy
ZOMETA SHOULD NOT BE USED DURING PREGNANCY. Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an IV dose of 4 mg based on an AUC comparison) resulted in pre- and postimplantation losses, decreases in viable fetuses and fetal skeletal, visceral, and external malformations. 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 [see Use In Specific Populations (8.1)].

5.6 Musculoskeletal Pain
In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes Zometa. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate [see Adverse Reactions (6.2)].

5.7 Patients with Asthma
While not observed in clinical trials with Zometa, there have been reports of bronchospastic constriction in aspirin sensitive patients receiving bisphosphonates.

5.8 Hepatic Impairment
Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypercalcemia of Malignancy
The safety of Zometa was studied in 185 patients with hypercalcemia of malignancy (HCM) who received either Zometa 4 mg given as a 5-minute intravenous infusion (n=86) or pamidronate 90 mg given as a 2-hour intravenous infusion (n=103). The population was aged 33-84 years, 60% male and 81% Caucasian, with breast, lung, and head and neck, and renal cancer as the most common forms of malignancy. NOTE: pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Renal Toxicity
Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to 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 Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes [see Warnings And Precautions (5) and Dosage And Administration (2)].

The most frequently observed adverse events were fever, nausea, constipation, anemia, and dyspnea (see Table 3).

Table 3 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or Pamidronate 90 mg from the two HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 3. Percentage of Patients with Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials by Body System

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Zometa 4 mg n (%)</th>
<th>Pamidronate 90 mg n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine1</td>
<td>2/86 (2%)</td>
<td>3/100 (3%)</td>
</tr>
<tr>
<td>Hypocalcemia2</td>
<td>1/86 (1%)</td>
<td>2/100 (2%)</td>
</tr>
<tr>
<td>Hypophosphatemia3</td>
<td>36/70 (51%)</td>
<td>27/81 (33%)</td>
</tr>
<tr>
<td>Hypomagnesemia4</td>
<td>0/71</td>
<td>0/84</td>
</tr>
</tbody>
</table>

The following adverse events from the two controlled multicenter HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug: Asthenia, chest pain, leg edema, mucositis, dysphagia, granulocytopenia, thrombocytopenia, pancytopenia, nonspecific infection, hypercalcemia, dehydration, arthralgia, headache and somnolence. Rare cases of rash, pruritus, and chest pain have been reported following treatment with Zometa.

Acute Phase Reaction-like Events
Symptoms consistent with acute phase reaction (APR) can occur with intravenous bisphosphonate use. Fever has been the most commonly associated symptom, occurring in 44% of patients treated with Zometa 4 mg and 35% of patients treated with Pamidronate 90 mg. Occasionally, patients experience 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.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 4 and 5.

Table 4. Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine1</td>
<td>2/86 (2%)</td>
<td>3/100 (3%)</td>
</tr>
<tr>
<td>Hypocalcemia2</td>
<td>1/86 (1%)</td>
<td>2/100 (2%)</td>
</tr>
<tr>
<td>Hypophosphatemia3</td>
<td>36/70 (51%)</td>
<td>27/81 (33%)</td>
</tr>
<tr>
<td>Hypomagnesemia4</td>
<td>0/71</td>
<td>0/84</td>
</tr>
</tbody>
</table>

Grade 3

6.2 Adverse Reactions

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine1</td>
<td>2/86 (2%)</td>
<td>3/100 (3%)</td>
</tr>
<tr>
<td>Hypocalcemia2</td>
<td>1/86 (1%)</td>
<td>2/100 (2%)</td>
</tr>
<tr>
<td>Hypophosphatemia3</td>
<td>36/70 (51%)</td>
<td>27/81 (33%)</td>
</tr>
<tr>
<td>Hypomagnesemia4</td>
<td>0/71</td>
<td>0/84</td>
</tr>
</tbody>
</table>
Table 5. Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine1</td>
<td>0/86</td>
<td>1/100</td>
</tr>
<tr>
<td>Hypocalcemia2</td>
<td>0/86</td>
<td>0/100</td>
</tr>
<tr>
<td>Hypophosphatemia3</td>
<td>1/70</td>
<td>4/81</td>
</tr>
<tr>
<td>Hypomagnesemia4</td>
<td>0/71</td>
<td>1/84</td>
</tr>
</tbody>
</table>

1Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
2Grade 3 (<7 mg/dL); Grade 4 (<8 mg/dL)
3Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
4Grade 3 (<0.8 mEq/L); Grade 4 (<0.5 mEq/L)

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 Zometa. No cases of iritis, scleritis or uveitis were reported during these clinical trials. However, cases have been seen in postmarketing use [see Adverse Reactions (6.2)].

Multiple Myeloma and Bone Metastases of Solid Tumors
The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2,042 patients treated with Zometa 4 mg, pamidronate 90 mg, or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients in these clinical trials. However, cases have been seen in postmarketing use [see Adverse Reactions (6.2)].

Table 6. Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Studied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of Patients</td>
<td>1031 (100)</td>
<td>556 (100)</td>
<td>455 (100)</td>
</tr>
<tr>
<td>Total No. of Patients with any AE</td>
<td>1015 (98)</td>
<td>548 (99)</td>
<td>445 (98)</td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>344 (33)</td>
<td>175 (32)</td>
<td>128 (28)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>124 (12)</td>
<td>83 (15)</td>
<td>35 (8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>102 (10)</td>
<td>53 (10)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>476 (46)</td>
<td>266 (48)</td>
<td>171 (38)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>333 (32)</td>
<td>183 (33)</td>
<td>122 (27)</td>
</tr>
<tr>
<td>Constipation</td>
<td>320 (31)</td>
<td>162 (29)</td>
<td>174 (38)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>249 (24)</td>
<td>162 (29)</td>
<td>83 (18)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>143 (14)</td>
<td>81 (15)</td>
<td>48 (11)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>105 (10)</td>
<td>74 (13)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>86 (8)</td>
<td>65 (12)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>82 (8)</td>
<td>61 (11)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>General Disorders and Administration Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>398 (39)</td>
<td>240 (43)</td>
<td>130 (29)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>328 (32)</td>
<td>172 (31)</td>
<td>89 (20)</td>
</tr>
<tr>
<td>Weakness</td>
<td>252 (24)</td>
<td>108 (19)</td>
<td>114 (25)</td>
</tr>
<tr>
<td>Edema Lower Limb</td>
<td>215 (21)</td>
<td>126 (23)</td>
<td>84 (19)</td>
</tr>
<tr>
<td>Rigors</td>
<td>112 (11)</td>
<td>62 (11)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>124 (12)</td>
<td>50 (9)</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>101 (10)</td>
<td>82 (15)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>231 (22)</td>
<td>81 (15)</td>
<td>105 (23)</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>164 (16)</td>
<td>50 (9)</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>145 (14)</td>
<td>60 (11)</td>
<td>59 (13)</td>
</tr>
<tr>
<td>Appetite Decreased</td>
<td>130 (13)</td>
<td>48 (9)</td>
<td>45 (10)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Pain</td>
<td>569 (55)</td>
<td>316 (57)</td>
<td>284 (62)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>239 (23)</td>
<td>143 (26)</td>
<td>74 (16)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>216 (21)</td>
<td>131 (24)</td>
<td>73 (16)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>156 (15)</td>
<td>106 (19)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>Pain in Limb</td>
<td>143 (14)</td>
<td>84 (15)</td>
<td>52 (11)</td>
</tr>
</tbody>
</table>

(continued)
following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials (see Table 9).

Table 9. Percentage of Patients with Treatment Emergent Renal Function Deterioration by Baseline Serum Creatinine

<table>
<thead>
<tr>
<th>Patient Population/Baseline Creatinine</th>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>27/246 (11%)</td>
<td>23/246 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>29/272 (11%)</td>
<td>25/268 (9%)</td>
</tr>
</tbody>
</table>

- *Solid Tumors Zometa 4 mg Placebo n/N (%) n/N (%)*

| Normal                                 | 17/154 (11%)| 10/143 (7%)      |
| Abnormal                               | 1/11 (9%)   | 1/20 (5%)        |
| Total                                  | 18/165 (11%)| 11/163 (7%)      |

- *Prostate Cancer Zometa 4 mg Placebo n/N (%) n/N (%)*

| Normal                                 | 12/62 (15%)| 8/68 (12%)       |
| Abnormal                               | 4/10 (40%) | 2/10 (20%)       |
| Total                                  | 16/92 (17%)| 10/78 (13%)      |

*Table includes only patients who were randomized to the trial after a protocol amendment that lengthened the infusion duration of Zometa to 15 minutes.

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.

6.2 Postmarketing Experience
The following adverse reactions have been reported during postapproval use of Zometa. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Osteonecrosis of the Jaw
Cases of osteonecrosis (primarily involving the jaws) have been reported predominantly in cancer patients treated with intravenous bisphosphonates including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be a risk factor for ONJ. Data suggests a greater frequency of reports of ONJ in certain cancers, such as advanced breast cancer and multiple myeloma. The majority of the reported cases are in cancer patients following invasive dental procedures, such as tooth extraction. It is therefore prudent to avoid invasive dental procedures as recovery may be prolonged [see Warnings And Precautions (5)].

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with bisphosphonate use [see Warnings And Precautions (5)].

Ocular Adverse Events
Cases of uveitis, scleritis, episcleritis, conjunctivitis, iritis, and orbital inflammation including orbital edema have been reported during postmarketing use. In some cases, symptoms resolved with topical steroids.

Hypersensitivity Reactions
There have been rare reports of allergic reaction with intravenous zoledronic acid including angioedema, and bronchoconstriction. Very rare cases of anaphylactic reaction/shock have also been reported.

Additional adverse reactions reported in postmarketing use include:
- **CNS:** taste disturbance, hyperesthesia, tremor; **Special Senses:** blurred vision.
- **Gastrointestinal:** dry mouth; **Skin:** increased sweating.
- **Musculoskeletal:** muscle cramps; **Cardiovascular:** hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse primarily in patients with underlying risk factors); **Respiratory:** bronchoconstriction; **Renal:** hematuria, proteinuria; **General Disorders and Administration Site:** weight increase; **Laboratory Abnormalities:** hyperkalemia, hyperuricemia.

7 DRUG INTERACTIONS

*In-vivo* studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. *In-vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In-vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug. However, no *in-vivo* drug interaction studies have been performed.

7.1 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. This effect has not been reported in Zometa clinical trials.

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

7.3 Nephrotoxic Drugs
Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

7.4 Thalidomide
In multiple myeloma patients, the risk of renal dysfunction may be increased when Zometa is used in combination with thalidomide.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
ZOMETA SHOULD NOT BE USED DURING PREGNANCY. There are no studies in pregnant women using Zometa. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant [see Warnings And Precautions (5)].

Pregnancy Category D
Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

In female 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 stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥0.07 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and parturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate-class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and postimplantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≥0.5 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (with systemic exposure of 0.1 times the human systemic exposure following an intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

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

8.4 Pediatric Use
Zometa is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a one-year active-controlled trial of 152 pediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine BMD of 0.431 g/cm², which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At one year, increases in BMD were observed in the zoledronic acid treatment group. However, changes in BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with Zometa use in children did not raise any new safety findings beyond those previously seen in adults treated for hypercalcemia of malignancy or bone metastases.
However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypercalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within 3 days after the first infusion and became less common with repeat dosing. Because of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteonecrosis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 min. Mean Cmax and AUC(0-24h) was 167 ng/mL and 220 ng·h/mL, respectively. The plasma concentration time profile of zoledronic acid in pediatric patients represent a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

8.5 Geriatric Use
Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

10 OVERDOSAGE
Clinical experience with acute overdose of Zometa is limited. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdose may cause clinically significant hypercalcemia, hypophosphatemia, and hypomagnesemia. 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, respectively.

In an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose, the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin’s lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 1000 IU/L, each value unknown). The outcome of this case is not known.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy [see Dosage And Administration (2.4)].

11 DESCRIPTION
Zometa contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl)phosphonic acid monohydrate and its structural formula is

Zoledronic acid is a white crystalline powder. Its molecular formula is C12H17N5O7P2 and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1% hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 5-mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: mannitol, USP, as bulking agent, water for injection and sodium citrate, USP, as buffering agent.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. At the cellular level, 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.

12.2 Pharmacodynamics
Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion. Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiological derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. 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, in turn, results in increasing renal calcium excretion and a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiological mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated independently and not by normal stimuli such as parathyroid hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous cell malignancies of the lung or head and neck or in genitourinary tumors such as renal cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypohumulinemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available. Therefore, many clinical situations of hypercalcemia require use of the calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation [see Dosage And Administration (2)].

12.3 Pharmacokinetics
Pharmacokinetic data in patients with hypercalcemia are not available.

Distribution
Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa were given to 64 patients with cancer and bone metastases. The postinfusion 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% of Cmax 24 hours postinfusion with population half-lives of 0.24 hours and 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 of 146 hours. The area under the plasma concentration versus time curve (AUC(0-24h)) of zoledronic acid was dose proportional from 2-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC0-3th ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In-vivo and ex-vivo studies showed low affinity of zoledronic acid for the cellular components of human blood. In-vitro, mean zoledronic acid protein binding in human plasma ranged from 28% to 200 ng/mL to 53% at 50 ng/mL.

Metabolism
Zoledronic acid does not inhibit human P450 enzymes in vitro. Zoledronic acid does not undergo biotransformation in vivo. In animal studies, <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 ng 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 (± s.d.) 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 trapped in 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. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of infusion and a 31% increase in the total AUC (378 ± 116 ng·h/mL versus 264 ± 86 ng·h/mL) and a 10% increase in the total AUC (378 ± 116 ng·h/mL versus 420 ± 218 ng·h/mL). The difference between the AUC means was not statistically significant.

Special Populations
Pediatrics
Zometa is not indicated for use in children [see Pediatric Use (8.4)].

Geriatrics
The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.
Race
Population pharmacokinetic analyses did not indicate any differences in pharmacokinetics among Japanese and North American (Caucasian and African American) patients with cancer and bone metastases.

Hepatic Insufficiency
No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency
The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa 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. Creatinine clearance is calculated by the Cockcroft-Gault formula:

\[
CrCl = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}
\]

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=6.5(6.5)(0.78). These formulae can be used to predict the Zometa AUC in patients, where CL = Dose/AUC. The average AUC in patients with normal renal function was 0.42 mg•h/L, and the calculated AUC in patients with creatinine clearance of 75 mL/min was 0.66 mg•h/L following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed (see Warnings And Precautions (5.2)).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.02 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

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

Impairment of Fertility
Female rats were 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. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≥0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

14 CLINICAL STUDIES
14.1 Hypercalcemia of Malignancy
Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). Note: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to 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 Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes (see Warnings And Precautions (5.1, 5.2) and Dosage And Administration (2.4)).

The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were Black, and 4% were of other races. 60% of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of ≥12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to <10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion. To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a preplanned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (P=0.002) (see Figure 1). In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.

Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of serum calcium (CSC) by Day 4; the proportion of patients who had normalization of serum calcium by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value <11.6 mg/dL (<2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 10.

Table 10. Secondary Efficacy Variables in Pooled HCM Studies

<table>
<thead>
<tr>
<th>Zometa 4 mg</th>
<th>Pamidronate 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>N</td>
</tr>
<tr>
<td>By Day 4</td>
<td>86</td>
</tr>
<tr>
<td>By Day 7</td>
<td>86</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>N</td>
</tr>
<tr>
<td>Time to Relapse</td>
<td>86</td>
</tr>
<tr>
<td>Duration of Complete Response</td>
<td>76</td>
</tr>
</tbody>
</table>

*less than 0.05 versus pamidronate 90 mg.

14.2 Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors
Table 11 describes an overview of the efficacy population in three randomized Zometa trials in patients with 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 prostate cancer, and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, including NSCLC, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, GI/gynecotinal cancer, head and neck cancer, and others. These trials were comprised of a core phase and an extension phase. In the solid tumor, breast cancer and multiple myeloma trials, only the core phase was evaluated for efficacy as a high percentage of patients did not choose to participate in the extension phase. In the prostate cancer trials, both the core and extension phases were evaluated for efficacy showing the Zometa effect during the first 15 months was maintained without decrement or improvement for another 9 months. The design of these clinical trials does not permit assessment of whether more than one-year administration of Zometa is beneficial. The optimal duration of Zometa administration is not known.

The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8 mg Zometa treatment arm were switched to 4 mg due to toxicity. Patients who were randomized to the Zometa 8 mg group are not included in these analyses.

Table 11. Overview of Efficacy Population for Phase III Studies

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>No. of Patients</th>
<th>Zometa Dose</th>
<th>Control</th>
<th>Median Duration (Planned Duration) Zometa 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma or metastatic breast cancer</td>
<td>1,548</td>
<td>4 and 8* mg</td>
<td>Pamidronate 90 mg</td>
<td>12.0 months (13 months)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Q3-4 weeks</td>
<td>Q3-4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic prostate cancer</td>
<td>643</td>
<td>4 and 8* mg</td>
<td>Placebo</td>
<td>10.5 months (15 months)</td>
</tr>
<tr>
<td>Metastatic solid tumor other than breast or prostate cancer</td>
<td>773</td>
<td>4 and 8* mg</td>
<td>Placebo</td>
<td>3.8 months (9 months)</td>
</tr>
</tbody>
</table>

*Patients who were randomized to the 8 mg Zometa group are not included in any of the analyses in this package insert.
Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study and time to the first SRE. Results for the two Zometa placebo-controlled studies are given in Table 12.

<table>
<thead>
<tr>
<th>Study</th>
<th>Analysis of Proportion of Patients with a SRE</th>
<th>Analysis of Time to the First SRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Subject &amp; Patient Number</td>
<td>Proportion &amp; 95% CI</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Zometa 4 mg (n=214)</td>
<td>33% (-11%, 0%)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=208)</td>
<td>44%</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>Zometa 4 mg (n=257)</td>
<td>38% (-7%, 2%)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=250)</td>
<td>44%</td>
</tr>
</tbody>
</table>

1 SRE = Skeletal-Related Event
2 Difference for the proportion of patients with a SRE of Zometa 4 mg versus placebo.
3 Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus placebo.

In the breast cancer and myeloma trial, efficacy was determined by a noninferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1,128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI = 7.3%, 18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 13.

<table>
<thead>
<tr>
<th>Study</th>
<th>Analysis of Proportion of Patients with a SRE</th>
<th>Analysis of Time to the First SRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Subject &amp; Patient Number</td>
<td>Proportion &amp; 95% CI</td>
</tr>
<tr>
<td>Multiple Myeloma &amp; Breast Cancer</td>
<td>Zometa 4 mg (n=561)</td>
<td>44% (-7.9%, 3.7%)</td>
</tr>
<tr>
<td></td>
<td>Pamidronate (n=555)</td>
<td>46%</td>
</tr>
</tbody>
</table>

1 SRE = Skeletal-Related Event
2 Difference for the proportion of patients with a SRE of Zometa 4 mg versus pamidronate 90 mg.
3 Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus pamidronate 90 mg.

16 HOW SUPPLIED/STORAGE AND HANDLING
Each 5 mL vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection, and 24 mg of sodium citrate, USP.
Carton of 1 vial..........................................................NDC 0078-0387-25
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION
- Patients should be instructed to tell their doctor if they have kidney problems before being given Zometa.
- Patients should be informed of the importance of getting their blood tests (serum creatinine) during the course of their Zometa therapy.
- Zometa should not be given if the patient is pregnant or plans to become pregnant, or if she is breast-feeding.
- Patients should be advised to have a dental examination prior to treatment with Zometa and should avoid invasive dental procedures during treatment.
- Patients should be informed of the importance of good dental hygiene and routine dental care.
- Patients with multiple myeloma and bone metastasis of solid tumors should be advised to take an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.
- Patients should be aware of the most common side effects including; anemia, nausea, vomiting, constipation, diarrhea, fatigue, pyrexia, weakness, lower limb edema, anorexia, decreased weight, bone pain, myalgia, arthralgia, back pain, malignant neoplasm aggravated, headache, dizziness, insomnia, paresthesia, dyspnea, cough, and abdominal pain.

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