CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-080

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Reclast safely and effectively. See full prescribing information for Reclast.

Reclast ® (zoledronic acid) Injection
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Indications and Usage 8/2007
Treatment of osteoporosis in postmenopausal women (1.1)
Dosage and Administration 8/2007
Treatment of osteoporosis in postmenopausal women (2.1)

----------INDICATIONS AND USAGE----------

Reclast is a bisphosphonate indicated for:
- Treatment of osteoporosis in postmenopausal women (1.1)
- Treatment of Paget's disease of bone in men and women (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Treatment of postmenopausal osteoporosis: a single 5 mg infusion once a year given intravenously over no less than 15 minutes (2.1)
- Treatment of Paget's disease of bone: a single 5 mg infusion given intravenously over no less than 15 minutes (2.2)
- Patients with Paget's disease should receive 1500 mg elemental calcium and 800 IU vitamin D daily, particularly during the 2 weeks after dosing (2.2)
- 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----------

5 mg in a 100 mL ready to infuse solution (3).

----------CONTRAINDICATIONS----------

- Hypocalcemia (4.1)
- Hypersensitivity to any component of Reclast (4.2, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- Reclast contains the same active ingredient found in Zometa Patients receiving Zometa should not receive Reclast (5.1)
- Patients must be adequately supplemented with calcium and vitamin D (5.2)
- A single dose should not exceed 5 mg and the duration of infusion should be no less than 15 minutes (2.1, 2.2, 5.3)
- Renal toxicity may be greater in patients with renal impairment. Treatment in patients with severe renal impairment (creatinine clearance <35 mL/min) is not recommended. Monitor serum creatinine before each dose (5.3)
- Osteonecrosis of the jaw has been reported rarely in postmenopausal osteoporosis patients treated with bisphosphonates, including zoledronic acid. All patients should have a routine oral exam by the prescriber prior to treatment (5.4)
- Reclast 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. Withhold future doses of Reclast if severe symptoms occur (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions (>10%) were pyrexia, myalgia, headache, arthralgia, and pain in extremity (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact NOVARTIS PHARMACEUTICALS CORPORATION at 1 888 NOW-NOVA 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 Reclast may increase risk of hypocalcemia (7.2)
- Nephrotoxic drugs: Use with caution (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: August 2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Postmenopausal Osteoporosis

Reclast is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, Reclast reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures) [*see Clinical Studies (14.1)*].

1.2 Paget's Disease of Bone

Reclast is indicated for treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Patients must be appropriately hydrated prior to administration of Reclast [*see Warnings and Precautions (5.3)*].

Administration of acetaminophen or ibuprofen following Reclast administration may reduce the incidence of acute-phase reaction symptoms.

The following recommended doses of Reclast are for patients with creatinine clearance ≥35 mL/min [*see Warnings and Precautions (5.3)*].

2.1 Treatment of Osteoporosis in Postmenopausal Women

The recommended regimen is a single 5 mg infusion once a year given intravenously over no less than 15 minutes.

For osteoporosis treatment, and to reduce the risk of hypocalcemia, patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. Postmenopausal women require an average of 1200 mg calcium and 400 – 800 IU vitamin D daily.

2.2 Treatment of Paget's Disease of Bone

The recommended dose is a 5 mg infusion. The infusion time must not be less than 15 minutes given over a constant infusion rate.

To reduce the risk of hypocalcemia, all patients with Paget's disease should receive 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following Reclast administration. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia [*see Warnings and Precautions (5.2)*].

Re-treatment of Paget's Disease

After a single treatment with Reclast in Paget's disease an extended remission period is observed. Specific re-treatment data are not available. However, re-treatment with Reclast may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

2.3 Method of Administration

The Reclast infusion time must not be less than 15 minutes given over a constant infusion rate.

Reclast solution for infusion must not be allowed to come in contact with any calcium or other divalent cation-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line.

If refrigerated, allow the refrigerated solution to reach room temperature before administration. After opening, the solution is stable for 24 hours at 2°C – 8 °C (36°F - 46°F) [*see How Supplied/Storage and Handling (16)*].

3 DOSAGE FORMS AND STRENGTHS

5 mg in a 100 mL ready to infuse solution.

4 CONTRAINDICATIONS

4.1 Hypocalcemia [*see Warnings and Precautions (5.2)*].

4.2 Hypersensitivity to zoledronic acid or any components of Reclast 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 Drug Products with Same Active Ingredient

Reclast contains the same active ingredient found in Zometa, used for oncology indications, and a patient being treated with Zometa should not be treated with Reclast.

5.2 Hypocalcemia and Mineral Metabolism

Pre-existing hypocalcemia and disturbances of mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine) must be effectively treated before initiating therapy with Reclast. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended for these patients [*see Contraindications (4)*].

Hypocalcemia following Reclast administration is a significant risk in Paget's disease. All patients should be instructed about the symptoms of hypocalcemia and the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [*see Dosage and Administration (2.2), Adverse Reactions (6.1), Information for Patients (17.1)*].

All postmenopausal osteoporosis patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [*see Dosage and Administration (2.1), Adverse Reactions (6.1), Information for Patients (17.1)*].

5.3 Renal Impairment

A single dose of Reclast should not exceed 5 mg and the duration of infusion should be no less than 15 minutes [*see Dosage and Administration (2.1)*].

Reclast is not recommended for use in patients with severe renal impairment (creatinine clearance <35 mL/min) due to lack of adequate clinical experience in this population [*see Adverse Reactions (6.1)*].

To help prevent renal impairment, patients especially those receiving diuretic therapy, should be appropriately hydrated prior to administration of Reclast. Reclast should be used with caution with other nephrotoxic drugs [*see Drug Interactions (7.3)*].

Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g., oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration, etc), the majority of whom received a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

Monitor serum creatinine before each Reclast dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; consider interim monitoring of serum creatinine in at-risk patients.

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including zoledronic acid. Most cases have been in cancer patients treated with intravenous bisphosphonates undergoing dental procedures. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, patients with concomitant risk factors 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. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment [*see Adverse Reactions (6.1)*].

5.5 Pregnancy

RECLAST SHOULD NOT BE USED DURING PREGNANCY. Reclast may cause fetal harm when administered to a pregnant woman. 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 while on Reclast therapy [*see Use in Specific Populations (8.1)*].

5.6 Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Reclast. The time to onset of symptoms varied from one day to several months after starting the drug. Consider withholding future Reclast treatment 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 Reclast, there have been reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates. Use Reclast with caution in aspirin-sensitive 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.

Postmenopausal Osteoporosis

The safety of Reclast in the treatment of postmenopausal osteoporosis was assessed in a large, randomized, double-blind, placebo-controlled, multinational study of 7736 women aged 65-89 years with postmenopausal osteoporosis. The duration of the trial was three years with 3862 patients exposed to Reclast and 3852 patients exposed to placebo administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was similar between groups: 3.4% in the Reclast group and 2.9% in the placebo group. The incidence of serious adverse events was 29.2% in the Reclast group and 30.1% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.4% and 4.8% for the Reclast and placebo groups, respectively.

Adverse reactions reported in at least 2.0% of the postmenopausal osteoporosis patients, and more frequently in the Reclast-treated patients than placebo-treated patients are shown in Table 1.

Table 1. Adverse Reactions Occurring in= 2.0% of Postmenopausal Osteoporosis Patients Receiving Reclast (5 mg IV Infusion Once Yearly) and More Frequently than in Placebo-Treated Patients Over 3 Years

System Organ Class	5 mg IV Reclast® once per year % (N=3862)	Placebo once per year % (N=3852)
Blood and the Lymphatic System Disorders		
Anemia	4.4	3.6
Metabolism and Nutrition Disorders		
Anorexia	2.0	1.1
Nervous System Disorders		
Headache	12.4	8.1
Dizziness	7.6	6.7
Vascular Disorders		
Hypertension	12.7	12.4
Ear and Labyrinth Disorders		
Vertigo	4.3	4.0
Cardiac Disorders		
Atrial Fibrillation	2.4	1.9
Gastrointestinal Disorders		
Nausea	8.5	5.2
Diarrhea	6.0	5.6
Vomiting	4.6	3.2
Abdominal Pain Upper	4.6	3.1
Dyspepsia	4.3	4.0
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	23.8	20.4
Myalgia	11.7	3.7
Pain in Extremity	11.3	9.9
Shoulder Pain	6.9	5.6
Bone Pain	5.8	2.3
Neck Pain	4.4	3.8
Muscle Spasms	3.7	3.4
General Disorders and Administrative Site Conditions		
Pyrexia	17.9	4.6
Influenza-like Illness	8.8	2.7
Fatigue	5.4	3.5
Chills	5.4	1.0

Asthenia	5.3	2.9
Peripheral Edema	4.6	4.2
Pain	3.3	1.3
Malaise	2.0	1.0

Renal Impairment.

Treatment with intravenous bisphosphonates, including zoledronic acid, has been associated with renal impairment manifested as deterioration in renal function (i.e., increased serum creatinine) and in rare cases, acute renal failure. In the clinical trial for postmenopausal osteoporosis, patients with baseline creatinine clearance < 30 mL/min, urine dipstick =2+ protein or increase in serum creatinine of >0.5 mg/dL during the screening visits were excluded. The change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the Reclast and placebo treatment groups over 3 years, including patients with mild to moderate renal impairment (creatinine clearance between 30-60 mL/min) at baseline. Overall, there was a transient increase in serum creatinine observed within 10 days of dosing in 1.8% of Reclast-treated patients versus 0.8% of placebo-treated patients which resolved without specific therapy [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction:

The signs and symptoms of acute phase reaction occurred following Reclast infusion including, fever (18%), myalgia (9%), and flu-like symptoms (8%), headache (7%), and arthralgia (7%). The majority of these symptoms occurred within the first 3 days following the dose of Reclast and usually resolved within 3 days of onset but resolution could take up to 7-14 days. The incidence of these symptoms decreased with subsequent doses of Reclast.

Laboratory Findings.

In the trial in women with postmenopausal osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (less than 7.5 mg/dL) following Reclast administration. No symptomatic cases of hypocalcemia were observed.

Injection Site Reactions:

In the postmenopausal osteoporosis trial, local reactions at the infusion site such as itching, redness and/or pain have been reported in 0.7% of patients following the administration of Reclast and 0.5% of patients following administration of placebo.

Osteonecrosis of the Jaw:

In the postmenopausal osteoporosis trial in 7736 patients, after initiation of therapy, symptoms consistent with ONJ occurred in one patient treated with placebo and one patient treated with Reclast. Both cases resolved after appropriate treatment [*see Warnings and Precautions (5.4)*].

Atrial Fibrillation:

In the postmenopausal osteoporosis trial, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.3% of patients (50 out of 3862) compared to 0.4% (17 out of 3852) in the placebo group. The overall incidence of all atrial fibrillation adverse events in the zoledronic acid treatment group was, reported in 2.5% of patients (96 out of 3862) in the Reclast group vs. 1.9% of patients (75 out of 3852) in the placebo group. Over 90% of these events in both treatment groups occurred more than a month after the infusion. In an ECG sub-study, ECG measurements were performed on a subset of 559 patients before and 9 to 11 days after treatment. There was no difference in the incidence of atrial fibrillation between treatment groups suggesting these events were not related to the acute infusions.

Ocular Adverse Events:

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the postmenopausal osteoporosis trial, 9 (0.2%) patients treated with Reclast and 1 (<0.1%) patient treated with placebo developed iritis/uveitis/episcleritis.

Paget's Disease of Bone

In the Paget's disease trials, two 6-month, double-blind, comparative, multinational studies of 349 men and women aged > 30 years with moderate to severe disease and with confirmed Paget's disease of bone, 177 patients were exposed to Reclast and 172 patients exposed to risedronate. Reclast was administered once as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. Risedronate was given as an oral daily dose of 30 mg for 2 months.

The incidence of serious adverse events was 5.1% in the Reclast group and 6.4% in the risedronate group. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 1.2% for the Reclast and risedronate groups, respectively.

Adverse reactions occurring in at least 2% of the Paget's patients receiving Reclast (single 5 mg IV infusion) or risedronate (30 mg oral daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 2.

Table 2. Adverse Reactions Reported in at Least 2% of Paget's Patients Receiving Reclast (Single 5 mg IV Infusion) or Risedronate (Oral 30 mg Daily for 2 Months) Over a 6-Month Follow-Up Period

	5 mg IV Reclast®	**30 mg/day x 2 Months**

System Organ Class	% (N = 177)	risedronate % (N = 172)
Infections and Infestations		
Influenza	7	5
Metabolism and Nutrition Disorders		
Hypocalcemia	3	1
Anorexia	2	2
Nervous System Disorders		
Headache	11	10
Dizziness	9	4
Lethargy	5	1
Paresthesia	2	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	5	1
Gastrointestinal Disorders		
Nausea	9	6
Diarrhea	6	6
Constipation	6	5
Dyspepsia	5	4
Abdominal Distension	2	1
Abdominal Pain	2	2
Vomiting	2	2
Abdominal Pain Upper	1	2
Skin and Subcutaneous Tissue Disorders		
Rash	3	2
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	9	11
Bone Pain	9	5
Myalgia	7	4
Back Pain	4	7
Musculoskeletal Stiffness	2	1
General Disorders and Administrative Site Conditions		
Influenza-like Illness	11	6
Pyrexia	9	2

Fatigue	8	4
Rigors	8	1
Pain	5	4
Peripheral Edema	3	1
Asthenia	2	1

Laboratory Findings

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels were observed. Approximately 21% of patients had serum calcium levels <8.4 mg/dL 9-11 days following Reclast administration.

Renal Impairment

In clinical trials in Paget's disease there were no cases of renal deterioration following a single 5 mg 15-minute infusion [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

The signs and symptoms of acute phase reaction (influenza-like illness, pyrexia, myalgia, arthralgia, and bone pain) were reported in 25% of patients in the Reclast-treated group compared to 8% in the risedronate-treated group. Symptoms usually occur within the first 3 days following Reclast administration. The majority of these symptoms resolved within 4 days of onset.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported with zoledronic acid [*see Warnings and Precautions (5.4)*].

6.2 Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post approval use of Reclast: hypocalcemia, arthralgia, myalgia, flu-like symptoms, fever, headache, and urticaria.

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.

7 DRUG INTERACTIONS

No *in vivo* drug interaction studies have been performed for Reclast. *In vitro* 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% at 200 ng/mL to 53% at 50 ng/mL. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

7.1 Aminoglycosides

Caution is advised when bisphosphonates, including zoledronic acid, 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 zoledronic acid clinical trials.

7.2 Loop Diuretics

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

7.3 Nephrotoxic Drugs

Caution is indicated when Reclast is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.5)*].

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate 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 space, 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 (=0.3 times the anticipated human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (=0.1 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality was considered 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 daily subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg during gestation, adverse fetal effects were observed in the mid- and high-dose groups (about 2 and 4 times human systemic exposure following a 5 mg intravenous dose, based on AUC comparison). These adverse effects included increases in pre- and post-implantation 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 (about 1.2 times the anticipated human systemic exposure, 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 (at doses = 0.4 times the anticipated human systemic exposure following a 5 mg intravenous dose, based on mg/m^2 comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses = 0.04 times the human 5 mg intravenous dose, based on mg/m^2 comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia [*see Warnings and Precautions (5.5)*].

RECLAST SHOULD NOT BE USED DURING PREGNANCY. 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 while receiving Reclast [*see Warnings and Precautions (5.5)*].

8.2 Nursing Mothers

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

8.3 Pediatric Use

The safety and effectiveness of Reclast in pediatric patients have not been established and Reclast is not indicated for use in children.

8.4 Geriatric Use

The postmenopausal osteoporosis trial included 3868 Reclast-treated patients who were at least 65 years of age, while 1497 patients were at least 75 years old. No overall differences in efficacy or safety were observed between patients under 75 years of age with those at least 75 years of age, except that the acute phase reactions occurred less frequently in the older patients.

However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

Phase 3 studies of Reclast in the treatment of Paget's disease of bone included 132 Reclast-treated patients who were at least 65 years of age, while 68 Reclast-treated patients were at least 75 years old. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.5 Renal Impairment

Reclast is not recommended for patients with severe renal impairment (creatinine clearance <35 mL/min) due to lack of adequate clinical experience in this population. No dosage adjustment is required in patients with a creatinine clearance of ≥ 35 mL/min [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

Reclast is not metabolized in the liver. No clinical data are available for use of Reclast in patients with hepatic impairment.

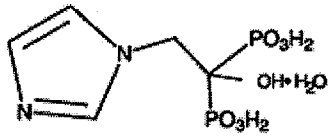
10 OVERDOSAGE

Clinical experience with acute overdosage of zoledronic acid (Reclast) solution for intravenous infusion is limited. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant renal impairment, hypocalcemia, 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.

Single doses of Reclast should not exceed 5 mg and the duration of the intravenous infusion should be no less than 15 minutes [*see Dosage and Administration (2)*].

11 DESCRIPTION

Reclast 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 monohydrate is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and a molar mass of 290.1 g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.

Reclast Injection is available as a sterile solution in bottles for intravenous infusion. One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: 4950 mg of mannitol, USP; and 30 mg of sodium citrate, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Reclast is a bisphosphonateand acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and localizes preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity to bone mineral.

12.2 Pharmacodynamics

In the osteoporosis treatment trial, the effect of Reclast treatment on markers of bone resorption (serum beta-C-telopeptides (b-CTx)) and bone formation (bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP)) was evaluated in patients (subsets ranging from 517 to 1246 patients) at periodic intervals. Treatment with a 5 mg annual dose of Reclast reduces bone turnover markers to the pre-menopausal range with an approximate 55% reduction in b-CTx, a 29% reduction in BSAP and a 52 % reduction in P1NP over 36 months. There was no progressive reduction of bone turnover markers with repeated annual dosing.

12.3 Pharmacokinetics

Pharmacokinetic data in patients with postmenopausal osteoporosis and Paget's disease of bone are not available.

Distribution: Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 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 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 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 nCi ^{14}C-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 bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

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 the infusion ([mean ± SD] 403 ± 118 ng/mL vs. 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs. 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pediatrics: Pharmacokinetic data in pediatric pat ients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid was not affected by age in patients with cancer and bone metastases whose age ranged from 38 years to 84 years.

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

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

Renal Impairment: 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 (creatinine clearance > 80 mL/min, N=37), patients with mild renal impairment (creatinine clearance = 50-80 mL/min, N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (creatinine clearance = 30-50 mL/min, N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of = 35 mL/min. Reclast is not recommended for patients with severe renal

impairment (creatinine clearance <35 mL/min) due to lack of clinical experience in this population [*see Warnings and Precautions (5.3), Use in Specific Populations (8.5)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given daily 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 =0.002 times the human intravenous dose of 5 mg, based on mg/m^2 comparison). Rats were given daily 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 ≤ 0.1 times the human intravenous dose of 5 mg, based on mg/m^2 comparison).

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 vivo* rat micronucleus assay.

Impairment of Fertility: Female rats were given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (equivalent to human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group (0.3 to 1 times human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

13.2 Animal Toxicology and/or Pharmacology

Bone safety studies: Zoledronic acid is a potent inhibitor of osteoclastic bone resorption. In the ovariectomized rat, single IV doses of zoledronic acid of 4-500 µg/kg (<0.1 to 3.5 times human exposure at the 5 mg intravenous dose, based on mg/m^2 comparison) suppressed bone turnover and protected against trabecular bone loss, cortical thinning and the reduction in vertebral and femoral bone strength in a dose-dependent manner. At a dose equivalent to human exposure at the 5 mg intravenous dose, the effect persisted for 8 months, which corresponds to approximately 8 remodeling cycles or 3 years in humans.

In ovariectomized rats and monkeys, weekly treatment with zoledronic acid dose-dependently suppressed bone turnover and prevented the decrease in cancellous and cortical BMD and bone strength, at yearly cumulative doses up to 3.5 times the intravenous human dose of 5 mg, based on mg/m^2 comparison. Bone tissue was normal and there was no evidence of a mineralization defect, no accumulation of osteoid, and no woven bone.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis

The efficacy and safety of Reclast in the treatment of postmenopausal osteoporosis was demonstrated in a randomized, double-blind, placebo-controlled, multinational study of 7736 women aged 65-89 years (mean age of 73) with either: a femoral neck BMD T-score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). Women were stratified into two groups: Stratum I: no concomitant use of osteoporosis therapy or Stratum II: baseline concomitant use of osteoporosis therapies which included calcitonin, raloxifene, tamoxifen, hormone replacement therapy; but excluded other bisphosphonates.

Women enrolled in Stratum I (n=5661) were evaluated annually for incidence of vertebral fractures. All women (Strata I and II) were evaluated for the incidence of hip and other clinical fractures. Reclast was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplementation per day.

The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years and the incidence of hip fractures over a median duration of 3 years. The diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the radiologist and quantitative morphometric criterion. The morphometric criterion required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height.

Effect on Vertebral Fractures:

Reclast significantly decreased the incidence of new vertebral fractures at one, two, and three years as shown in Table 3.

Table 3. Proportion of Patients with New Morphometric Vertebral Fractures

Outcome	Reclast (%)	Placebo (%)	Absolute reduction in fracture incidence % (95% CI)	Relative reduction in fracture incidence % (95% CI)
At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)**
At least one new vertebral fracture (0–2 years)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)**
At least one new vertebral	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)**

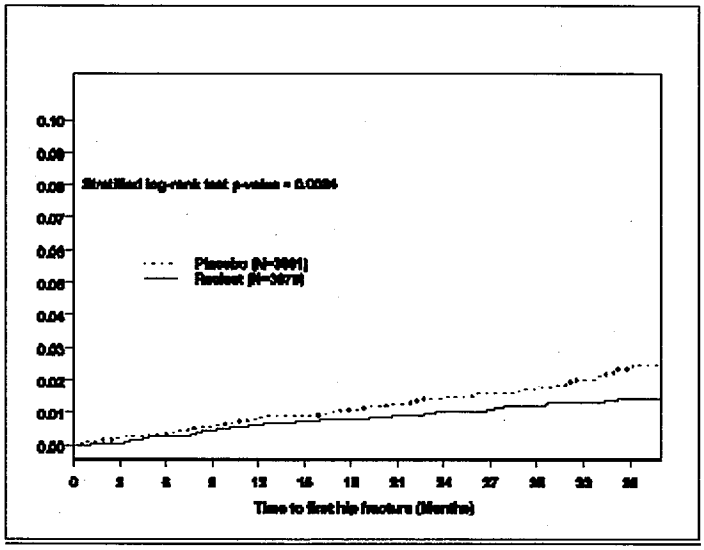
fracture (0– 3 years)				
** p <0.0001				

The reductions in vertebral fractures over three years were consistent (including new/worsening and multiple vertebral fractures) and significantly greater than placebo regardless of age, geographical region, baseline body mass index, number of baseline vertebral fractures, femoral neck BMD T-score, or prior bisphosphonate usage.

Effect on Hip Fracture over 3 years:

Reclast demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The hip fracture event rate was 1.4% for Reclast-treated patients compared to 2.5% for placebo-treated patients.

Figure 1. Cumulative Incidence of Hip Fracture Over 3 Years



The reductions in hip fractures over three years were greater for Reclast than placebo regardless of femoral neck BMD T-score.

Effect on All Clinical Fractures:

Reclast demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical (symptomatic) vertebral and non-vertebral fractures (excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures). All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 4.

Table 4. Between –Treatment Comparisons of the Incidence of Clinical Fracture Variables Over 3 Years

Outcome	Reclast (N= 3875) Event rate n (%)	Placebo (N= 3861) Event rate n (%)	Absolute reduction in fracture incidence (%) (95% CI)	Relative risk reduction in fracture incidence (%) (95% CI)
Any clinical fracture [1]	308 (8.4)	456 (12.8)	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture [2]	19 (0.5)	84 (2.6)	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture [3]	292 (8.0)	388 (10.7)	2.7 (1.4, 4.0)	25 (13, 36)*

*p-value < 0.001, **p-value <0.0001

[1] Excluding finger, toe, and facial fractures

[2] Includes clinical thoracic and clinical lumbar vertebral fractures

[3] Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

Effect on Bone Mineral Density:

Reclast significantly increased BMD at the lumbar spine, total hip and femoral neck, relative to treatment with placebo at time points 12, 24, and 36 months. Treatment with Reclast resulted in a 6.7% increase in BMD at the lumbar spine, 6.0 % at the total hip, and 5.1% at the femoral neck, over 3 years as compared to placebo.

Bone Histology:

Bone biopsy specimens were obtained between Months 33 and 36 from 82 postmenopausal patients with osteoporosis treated with 3 annual doses of Reclast. Of the biopsies obtained, 81 were adequate for qualitative histomorphometry assessment, 59 were adequate for partial quantitative histomorphometry assessment, and 38 were adequate for full quantitative histomorphometry assessment. Micro CT analysis was performed on 76 specimens. Qualitative, quantitative and micro CT assessments showed bone of normal architecture and quality without mineralization defects.

Effect on Height

In the 3-year osteoporosis study standing height was measured annually using a stadiometer. The Reclast group revealed less height loss compared to placebo (4.2 mm vs. 7.0 mm, respectively ($p<0.001$)).

14.2 Treatment of Paget's Disease of Bone

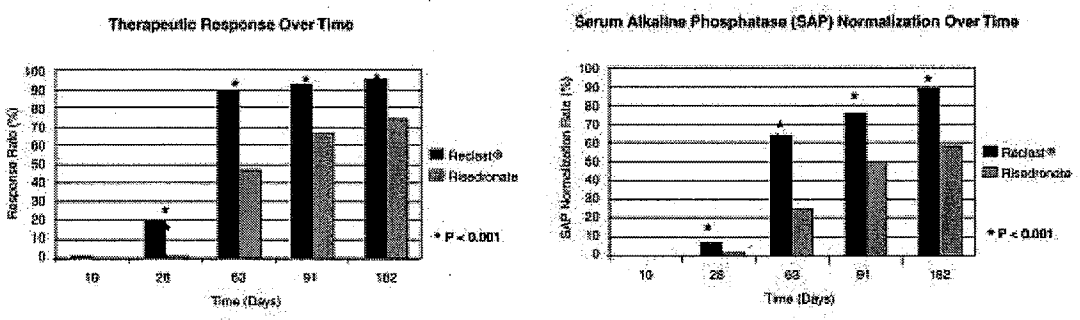
Reclast was studied in male and female patients with moderate to severe Paget's disease of bone, defined as serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry. Diagnosis was confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg Reclast vs. oral daily doses of 30 mg risedronate for 2 months was demonstrated in two identically designed 6-month randomized, double blind trials. The mean age of patients in the two trials was 70. Ninety-three percent (93%) of patients were Caucasian. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of normal range.

In both trials Reclast demonstrated a superior and more rapid therapeutic response compared with risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of formation (SAP, serum N-terminal propeptide of type I collagen [P1NP]) and resorption (serum CTx 1 [cross-linked C-telopeptides of type I collagen] and urine α-CTx).

The 6-month combined data from both trials showed that 96% (169/176) of Reclast-treated patients achieved a therapeutic response as compared with 74% (127/171) of patients treated with risedronate. Most Reclast patients achieved a therapeutic response by the Day 63 visit. In addition, at 6 months, 89% (156/176) of Reclast-treated patients achieved normalization of SAP levels, compared to 58% (99/171) of patients treated with risedronate ($p<0.0001$) (see Figure 2).

Figure 2. Therapeutic Response/ Serum Alkaline Phosphatase (SAP) Normalization Over Time



The therapeutic response to Reclast was similar across demographic and disease-severity groups defined by gender, age, previous bisphosphonate use, and disease severity. At 6 months the percentage of Reclast-treated patients who achieved therapeutic response was 97% and 95%, respectively, in each of the baseline disease severity subgroups (baseline SAP < 3xULN, ≥ 3xULN) compared to 75% and 74%, respectively, for the same disease severity subgroups of risedronate-treated patients.

In patients who had previously received treatment with oral bisphosphonates, therapeutic response rates were 96% and 55% for Reclast and risedronate, respectively. The comparatively low risedronate response was due to the low response rate (7/23, 30%) in patients previously treated with risedronate. In patients naïve to previous treatment, a greater therapeutic response was also observed with Reclast (98%) relative to risedronate (86%). In patients with symptomatic pain at screening, therapeutic response rates were 94% and 70% for Reclast and risedronate respectively. For patients without pain at screening, therapeutic response rates were 100% and 82% for Reclast and risedronate respectively.

Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with Reclast 5 mg. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each bottle contains 5 mg/100mL.NDC 0078-0435-61

Handling

After opening the solution, it is stable for 24 hours at 2°C – 8 °C (36°F - 46°F).

If refrigerated, allow the refrigerated solution to reach room temperature before administration.

Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2).

17.1 Information for Patients

Patients should be made aware that Reclast contains the same active ingredient (zoledronic acid) found in Zometa®, and that patients being treated with Zometa should not be treated with Reclast.

Before being given Reclast patients should tell their doctor if they have kidney problems and what medications they are taking.

Reclast should not be given if the patient is pregnant or plans to become pregnant, or if she is breast-feeding [*see Contraindications (4)*].

If the patient had surgery to remove some or all of the parathyroid glands in their neck, or had sections of their intestine removed, or are unable to take calcium supplements they should tell their doctor.

Reclast is given as an infusion into a vein by a nurse or a doctor, and the infusion time must not be less than 15 minutes.

On the day of treatment the patient should eat and drink normally, which includes drinking at least 2 glasses of fluid such as water within a few hours prior to the infusion, as directed by their doctor, before receiving Reclast.

After getting Reclast it is strongly recommended patients with Paget's disease take calcium in divided doses (for example, 2 to 4 times a day) for a total of 1500 mg calcium a day to prevent low blood calcium levels. This is especially important for the two weeks after getting Reclast [*see Warnings and Precautions (5.2)*].

Adequate calcium and vitamin D intake is important in women with osteoporosis and the current recommended daily intake of calcium is 1200 mg and vitamin D 400IU – 800IU daily. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels.

Patients should be aware of the most commonly associated side effects of therapy. Patients may experience one or more side effects that could include: fever, flu-like symptoms, myalgia, arthralgia, and headache. Most of these side effects occur within the first 3 days following the dose of Reclast. They usually resolve within 3 days of onset but may last for up to 7 to 14 days. Patients should consult their physician if they have questions or if these symptoms persist. The incidence of these symptoms decreased markedly with subsequent doses of Reclast. Administration of acetaminophen or ibuprofen following Reclast administration may reduce the incidence of these symptoms.

Physicians should inform their patients there have been reports, primarily in patients treated with bisphosphonates for other illnesses, of persistent pain and/or a non-healing sore of the mouth or jaw, and if they experience these symptoms to tell their physician or dentist.

17.2 FDA-Approved Patient Labeling

Reclast® (pronounced RE-klast)
(zoledronic acid)
Injection

IMPORTANT: You should not receive Reclast if you are already receiving Zometa. Reclast and Zometa are the same medicine. They both contain zoledronic acid.

Read the Patient information carefully before your first infusion of Reclast and before each infusion. There may be new information. This leaflet does not replace talking with your doctor.

What is the most important information I should know about Reclast?

Patients with severe kidney problems should not receive Reclast Injection.

Low blood calcium should be corrected prior to receiving Reclast. If you are being treated for Paget's disease of the bone it is important to take 1500 mg of calcium and 800 IU of vitamin D daily, especially during the first 2 weeks after getting Reclast. You should take calcium and vitamin D daily as recommended by your health care professional.

What is Reclast?

Reclast is a medicine used to treat:

- Osteoporosis in women after menopause
- Men and women with Paget's disease of the bone

Reclast strengthens your bones by increasing bone mass and lowers the chance of breaking bones (fractures).

Who should not get Reclast?

You should not get Reclast if:

- Your blood calcium level is too low
- You are allergic to anything in Reclast. See section 'What are the ingredients in Reclast' for a complete list of ingredients

What should I tell my doctor before getting Reclast?

Reclast may not be right for you. Tell your doctor about all your medical conditions, including if you:

- have kidney problems
- have a history of low blood calcium
- are not able to take daily calcium and vitamin D supplements
- had parathyroid or thyroid surgery (these glands are located in your neck)
- have a malabsorption syndrome
- had sections of your intestine removed
- have asthma (wheezing) from taking aspirin
- have a planned dental surgery such as tooth extraction
- are pregnant or plan to become pregnant; Reclast may harm your unborn baby
- are breast-feeding or planning to breast-feed. It is not known if Reclastpasses into breast milk

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, herbal supplements, and vitamins. Some medicines may increase your chance for low blood calcium levels or kidney problems when used with Reclast. **Especially tell your doctor if you are taking:**

- Zometa
- A diuretic or "water pill"
- An antibiotic. Certain antibiotics called aminoglycosides may increase the effect of Reclast in lowering your blood calcium for a long period of time.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist each time you get a new medicine.

How will I receive Reclast?

- Reclast is given by infusion into a vein (IV) thattakes at least 15 minutes time. Reclast is always infused by your doctor or nurse
- Drink at least 2 glasses of fluid (such as water), within a few hours before receiving Reclast, as directed by your doctor. You may eat normally before your infusion.

For Osteoporosis:

- Reclast is given once a year
- In women with osteoporosis, the current recommended daily intake of calcium is 1200 mg and vitamin D 400 IU to 800 IU daily. If you have osteoporosis you should take calcium and vitamin D daily as recommended by your doctor.
- During treatment with Reclast, your doctor may order a bone mineral density test to check your osteoporosis

For Paget's Disease:

- Is given as a single treatment or your doctor may choose to give you more Reclast infusions based on signs or symptoms of your disease.
- To prevent low blood calcium, it is important to take calcium and vitamin D supplements. If you have Paget's disease you should take 1500 mg of calcium a day in divided doses (for example, 750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D a day. It is especially important to take the calcium and vitamin D supplements during the first 2 weeks after getting Reclast.
- During treatment with Reclast, your doctor may order a blood test to check your Paget's disease

What are the possible side effects of Reclast?

Possible serious side effects include:

- **Low blood calcium (hypocalcemia)**. Symptoms may include numbness or tingling feeling (especially in the area around the mouth) or muscle spasms. Call your doctor right away if you notice any of these symptoms after receiving Reclast.
- **Kidney problems**. Your doctor may do a blood test to check your kidney function before each dose of Reclast. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving Reclast, as directed by your doctor.
- **Jaw-bone problems (Osteonecrosis of the jaw).** Jaw-bone problems may occur in some people and include: infection, delayed healing after teeth are pulled.
- **Severe muscle, bone and joint pain.** Tell your doctor if you have severe muscle, bone, or joint pain after receiving Reclast.

The most common side effects of Reclast include: flu-like illness, fever, pain in your muscles or joints, and headache that can happen in the days after you get Reclast. A mild pain reliever such as ibuprofen or acetaminophen may reduce these symptoms. The chance of getting these side effects goes down with repeat dosing of Reclast.

Tell your doctor about any side effect that bothers you or does not go away. These are not all the possible side effects of Reclast. If you have questions, talk to your doctor.

General Information about Reclast

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.

This leaflet is a summary of the most important information about Reclast. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Reclast that is written for healthcare professionals. For more information, go to www.reclast.com or call 1-866-732-5278.

What are the ingredients in Reclast?

Active ingredient: zoledronic acid. **Inactive ingredients:** mannitol, USP; sodium citrate, USP; and water for injection, USP.

What is Osteoporosis?

Osteoporosis is a disease that is a thinning and weakening of the bones. Weaker bone can break more easily. Throughout life your body keeps your bones strong and healthy by replacing old bone with new bone. In osteoporosis, however, the body removes bone faster than it is formed. This causes loss of bone mass and weakening of bones. Weak bones are more likely to break. Osteoporosis is common in women after menopause and with increasing age. People who have an increased risk of osteoporosis: 1) are white (Caucasian) or oriental (Asian); 2) are thin; 3) have a family member with osteoporosis; 4) do not get enough calcium or vitamin D; 5) do not exercise; 6) smoke or drink alcohol often or 7) take medicines that cause bone loss (like prednisone) over a long period of time.

At first, osteoporosis usually has no symptoms, but people with osteoporosis are more likely to break (fracture) their bones. Fractures most often occur at the hip, back (spine), or wrist bones. Fractures of the spine may not be painful, but over time they can make you shorter. Over time fractures can lead to pain, severe disability, or loss of ability to move around. Reclast strengthens your bones and therefore makes them less likely to break.

What is Paget's disease of bone?

Normally bone breaks down and is replaced by new bone. In Paget's disease, bone breaks down too much and the new bone made is not normal. Bones affected by Paget's disease like the skull, spine, and legs, become deformed and weaker than normal. This can cause problems like bone pain and the bones can bend or break.

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