

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**NDA 21817/S-012**

*Trade Name:*      **RECLAST**

*Generic Name:*    Zoledronic Acid

*Sponsor:*          Novartis Pharmaceuticals Corp.

*Approval Date:*    8/31/2011

*Indications:*      Reclast is a bisphosphonate indicated for:

- Treatment and prevention of postmenopausal osteoporosis
- Treatment to increase bone mass in men with osteoporosis
- Treatment and prevention of glucocorticoid-induced osteoporosis
- Treatment of Paget's disease of bone in men and women

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**NDA 21817/S-012**

**APPROVAL LETTER**



NDA 21817/S-012

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corp.  
Attention: Bijal Pandi, Pharm.D.  
Global Program Regulatory Manager  
One Health Plaza  
East Hanover, NJ 07936

Dear Dr. Pandi:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Reclast® (zoledronic acid) Injection 5 mg in a 100 mL ready-to-infuse solution.

We acknowledge receipt of your amendments dated August 15 and 30, 2011.

This “Prior Approval” supplemental new drug application provides for changes to the **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, USE IN SPECIAL POPULATIONS, CLINICAL PHARMACOLOGY,** and **PATIENT COUNSELING INFORMATION** sections of the physician insert regarding renal impairment, specifically creatinine clearance. This supplement also provides for changes to the Medication Guide to be consistent with the changes in the physician labeling.

We also note in your submission your intent to issue a “Dear Healthcare Provider Letter” regarding these changes.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jennifer Mercier, Chief, Project Management Staff, at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.  
Deputy Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling  
Medication Guide

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEORGE S BENSON  
08/31/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
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**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 (1.6)	01/2011
Dosage and Administration (2, 2.6)	03/2011
Contraindications (4.2)	08/2011
Warnings and Precautions (5.3)	08/2011
Warnings and Precautions (5.5)	01/2011

### INDICATIONS AND USAGE

Reclast is a bisphosphonate indicated for:

- Treatment and prevention of postmenopausal osteoporosis (1.1, 1.2)
  - Treatment to increase bone mass in men with osteoporosis (1.3)
  - Treatment and prevention of glucocorticoid-induced osteoporosis (1.4)
  - Treatment of Paget's disease of bone in men and women (1.5)
- The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (1.6)

### DOSAGE AND ADMINISTRATION

Infusion given intravenously over no less than 15 minutes:

- Treatment of postmenopausal osteoporosis (2.1); treatment to increase bone mass in men with osteoporosis (2.3); treatment and prevention of glucocorticoid-induced osteoporosis (2.4): 5 mg once a year
- Prevention of postmenopausal osteoporosis: 5 mg once every 2 years (2.2)
- Treatment of Paget's disease of bone: a single 5 mg infusion. Patients should receive 1500 mg elemental calcium and 800 IU vitamin D daily (2.5)

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

- Hypocalcemia (4.1)
- Patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment (4.2, 5.3)
- Hypersensitivity to any component of Reclast (4.3, 6.2)

### WARNINGS AND PRECAUTIONS

- 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. Renal toxicity may be greater in patients with underlying renal impairment or with other risk factors, including advanced age or dehydration. Monitor creatinine clearance before each dose (2.1, 2.2, 5.3)
- Osteonecrosis of the jaw has been reported. All patients should have a routine oral exam by the prescriber prior to treatment (5.4)
- Atypical femur fractures have been reported. Patients with thigh or groin pain should be evaluated to rule out a femoral fracture (5.5)
- Reclast can cause fetal harm. Women of childbearing potential should be advised (5.6, 8.1)
- Severe incapacitating bone, joint, and/or muscle pain may occur. Withhold future doses of Reclast if severe symptoms occur (5.7)

### ADVERSE REACTIONS

The most common adverse reactions (>10%) were pyrexia, myalgia, headache, arthralgia, pain in extremity (6.1). Other important adverse reactions were flu-like illness, nausea, vomiting, diarrhea (6.2), and eye inflammation (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](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Aminoglycosides: May lower serum calcium for prolonged periods (7.1)
- Loop diuretics: May increase risk of hypocalcemia (7.2)
- Nephrotoxic drugs: Use with caution (7.3)
- Drugs primarily excreted by the kidney: Exposure may be increased with renal impairment. Monitor serum creatinine in patients at risk (7.4)

### USE IN SPECIFIC POPULATIONS

Nursing Mothers: Reclast should not be given to nursing women (8.3)  
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 and FDA-approved patient labeling

Revised: 08/2011

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Treatment of Osteoporosis in Postmenopausal Women

Reclast is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Reclast reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Reclast reduces the incidence of new clinical fractures [*see Clinical Studies (14.1)*].

#### 1.2 Prevention of Osteoporosis in Postmenopausal Women

Reclast is indicated for prevention of osteoporosis in postmenopausal women [*see Clinical Studies (14.2)*].

#### 1.3 Osteoporosis in Men

Reclast is indicated for treatment to increase bone mass in men with osteoporosis [*see Clinical Studies (14.3)*].

#### 1.4 Glucocorticoid-Induced Osteoporosis

Reclast is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months [*see Clinical Studies (14.4)*].

#### 1.5 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 (14.5)*].

#### 1.6 Important Limitations of Use

The safety and effectiveness of Reclast for the treatment of osteoporosis is based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

### 2 DOSAGE AND ADMINISTRATION

A 5 mg dose of Reclast administered intravenously is recommended for patients with creatinine clearance  $\geq 35$  mL/min [*see Warnings and Precautions (5.3)*].

Reclast is contraindicated in patients with creatinine clearance  $<35$  mL/min and in those with evidence of acute renal impairment [*see Contraindications (4.2)*].

There are no safety or efficacy data to support the adjustment of the Reclast dose based on baseline renal function. Therefore, no dose adjustment is required in patients with CrCl  $\geq 35$  mL/min.

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)*].

The i.v. infusion should be followed by a 10 mL normal saline flush of the intravenous line.

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

#### 2.1 Treatment of Osteoporosis in Postmenopausal Women

The recommended regimen is a 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 at least 1200 mg calcium and 800-1000 IU vitamin D daily.

## 2.2 Prevention of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion given once every 2 years intravenously over no less than 15 minutes. 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 800-1000 IU vitamin D daily.

## 2.3 Osteoporosis in Men

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. An average of at least 1200 mg calcium and 800-1000 IU vitamin D daily is recommended.

## 2.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. An average of at least 1200 mg calcium and 800-1000 IU vitamin D daily is recommended.

## 2.5 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.

## 2.6 Method of Administration

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

The i.v. infusion should be followed by a 10 mL normal saline flush of the intravenous line.

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 Renal Failure

Reclast is contraindicated in patients with creatinine clearance < 35 ml/min and in those with evidence of acute renal impairment due to an increased risk of renal failure [*see Warnings and Precautions (5.3)*]

### 4.3 Hypersensitivity to Zoledronic Acid or Any Components of Reclast

Hypersensitivity reactions including rare cases of urticaria, angioedema, and anaphylactic reaction/shock have been reported [*see Post-Marketing Experience (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)*, *Adverse Reactions (6.1)*, *Information for Patients (17)*].

All osteoporosis patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [see *Dosage and Administration (2)*, *Adverse Reactions (6.1)*, *Information for Patients (17)*].

### 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 contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment. [See *Contraindications (4.2)*]. If history or physical signs suggest dehydration, Reclast therapy should be withheld until normovolemic status has been achieved. [See *Post-marketing Experience (6.2)*]

Reclast should be used with caution in patients with chronic renal impairment. Acute renal impairment, including renal failure, has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise, advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Reclast administration. Acute renal failure (ARF) has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis or fatal outcome occurred in patients with underlying moderate to severe renal impairment or with any of the risk factors described in this section [see *Post-Marketing Experience (6.2)*]. Renal impairment may lead to increased exposure of concomitant medications and/or their metabolites that are primarily renally excreted [see *Drug Interactions (7.4)*].

Creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each Reclast dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; interim monitoring of creatinine clearance should be performed in at-risk patients. Elderly patients and those receiving diuretic therapy are at increased risk of acute renal failure. These patients should have their fluid status assessed and be appropriately hydrated prior to administration of Reclast. Reclast should be used with caution with other nephrotoxic drugs [see *Drug Interactions (7.3)*]. Consider monitoring creatinine clearance in patients at-risk for ARF who are taking concomitant medications that are primarily excreted by the kidney [see *Drug Interactions (7.4)*].

### 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, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy).

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 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

## 5.6 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)*].

## 5.7 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)*].

## 5.8 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.

### **Treatment of Osteoporosis in Postmenopausal Women**

The safety of Reclast in the treatment of postmenopausal osteoporosis was assessed in Study 1, a large, randomized, double-blind, placebo-controlled, multinational study of 7736 postmenopausal women aged 65-89 years with osteoporosis, diagnosed by bone mineral density or the presence of a prevalent vertebral fracture. 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.

The safety of Reclast in the treatment of osteoporosis patients with a recent (within 90 days) low-trauma hip fracture was assessed in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint-driven study of 2127 men and women aged 50-95 years; 1065 patients were randomized to Reclast and 1062 patients were randomized to placebo. Reclast was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. The study continued until at least 211 patients had a confirmed clinical fracture in the study population who were followed for an average of approximately 2 years on study drug. Vitamin D levels were not routinely measured but a loading dose of

vitamin D (50,000 to 125,000 IU orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day for at least 14 days prior to the study drug infusions.

The incidence of all-cause mortality was 9.6% in the Reclast group and 13.3% in the placebo group. The incidence of serious adverse events was 38.3% in the Reclast group and 41.3% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.3% and 4.7% for the Reclast and placebo groups, respectively.

Adverse reactions reported in at least 2% of patients with osteoporosis and more frequently in the Reclast-treated patients than placebo-treated patients in either osteoporosis trial are shown below in Table 1.

**Table 1. Adverse Reactions Occurring in  $\geq 2.0\%$  of Patients with Osteoporosis and More Frequently than in Placebo-Treated Patients**

System Organ Class	Study 1		Study 2	
	5 mg IV Reclast once per year % (N=3862)	Placebo once per year % (N=3852)	5 mg IV Reclast once per year % (N=1054)	Placebo once per year % (N=1057)
<b>Blood and the Lymphatic System Disorders</b>				
Anemia	4.4	3.6	5.3	5.2
<b>Metabolism and Nutrition Disorders</b>				
Dehydration	0.6	0.6	2.5	2.3
Anorexia	2.0	1.1	1.0	1.0
<b>Nervous System Disorders</b>				
Headache	12.4	8.1	3.9	2.5
Dizziness	7.6	6.7	2.0	4.0
<b>Ear and Labyrinth Disorders</b>				
Vertigo	4.3	4.0	1.3	1.7
<b>Cardiac Disorders</b>				
Atrial Fibrillation	2.4	1.9	2.8	2.6
<b>Vascular Disorders</b>				
Hypertension	12.7	12.4	6.8	5.4
<b>Gastrointestinal Disorders</b>				
Nausea	8.5	5.2	4.5	4.5
Diarrhea	6.0	5.6	5.2	4.7
Vomiting	4.6	3.2	3.4	3.4
Abdominal Pain Upper	4.6	3.1	0.9	1.5
Dyspepsia	4.3	4.0	1.7	1.6
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>				
Arthralgia	23.8	20.4	17.9	18.3
Myalgia	11.7	3.7	4.9	2.7
Pain in Extremity	11.3	9.9	5.9	4.8
Shoulder Pain	6.9	5.6	0.0	0.0
Bone Pain	5.8	2.3	3.2	1.0
Neck Pain	4.4	3.8	1.4	1.1
Muscle Spasms	3.7	3.4	1.5	1.7
Osteoarthritis	9.1	9.7	5.7	4.5
Musculoskeletal Pain	0.4	0.3	3.1	1.2
<b>General Disorders and Administrative Site Conditions</b>				
Pyrexia	17.9	4.6	8.7	3.1
Influenza-like Illness	8.8	2.7	0.8	0.4
Fatigue	5.4	3.5	2.1	1.2
Chills	5.4	1.0	1.5	0.5
Asthenia	5.3	2.9	3.2	3.0
Peripheral Edema	4.6	4.2	5.5	5.3
Pain	3.3	1.3	1.5	0.5
Malaise	2.0	1.0	1.1	0.5
Hyperthermia	0.3	<0.1	2.3	0.3
Chest Pain	1.3	1.1	2.4	1.8
<b>Investigations</b>				
Creatinine Renal Clearance Decreased	2.0	2.4	2.1	1.7

### **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 (based on actual body weight), urine dipstick  $\geq 2+$  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 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 in Study 1 following Reclast infusion including fever (18%), myalgia (9%), 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. In Study 2, patients without a contraindication to acetaminophen were provided with a standard oral dose at the time of the IV infusion and instructed to use additional acetaminophen at home for the next 72 hours as needed. Reclast was associated with fewer signs and symptoms of a transient acute phase reaction in this trial: fever (7%) and arthralgia (3%). The incidence of these symptoms decreased with subsequent doses of Reclast.

### ***Laboratory Findings***

In Study 1, 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. In Study 2, following pre-treatment with vitamin D, no patients had treatment emergent serum calcium levels below 7.5 mg/dL.

### ***Injection Site Reactions***

In the osteoporosis trials, local reactions at the infusion site such as itching, redness and/or pain have been reported in 0% to 0.7% of patients following the administration of Reclast and 0% to 0.5% of patients following administration of placebo.

### ***Osteonecrosis of the Jaw***

In the postmenopausal osteoporosis trial, Study 1, 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)*]. No reports of osteonecrosis of the jaw were reported in either treatment group in Study 2.

### ***Atrial Fibrillation***

In the postmenopausal osteoporosis trial, Study 1, 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. In Study 2, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.0% of patients (11 out of 1054) compared to 1.2% (13 out of 1057) in the placebo group demonstrating no difference between treatment groups.

### ***Ocular Adverse Events***

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis trials, 1 (<0.1%) to 9 (0.2%) patients treated with Reclast and 0 (0%) to 1 (<0.1%) patient treated with placebo developed iritis/uveitis/episcleritis.

### **Prevention of Osteoporosis in Postmenopausal Women**

The safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged  $\geq 45$  years. Patients were randomized to one of three treatment groups: (1) Reclast given at randomization and Month 12 (n=198); (2) Reclast given at randomization and placebo at Month 12 (n=181); and (3) placebo given at randomization and Month 12 (n=202).

Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day.

The incidence of serious adverse events was similar for subjects given (1) Reclast at randomization and at Month 12 (10.6%), (2) Reclast at randomization and placebo given at Month 12 (9.4%), and (3) placebo at randomization and at Month 12 (11.4%). The percentages of patients who withdrew from the study due to adverse events were 7.1%, 7.2%, and 3.0% in the two Reclast groups and placebo group, respectively. Adverse reactions reported in at least 2% of patients with osteopenia and more frequently in the Reclast-treated patients than placebo-treated patients are shown in Table 2.

**Table 2. Adverse Reactions Occurring in  $\geq$  2% of Patients with Osteopenia and More Frequently than in Placebo-Treated Patients**

<b>System Organ Class</b>	<b>5 mg IV Reclast Once Per Year % (n=198)</b>	<b>5 mg IV Reclast Once % (n=181)</b>	<b>Placebo once per year % (n=202)</b>
<b>Metabolism and nutrition disorders</b>			
Anorexia	2.0	0.6	0.0
<b>Nervous system disorders</b>			
Headache	14.6	20.4	11.4
Dizziness	7.6	6.1	3.5
Hypoesthesia	5.6	2.2	2.0
<b>Ear and labyrinth disorders</b>			
Vertigo	2.0	1.7	1.0
<b>Vascular disorders</b>			
Hypertension	5.1	8.3	6.9
<b>Gastrointestinal disorders</b>			
Nausea	17.7	11.6	7.9
Diarrhea	8.1	6.6	7.9
Vomiting	7.6	5.0	4.5
Dyspepsia	7.1	6.6	5.0
Abdominal pain*	8.6	6.6	7.9
Constipation	6.6	7.2	6.9
Abdominal discomfort	2.0	1.1	0.5
Abdominal distension	2.0	0.6	0.0
<b>Skin and subcutaneous tissue disorders</b>			
Rash	3.0	2.2	2.5
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	27.3	18.8	19.3
Myalgia	19.2	22.7	6.9
Back pain	18.2	16.6	11.9
Pain in extremity	11.1	16.0	9.9
Muscle spasms	5.6	2.8	5.0
Musculoskeletal pain**	8.1	7.2	7.9
Bone pain	5.1	3.3	1.0
Neck pain	5.1	6.6	5.0
Arthritis	4.0	2.2	1.5
Joint stiffness	3.5	1.1	2.0
Joint swelling	3.0	0.6	0.0
Flank pain	2.0	0.6	0.0
Pain in jaw	2.0	3.9	2.5
<b>General disorders and administration site conditions</b>			
Pain	24.2	14.9	3.5
Pyrexia	21.7	21.0	4.5
Chills	18.2	18.2	3.0
Fatigue	14.6	9.9	4.0
Asthenia	6.1	2.8	1.0
Peripheral edema	5.6	3.9	3.5
Non-cardiac chest pain	3.5	7.7	3.0
Influenza like illness	1.5	3.3	2.0
Malaise	1.0	2.2	0.5

\* Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR

\*\* Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

### ***Ocular Adverse Events***

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis prevention trial, 4 (1.1%) patients treated with Reclast and 0 (0%) patients treated with placebo developed iritis/uveitis.

### ***Acute Phase Reaction***

In patients given Reclast at randomization and placebo at Month 12, Reclast was associated with signs and symptoms of an acute phase reaction: myalgia (20.4%), fever (19.3%), chills (18.2%), pain (13.8%), headache (13.3%), fatigue (8.3%), arthralgia (6.1%), pain in extremity (3.9%), influenza-like illness (3.3%), and back pain (1.7%), which occurred within the first 3 days following the dose of Reclast. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset but resolution could take up to 7-14 days.

### **Osteoporosis in Men**

The safety of Reclast in men with osteoporosis or osteoporosis secondary to hypogonadism was assessed in a two year randomized, multicenter, double-blind, active controlled group study of 302 men aged 25-86 years. One hundred fifty three (153) patients were exposed to Reclast administered once annually with a 5 mg dose in 100 mL infused over 15 minutes for up to a total of two doses, and 148 patients were exposed to a commercially-available oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 IU of vitamin D supplementation per day.

The incidence of all-cause mortality (one in each group) and serious adverse events were similar between the Reclast and active control treatment groups. The percentage of patients experiencing at least one adverse event was comparable between the Reclast and active control groups, with the exception of a higher incidence of post-dose symptoms in the Reclast group that occurred within 3 days after infusion. The overall safety and tolerability of Reclast was similar to the active control.

Adverse reactions reported in at least 2% of men with osteoporosis and more frequently in the Reclast-treated patients than the active control-treated patients and either (1) not reported in the postmenopausal osteoporosis treatment trial or (2) reported more frequently in the trial of osteoporosis in men are presented in Table 3. Therefore, Table 3 should be viewed in conjunction with Table 1.

**Table 3: Adverse Reactions Occurring in  $\geq 2\%$  of Men with Osteoporosis and More Frequently in the Reclast-Treated Patients than the Active Control-Treated Patients and either (1) Not Reported in the Postmenopausal Osteoporosis Treatment Trial or (2) Reported More Frequently in this Trial**

System Organ Class	5 mg IV Reclast once per year % (N=153)	Active Control once weekly % (N=148)
<b>Nervous System Disorders</b>		
Headache	15.0	6.1
Lethargy	3.3	1.4
<b>Eye Disorders</b>		
Eye pain	2.0	0.0
<b>Cardiac Disorders</b>		
Atrial fibrillation	3.3	2.0
Palpitations	2.6	0.0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnea	6.5	4.7
Abdominal pain*	7.9	4.1
<b>Skin and Subcutaneous Tissue Disorders</b>		
Hyperhidrosis	2.6	2.0
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>		
Myalgia	19.6	6.8
Musculoskeletal pain**	12.4	10.8
Musculoskeletal stiffness	4.6	0.0
<b>Renal and Urinary Disorders</b>		
Blood creatinine increased	2.0	0.7
<b>General Disorders and Administrative Site Conditions</b>		
Fatigue	17.6	6.1
Pain	11.8	4.1
Chills	9.8	2.7
Influenza like illness	9.2	2.0
Malaise	7.2	0.7
Acute phase reaction	3.9	0.0
<b>Investigations</b>		
C-reactive protein increased	4.6	1.4

\* Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR

\*\* Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

### ***Renal Impairment***

Creatinine clearance was measured annually prior to dosing and changes in long-term renal function over 24 months were comparable in the Reclast and active control groups [see *Warnings and Precautions (5.3)*].

### ***Acute Phase Reaction***

Reclast was associated with signs and symptoms of an acute phase reaction: myalgia (17.1%), fever (15.7%), fatigue (12.4%), arthralgia (11.1%), pain (10.5%), chills (9.8%), headache (9.8%), influenza-like illness (8.5%), malaise (5.2%), and back pain (3.3%), which occurred within the first 3 days following the dose of Reclast. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset but resolution could take up to 7-14 days. The incidence of these symptoms decreased with subsequent doses of Reclast.

### ***Atrial Fibrillation***

The incidence of all atrial fibrillation adverse events in the Reclast treatment group was 3.3% (5 out of 153) compared to 2.0% (3 out of 148) in the active control group. However, there were no patients with adjudicated serious adverse events of atrial fibrillation in the Reclast treatment group.

### ***Laboratory Findings***

There were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

### ***Injection Site Reactions***

There were 4 patients (2.6%) on Reclast vs. 2 patients (1.4%) on active control with local site reactions.

### ***Osteonecrosis of the Jaw***

In this trial there were no cases of osteonecrosis of the jaw [*see Warnings and Precautions (5.4)*].

### **Glucocorticoid-Induced Osteoporosis**

The safety of Reclast in men and women in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in a randomized, multicenter, double-blind, active controlled, stratified study of 833 men and women aged 18-85 years treated with  $\geq 7.5$  mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy:  $\leq 3$  months prior to randomization (prevention subpopulation), and  $> 3$  months prior to randomization (treatment subpopulation).

The duration of the trial was one year with 416 patients exposed to Reclast administered once as a single 5 mg dose in 100 mL infused over 15 minutes, and 417 patients exposed to a commercially-available oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was similar between treatment groups: 0.9% in the Reclast group and 0.7% in the active control group. The incidence of serious adverse events was similar between the Reclast treatment and prevention groups, 18.4% and 18.1%, respectively, and the active control treatment and prevention groups, 19.8% and 16.0%, respectively. The percentage of subjects who withdrew from the study due to adverse events was 2.2% in the Reclast group vs. 1.4% in the active control group. The overall safety and tolerability were similar between Reclast and active control groups with the exception of a higher incidence of post-dose symptoms in the Reclast group that occurred within 3 days after infusion. The overall safety and tolerability profile of Reclast in glucocorticoid-induced osteoporosis was similar to the adverse events reported in the Reclast postmenopausal osteoporosis clinical trial.

Adverse reactions reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis treatment trial or reported more frequently in the treatment and prevention of glucocorticoid-induced osteoporosis trial included the following: abdominal pain (Reclast 7.5%; active control 5.0%), and musculoskeletal pain (Reclast 3.1%; active control 1.7%). Other musculoskeletal events included back pain (Reclast 4.3%, active control 6.2%), bone pain (Reclast 3.1%, active control 2.2%), and pain in the extremity (Reclast 3.1%, active control 1.2%). In addition, the following adverse events occurred more frequently than in the postmenopausal osteoporosis trial: nausea (Reclast 9.6%; active control 8.4%), and dyspepsia (Reclast 5.5%; active control 4.3%).

### ***Renal Impairment***

Renal function measured prior to dosing and at the end of the 12 month study was comparable in the Reclast and active control groups [*see Warnings and Precautions (5.3)*].

### ***Acute Phase Reaction***

Reclast was associated with signs and symptoms of a transient acute phase reaction that was similar to that seen in the Reclast postmenopausal osteoporosis clinical trial.

### ***Atrial Fibrillation***

The incidence of atrial fibrillation adverse events was 0.7% (3 of 416) in the Reclast group compared to no adverse events in the active control group. All subjects had a prior history of atrial fibrillation and no cases were adjudicated as serious adverse events. One patient had atrial flutter in the active control group.

### ***Laboratory Findings***

There were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

### ***Injection Site Reactions***

There were no local reactions at the infusion site.

### ***Osteonecrosis of the Jaw***

In this trial there were no cases of osteonecrosis of the jaw [*see Warnings and Precautions (5.4)*].

## **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 4.

**Table 4. 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**

<b>System Organ Class</b>	<b>5 mg IV Reclast % (N = 177)</b>	<b>30 mg/day x 2 Months risedronate % (N = 172)</b>
<b>Infections and Infestations</b>		
Influenza	7	5
<b>Metabolism and Nutrition Disorders</b>		
Hypocalcemia	3	1
Anorexia	2	2
<b>Nervous System Disorders</b>		
Headache	11	10
Dizziness	9	4
Lethargy	5	1
Paresthesia	2	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnea	5	1
<b>Gastrointestinal Disorders</b>		
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
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	3	2
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>		
Arthralgia	9	11
Bone Pain	9	5
Myalgia	7	4
Back Pain	4	7
Musculoskeletal Stiffness	2	1
<b>General Disorders and Administrative Site Conditions</b>		
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:

### ***Acute Phase Reactions***

Fever, headache, flu-like symptoms, nausea, vomiting, diarrhea, arthralgia, and myalgia. Symptoms may be significant and lead to dehydration.

### ***Acute Renal Failure***

Cases of acute renal failure requiring hospitalization and/or dialysis or with a fatal outcome have been rarely reported. Increased serum creatinine was reported in patients with 1) underlying renal disease, 2) dehydration secondary to fever, sepsis, gastrointestinal losses, or diuretic therapy, or 3) other risk factors such as advanced age, or concomitant nephrotoxic drugs in the post-infusion period. Transient rise in serum creatinine can be correctable with intravenous fluids;

### ***Allergic Reactions***

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

### ***Hypocalcemia***

Rare cases of hypocalcemia have been reported.

### ***Osteonecrosis of the Jaw***

Rare cases of osteonecrosis of the jaw have been reported.

### ***Ocular Adverse Events***

Rare cases of the following events have been reported: conjunctivitis, iritis, iridocyclitis, uveitis, episcleritis\_scleritis and orbital inflammation/edema.

### ***Other***

Rare cases of hypotension in patients with underlying risk factors have 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.

### 7.4 Drugs Primarily Excreted by the Kidney

Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise or other risk factors [*see Warnings and Precautions (5.3)*]. In patients with renal impairment, the exposure to concomitant medications that are primarily renally excreted (e.g., digoxin) may increase. Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidney.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.6)*].

**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.

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 daily subcutaneous doses of zoledronic acid beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased at approximately  $\geq 0.3$  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 at  $\geq 0.1$  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 during gestation, adverse fetal effects were observed at about 2 and 4 times human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations.

In pregnant rabbits given daily subcutaneous doses of zoledronic acid during gestation at doses  $\leq 0.4$  times the anticipated human systemic exposure following a 5 mg intravenous dose (based on a  $\text{mg}/\text{m}^2$  comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses  $\geq 0.04$  times the human 5 mg intravenous dose, based on a  $\text{mg}/\text{m}^2$  comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia [*see Nonclinical Toxicology (13.3)*].

### 8.3 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.

### 8.4 Pediatric Use

Reclast 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  $0.431 \text{ gm}/\text{cm}^2$ , 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 zoledronic acid use in children did not raise any new safety findings beyond those previously seen in adults treated for Paget's disease of bone and treatment of osteoporosis including osteonecrosis of the jaw (ONJ) and renal impairment. However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypocalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within three days after the first infusion and became less common with repeat dosing. No cases of ONJ or renal impairment were observed in this study. Because of long-term retention in bone, Reclast 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 osteogenesis 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 minutes. Mean  $C_{max}$  and  $AUC_{(0-last)}$  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**

The combined osteoporosis trials included 4863 Reclast-treated patients who were at least 65 years of age, while 2101 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.

Of the patients receiving Reclast in the osteoporosis study in men, glucocorticoid-induced osteoporosis, and Paget's disease studies, 83, 116, and 132 patients, respectively were 65 years of age or over, while 24, 29, and 68 patients, respectively were at least 75 years of age.

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

### **8.6 Renal Impairment**

Reclast is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment. There are no safety or efficacy data to support the adjustment of the Reclast dose based on baseline renal function. Therefore, no dosage adjustment is required in patients with a creatinine clearance of  $\geq 35$  mL/min [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*]. Risk of acute renal failure may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, advanced age, etc. [*see Post-Marketing Experience (6.2)*].

### **8.7 Hepatic Impairment**

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

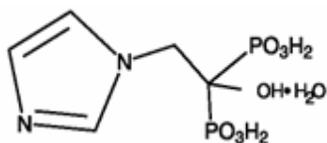
## **10 OVERDOSAGE**

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 the Reclast solution for infusion is approximately 6.0 – 7.0.

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 bisphosphonate and 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 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 hour 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 ( $AUC_{0-24h}$ ) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean  $AUC_{0-24h}$  ratios for cycles 2 and 3 versus 1 of  $1.13 \pm 0.30$  and  $1.16 \pm 0.36$ , 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 ( $\pm$  SD)  $39 \pm 16\%$  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  $3.7 \pm 2.0$  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  $\pm$  SD]  $403 \pm 118$  ng/mL vs.  $264 \pm 86$  ng/mL) and a 10% increase in the total AUC ( $378 \pm 116$  ng x h/mL vs.  $420 \pm 218$  ng x h/mL). The difference between the AUC means was not statistically significant.

### **Specific Populations**

**Pediatrics:** Reclast is not indicated for use in children [see *Pediatric Use* (8.4)].

**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 creatinine clearance  $> 80$  mL/min (N=37), patients with creatinine clearance = 50-80 mL/min (N=15) showed an average increase in plasma AUC of 15%, whereas patients with 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  $\geq 35$  mL/min. Reclast is contraindicated in patients with creatinine clearance  $< 35$  mL/min and in those with evidence of acute renal impairment due to an increased risk of renal failure [see *Contraindications* (4.2), *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.6)].

## **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  $\geq 0.002$  times the human intravenous dose of 5 mg, based on a  $\text{mg}/\text{m}^2$  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  $\leq 0.1$  times the human intravenous dose of 5 mg, based on a  $\text{mg}/\text{m}^2$  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 an 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 an AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

### **13.2 Animal 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  $\mu\text{g}/\text{kg}$  ( $< 0.1$  to 3.5 times human exposure at the 5 mg intravenous dose, based on a  $\text{mg}/\text{m}^2$  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 a  $\text{mg}/\text{m}^2$  comparison. Bone tissue was normal and there was no evidence of a mineralization defect, no accumulation of osteoid, and no woven bone.

### 13.3 Reproductive and Developmental Toxicology

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 ( $\geq 0.3$  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 ( $\geq 0.1$  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 an 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  $\leq 0.4$  times the anticipated human systemic exposure following a 5 mg intravenous dose, based on a  $\text{mg}/\text{m}^2$  comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses  $\geq 0.04$  times the human 5 mg intravenous dose, based on a  $\text{mg}/\text{m}^2$  comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

## 14 CLINICAL STUDIES

### 14.1 Treatment of Postmenopausal Osteoporosis

**Study 1:** The efficacy and safety of Reclast in the treatment of postmenopausal osteoporosis was demonstrated in Study 1, 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, and 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 5.

**Table 5. Proportion of Patients with New Morphometric Vertebral Fractures**

Outcome	Reclast (%)	Placebo (%)	Absolute Reduction	Relative Reduction in
			in Fracture Incidence % (95% CI)	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 fracture (0–3 years)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)*

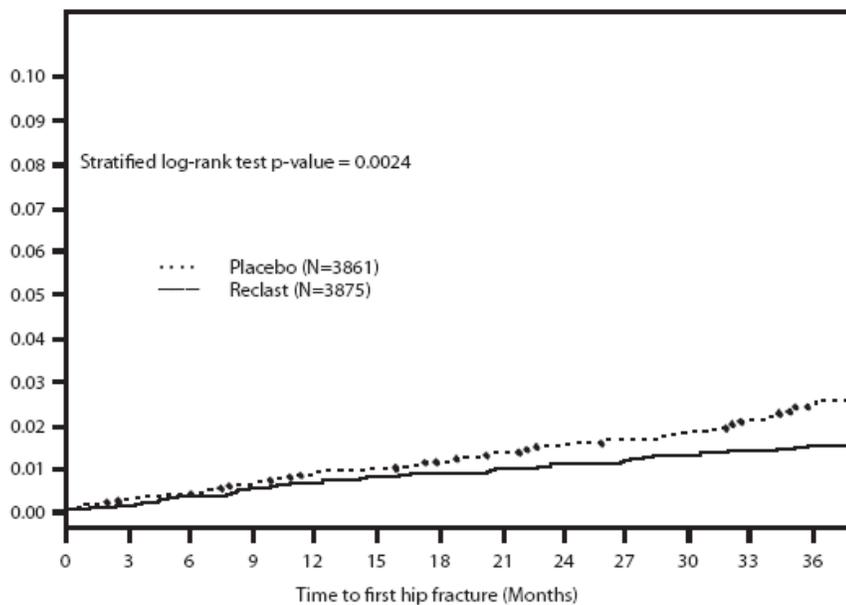
\* p < 0.0001

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 6.

**Table 6. Between-Treatment Comparisons of the Incidence of Clinical Fracture Variables Over 3 Years**

<b>Outcome</b>	<b>Reclast (N= 3875) Event Rate n (%)<sup>+</sup></b>	<b>Placebo (N= 3861) Event Rate n (%)<sup>+</sup></b>	<b>Absolute Reduction in Fracture Incidence % (95% CI)<sup>+</sup></b>	<b>Relative Risk Reduction in Fracture Incidence % (95% CI)</b>
Any clinical fracture <sup>(1)</sup>	308 (8.4)	456 (12.8)	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture <sup>(2)</sup>	19 (0.5)	84 (2.6)	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture <sup>(3)</sup>	292 (8.0)	388 (10.7)	2.7 (1.4, 4.0)	25 (13, 36)*

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

<sup>+</sup> Event rates based on Kaplan-Meier estimates at 36 months

<sup>(1)</sup> Excluding finger, toe, and facial fractures

<sup>(2)</sup> Includes clinical thoracic and clinical lumbar vertebral fractures

<sup>(3)</sup> Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

### ***Effect on Bone Mineral Density (BMD)***

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]).

**Study 2:** The efficacy and safety of Reclast in the treatment of patients with osteoporosis who suffered a recent low-trauma hip fracture was demonstrated in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50-95 years (mean age of 74.5). Concomitant osteoporosis therapies excluding other bisphosphonates and parathyroid hormone were allowed. Reclast was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes. The study continued until at least 211 patients had confirmed clinical fractures in the study population. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day for at least 14 days prior to the study drug infusions. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Reclast significantly reduced the incidence of any clinical fracture by 35%. There was also a 46% reduction in the risk of a clinical vertebral fracture (Table 7).

**Table 7. Between-Treatment Comparisons of the Incidence of Key Clinical Fracture Variables**

<b>Outcome</b>	<b>Reclast (N=1065) Event Rate n (%)<sup>+</sup></b>	<b>Placebo (N=1062) Event Rate n (%)<sup>+</sup></b>	<b>Absolute Reduction in Fracture Incidence % (95% CI)<sup>+</sup></b>	<b>Relative Risk Reduction in Fracture Incidence % (95% CI)</b>
Any clinical fracture <sup>(1)</sup>	92 (8.6)	139 (13.9)	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture <sup>(2)</sup>	21 (1.7)	39 (3.8)	2.1 (0.5, 3.7)	46 (8, 68)*

\*p-value <0.05, \*\*p-value <0.005

<sup>+</sup> Event rates based on Kaplan-Meier estimates at 24 months

<sup>(1)</sup> Excluding finger, toe and facial fractures

<sup>(2)</sup> Including clinical thoracic and clinical lumbar vertebral fractures

### ***Effect on Bone Mineral Density (BMD)***

Reclast significantly increased BMD relative to placebo at the hip and femoral neck at all timepoints (12, 24, and 36 months). Treatment with Reclast resulted in a 6.4% increase in BMD at the total hip and a 4.3% increase at the femoral neck over 36 months as compared to placebo.

### **14.2 Prevention of Postmenopausal Osteoporosis**

The efficacy and safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged  $\geq 45$  years, who were stratified by years since menopause: Stratum I women < 5 years from menopause (n=224); Stratum II women  $\geq 5$  years from menopause (n=357). Patients within Stratum I and II were randomized to one of three treatment groups: (1) Reclast given at randomization and at Month 12 (n=77) in Stratum I and (n=121) in Stratum II; (2) Reclast given at randomization and placebo at Month 12 (n=70) in Stratum I and (n=111) in Stratum II; and (3) Placebo given at randomization and Month 12 (n=202). Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline.

### ***Effect on Bone Mineral Density (BMD)***

Reclast significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 6.3% increase in BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

Reclast also significantly increased total hip BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 2.6% increase in BMD in Stratum I patients and 2.1% in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.1% decrease in BMD in Stratum I patients and 1.0% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 4.7% increase in BMD in Stratum I patients and 3.2% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

### **14.3 Osteoporosis in Men**

The efficacy and safety of Reclast in men with osteoporosis or significant osteoporosis secondary to hypogonadism, was assessed in a randomized, multicenter, double-blind, active controlled, study of 302 men aged 25-86 years (mean age of 64). The duration of the trial was two years. Patients were randomized to either Reclast which was administered once annually as a 5 mg dose in 100 mL infused over 15 minutes for a total of up to two doses, or to an oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 IU of vitamin D supplementation per day.

### ***Effect on Bone Mineral Density (BMD)***

An annual infusion of Reclast was non-inferior to the oral weekly bisphosphonate active control based on the percentage change in lumbar spine BMD at Month 24 relative to baseline (Reclast: 6.1% increase; active control: 6.2% increase).

## 14.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The efficacy and safety of Reclast to prevent and treat glucocorticoid-induced osteoporosis (GIO) was assessed in a randomized, multicenter, double-blind, stratified, active controlled study of 833 men and women aged 18-85 years (mean age of 54.4 years) treated with  $\geq 7.5$  mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy:  $\leq 3$  months prior to randomization (prevention subpopulation), and  $> 3$  months prior to randomization (treatment subpopulation). The duration of the trial was one year. Patients were randomized to either Reclast which was administered once as a 5 mg dose in 100 mL infused over 15 minutes, or to an oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 IU of vitamin D supplementation per day.

### *Effect on Bone Mineral Density (BMD)*

In the GIO treatment subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to the active control at one year (Reclast 4.1%, active control 2.7%) with a treatment difference of 1.4% ( $p < 0.001$ ). In the GIO prevention subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to active control at one year (Reclast 2.6%, active control 0.6%) with a treatment difference of 2.0% ( $p < 0.001$ ).

### *Bone Histology*

Bone biopsy specimens were obtained from 23 patients (12 in the Reclast treatment group and 11 in the active control treatment group) at Month 12 treated with an annual dose of Reclast or daily oral active control. Qualitative assessments showed bone of normal architecture and quality without mineralization defects. Apparent reductions in activation frequency and remodeling rates were seen when compared with the histomorphometry results seen with Reclast in the postmenopausal osteoporosis population. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

## 14.5 Treatment of Paget's Disease of Bone

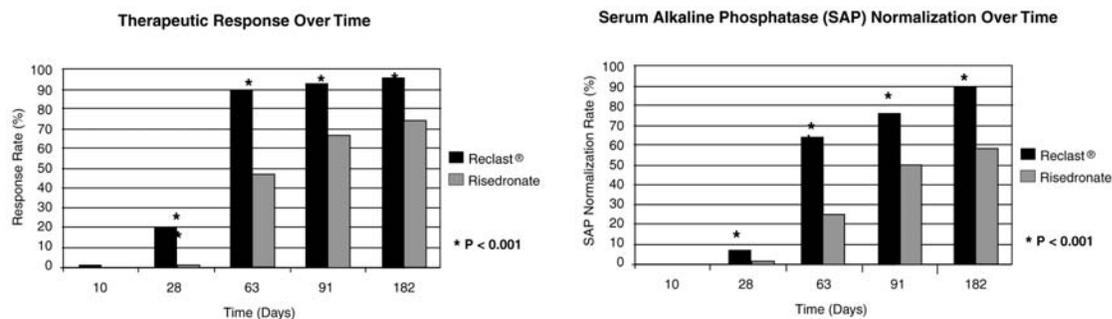
Reclast was studied in male and female patients with moderate to severe Paget's disease of bone, defined as serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry. Diagnosis was confirmed by radiographic evidence.

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  $\alpha$ -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/100 mL. 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.*

### Information for Patients

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

Reclast is contraindicated in patients with creatinine clearance < 35 ml/min. [*See Contraindications (4.2)*].

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 Warnings and Precautions (5.6)*].

There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates, including Reclast. Before being given Reclast, patients should tell their doctor if they are aspirin-sensitive.

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 patients with osteoporosis and the current recommended daily intake of calcium is 1200 mg and vitamin D is 800 IU – 1000 IU 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 following Reclast administration may reduce the incidence of these symptoms.

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

Severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Reclast. Consider withholding future Reclast treatment if severe symptoms develop.

Atypical femur fractures in patients on bisphosphonate therapy have been reported; patients with thigh or groin pain should be evaluated to rule out a femoral fracture.

T2011-XX

## MEDICATION GUIDE

### Reclast® (RE-clast)

#### (zoledronic acid)

#### Injection

Read the Medication Guide that comes with Reclast before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Reclast.

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

**You should not receive Reclast if you are already receiving Zometa. Both Reclast and Zometa contain zoledronic acid.**

#### **Reclast can cause serious side effects including:**

1. Low calcium levels in your blood (hypocalcemia)
2. Severe kidney problems
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint or muscle pain
5. Unusual thigh bone fractures

#### **1. Low calcium levels in your blood (hypocalcemia).**

Reclast may lower the calcium levels in your blood. If you have low blood calcium before you start taking Reclast, it may get worse during treatment. Your low blood calcium must be treated before you take Reclast. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take Reclast. Take calcium and vitamin D as your doctor tells you to.

#### **2. Severe kidney problems.**

Severe kidney problems may happen when you take Reclast. Severe kidney problems may lead to hospitalization or kidney dialysis and can be life-threatening. Your risk of kidney problems is higher if you:

- already have kidney problems
- take a diuretic or “water pill”
- do not have enough water in your body (dehydrated) before or after you receive Reclast
- are of advanced age since the risk increases as you get older
- take any medicines known to harm your kidneys

You should drink at least 2 glasses of fluid within a few hours before receiving Reclast to reduce the risk of kidney problems.

#### **3. Severe jaw bone problems (osteonecrosis).**

Severe jaw bone problems may happen when you take Reclast. Your doctor should examine your mouth before you start Reclast. Your doctor may tell you to see your dentist before you start Reclast. It is important for you to practice good mouth care during treatment with Reclast.

#### **4. Unusual thigh bone fractures.**

Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

## 5. Possible harm to your unborn baby.

**Reclast should not be used if you are pregnant.** Tell your doctor right away if you are pregnant or plan to become pregnant. Reclast may harm your unborn baby.

## 6. Bone, joint, or muscle pain

Some people who take bisphosphonates develop severe bone, joint, or muscle pain.

**Call your doctor right away if you have any of these side effects.**

### What is Reclast?

Reclast is a prescription medicine used to:

- Treat or prevent osteoporosis in women after menopause. Reclast helps reduce the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.
- Treat or prevent osteoporosis in either men or women who will be taking corticosteroid medicines for at least one year.
- Treat certain men and women who have Paget's disease of the bone.

It is not known how long Reclast works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if Reclast is still right for you.

Reclast is not for use in children.

### Who should not take Reclast?

Do not take Reclast if you:

- Have low levels of calcium in your blood
- Have kidney problems
- Are allergic to zoledronic acid or any of its ingredients. A list of ingredients is at the end of this leaflet.

### What should I tell my doctor before taking Reclast?

**Before you start Reclast, be sure to talk to your doctor if you:**

- Have low blood calcium.
- Have kidney problems.
- Had parathyroid or thyroid surgery (glands in your neck).
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome) or have had parts of your intestine removed.
- Have asthma (wheezing) from taking aspirin.
- Plan to have dental surgery or teeth removed.
- Are pregnant, or plan to become pregnant. Reclast may harm your unborn baby. **Reclast should not be used if you are pregnant.**
- Are breastfeeding or plan to breastfeed. It is not known if Reclast passes into your milk and may harm your baby.

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how Reclast works.

### Especially tell your doctor if you are taking:

- An antibiotic. Certain antibiotic medicines called aminoglycosides may increase the effect of Reclast in lowering your blood calcium for a long period of time.
- A diuretic or "water pill".
- Non-steroidal anti-inflammatory medicines (NSAIDs).

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

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

## How will I receive Reclast?

- Your doctor will tell you how often you will receive Reclast.
- Reclast is given by infusion into your vein (intravenously). Your infusion should last at least 15 minutes.
- Before you receive Reclast, drink at least 2 glasses of fluid (such as water) within a few hours as directed by your doctor.
- You may eat before your treatment with Reclast.
- If you miss a dose of Reclast, call your doctor or healthcare provider to schedule your next dose.

## What are the possible side effects of Reclast?

Reclast may cause serious side effects.

- See **“What is the most important information I should know about Reclast?”**

The most common side effects of Reclast included:

- Fever
- Pain in your bones, joints or muscles
- Pain in your arms and legs
- Headache
- Flu-like illness (fever, chills, bone, joint, or muscle pain, fatigue)
- Nausea
- Vomiting
- Diarrhea

Talk to your doctor about things you can do to help decrease some of these side effects that might happen with a Reclast infusion.

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Reclast. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## General information about safe and effective use of Reclast.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes 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 health professionals.

For more information, go to: [www.RECLAST.com](http://www.RECLAST.com) or call 1-866-732-5278.

## What are the ingredients in Reclast?

Active ingredient: zoledronic acid monohydrate

Inactive ingredients: mannitol and sodium citrate.

Distributed by:

Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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/s/  
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GEORGE S BENSON  
08/31/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21817/S-012**

**MEDICAL REVIEW(S)**

**Memorandum**

**To:**

NDA#	DARRTS SDN	EDR#	Document Type	Letter Date	Received Date
21-817	138	0058	General Correspondence- EU HCP letter	3/18/2010	3/18/2010
	146	0068	Labeling Supplement –S006	9/8/2010	9/8/2010
	--	N/A	OSE Review	--	2/4/2011
	158	0079	CBE-30 Labeling Supplement –S007	4/8/2011	4/8/2011
	162	0084	Prior Approval Supplement –S008	5-13-11	5-13-11

(b) (4)

**Through:** Theresa Kehoe, M.D., Team Leader, DRUP

**From:** Marcea Whitaker, M.D., Medical Officer, DRUP

**Date:** August 30, 2011

**Re:** Reclast/zoledronic acid- Renal Failure AERS update

**Sponsor:** Novartis

**Background:** Information regarding the effects of Reclast on renal function has been readily available and communicated to the medical community via Medwatch in June 2008<sup>1</sup>, updated label changes in March 2009, and an FDA Drug Safety Newsletter of 2009<sup>2</sup> (see table below). Due to continued reports of serious renal dysfunction requiring dialysis or with a fatal outcome associated with Reclast, and due to additional labeling changes proposed by the sponsor (September 2009), additional case analyses were performed in AERS.

Country/Agency	Date	Action
U.S.	June 2008	MedWatch
	March 2009	Labeling Update Drug Safety Newsletter
EMA	April 2010	Updated Label
	March 2010	DHCP letter
Canada	October 2010	DHCP letter

<sup>1</sup> <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm120143.htm>

<sup>2</sup> <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm167883.htm>

## Review:

Zoledronic acid, marketed for oncologic indications as Zometa®, contains a dose-adjustment for patients with decreased creatinine clearance (see Table 1) and represents a 25% dose reduction over the range of moderate renal impairment. The dose-adjustment was based on a rate of 9-15% of subjects who exhibited renal deterioration (defined as an increase in creatinine of 0.5 mg/dl over baseline) during the clinical trials.

**Table 1: Reduced Doses for Patients with Baseline CrCl  $\leq$ 60 mL/min**

Baseline Creatinine Clearance (mL/min)	Zometa Recommended Dose*
>60	4 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3 mg

\*Doses calculated assuming target AUC of 0.66(mg·hr/L) (CrCl = 75 mL/min)

When zoledronic acid was approved for the treatment of postmenopausal osteoporosis (marketed as Reclast® in the United States), the clinical pharmacology and pharmacometrics reviewers felt that no dose adjustments were required because 1) small numbers of trial participants developed renal deterioration (only 1.8% of subjects receiving Reclast vs 0.8% of placebo subjects), 2) Reclast would not be recommended in women with severe renal impairment, 3) the renal deterioration was transient, and 4) there was no cumulative effect or trend seen with repeat dosing (see review dated August 9, 2007). However, regular monitoring of renal function and discontinuation of treatment if renal function deteriorated were recommended.

In 2009, in accordance with a 1-year post-marketing review, DPVII identified and reviewed 30 cases of acute renal failure associated with Reclast (review dated January 8, 2009). Based on this case series, the renal dysfunction and postmarketing sections of the Reclast label were updated as follows:

### **Highlights**

- *Renal toxicity may be greater in patients with underlying renal impairment or with other risk factors such as dehydration that may occur in the post-dosing period. Patients with severe renal impairment (creatinine clearance <35 mL/min) should not receive Reclast. Monitor serum creatinine before each dose (5.3)*

### **Under Warning and Precautions**

#### **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 should not be used 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)].*

*Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or other risk factors including concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Reclast administration. Renal impairment has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis occurred in patients with underlying moderate to severe renal impairment [see Post-Marketing Experience (6.2)]. Renal impairment may lead to increased exposure of concomitant medications that are primarily renally excreted [see Drug Interactions (7.4)].*

*Serum creatinine should be measured 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. 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)]. Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidney [see Drug Interactions (7.4)].*

## **6.2 Postmarketing Experience**

### **Acute Renal Impairment**

*Transient rise in serum creatinine correctable with intravenous fluids; acute renal failure requiring hospitalization and/or dialysis. Increased serum creatinine was reported in patients with 1) underlying renal disease, 2) dehydration secondary to fever, gastrointestinal losses, or diuretic therapy, or 3) other risk factors such as concomitant nephrotoxic drugs in the post-infusion period.*

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

**OSE Review/Recommendations:**

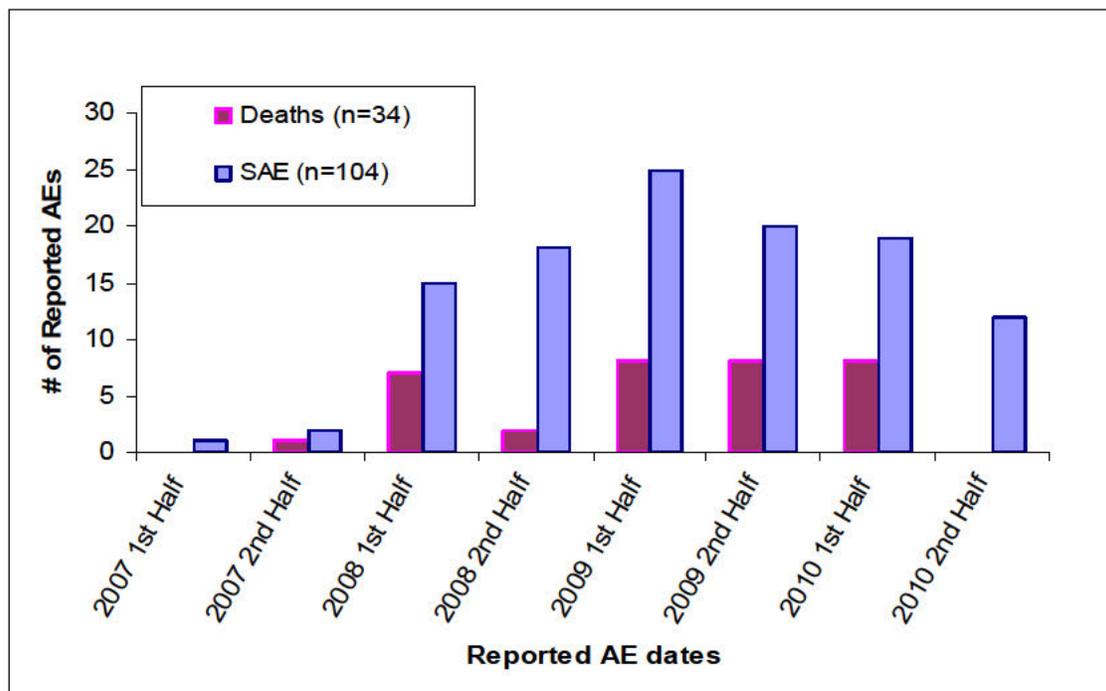
Due to additional labeling changes proposed by the sponsor, additional case analyses were performed in AERS. The current OSE review focused on cases involving fatal acute renal failure (n=11) or patients requiring dialysis (n=9) that occurred between March 2009 and January 2011. (Note: This case series does not include *all* renal dysfunction cases during this time interval). Excluded cases represent duplicates, those occurring prior to March 2009, and those with unknown or with oncology indications. The reviewer stated that the cases strongly supported a causal relationship between Reclast and the development of acute renal failure.

“The case series showed patients of advanced age (average, 78 years) receiving Reclast infusions have multiple risk factors (e.g., baseline moderate renal impairment) that may promote nephrotoxicity.”



**Reviewer’s comment: There are currently no data available supporting dose adjustments in the PMO patient population (see additional comments below).**

Using SMQ Acute Renal Failure, the number of fatalities and serious adverse events continued to be reported after the 2009 labeling update (see table below). However, no fatalities have been reported since March 2010.



In addition to the proposed renal updates, OSE recommended that additional measures be instituted to assure safe use, namely, 1) a Drug Safety Communication, 2) strengthening the label for use in elderly patients with moderate renal impairment based on creatinine clearance, 3) and strengthening the label regarding monitoring of serum creatinine in at-risk patients.

**Reviewer's comments:**

- 1) Based on the prior review, the majority of cases of Reclast-associated renal insufficiency involved transient decreases in renal function that recovered with hydration and did not involve dialysis or death.**
- 2) No specific labeling recommendations were proposed.**
- 3) There are currently no data available supporting dose adjustments in the PMO patient population. The clinical pharmacology review of August 9, 2007, states: "Since the sponsor only studied one dose (5 mg/yr) in the pivotal Phase 3 study, the efficacy and safety of lower doses such as 1, 2, or 4 mg zoledronic acid/year have not been evaluated in the treatment of PMO in women."**
- 4) Of note, no fatal cases of acute renal failure have been reported since March 2010, suggesting a lag effect of the March 2009 labeling possible due to the nature of the yearly dosing regimen. The absence of more recent reports suggests that current labeling may be sufficient. In addition, based on the graph above, renal SAE reports have decreased since the first half of 2009.**

**Medical Officer Review:**

The cases reviewed by OSE were subsequently reviewed by DRUP. See Appendix A for the listing of cases. Summary data are listed below.

Demographics: Of the 21 cases captured by OSE, 18 cases were reported from the US. The majority of cases involved females (n=18). The mean age was 73.8 years (range 62-85). Ten cases had confounding medical conditions such as HTN, CAD/CHF, or DM.

Pre-existing renal disease: Eleven cases out of the 21 cases had pre-existing renal disease based on reported or calculated GFR using serum creatinine and reported weight (Cockcroft-Gault). Nine cases had eGFR < 60 ml/min and one case had eGFR <30 ml/min (See case #2 in attached Appendix A). All other baseline renal function measures were reported as serum creatinine. Baseline creatinine or creatinine clearance was missing in 10 cases.

Temporal Association: Seventeen cases had a temporal association ranging from 1 day to < 4 weeks.

Concomitant medical conditions/medications: Eight cases had known concomitant diuretic use, one case had concomitant NSAID use, and 2 cases had emesis or diarrhea. Ten cases had other contributing or inciting factors as a more likely cause of the renal dysfunction (i.e., UTI, rhabdomyolysis, intestinal infarct, sepsis, pancreatitis, refractory epilepsy, methotrexate use, and aortic valve stenosis).

Other: The majority of cases involved the first dose of Reclast, however, three cases had received a prior Reclast infusion without incident. Four renal biopsies were reported; two showed acute tubular necrosis consistent with Reclast (although, one case also involved sepsis with 14% bands). Six cases had insufficient information that prevented adequate evaluation.

**Reviewer's comment: Overall, there was a strong temporal association for acute renal failure and/or death in those receiving Reclast infusion in this case series. These events occurred mainly in subjects who were between the ages of 70-85 (63% of cases); however, six cases occurred in patients between the ages of 62 and 69. Most subjects had multiple risk factors, with 86% of cases having any of the following: pre-existing renal disease, diuretic use, concomitant Naiads, or contributing/inciting factors that promoted dehydration or hypotension, with 50% of cases having more than one risk factor.**

Off-label use in patients with GFR < 30 ml/min has also been reported. Case #20 [see Appendix] (ISR# 6248401-3) was an 82 year-old female with hypertension and aortic valve stenosis who had a baseline creatinine of 1.4 but had a calculated creatinine clearance of 28 ml/min and should not have received Reclast therapy. In addition, during the National Osteoporosis Foundation, 8<sup>th</sup> International Symposium on Osteoporosis held in Washington, DC. (April 1-5, 2009), one speaker recommended "renal-dosing" for Reclast (defined as administering half the dose over 1 hour) in patients with stage 4/5 renal disease (<30 ml/min). However, no efficacy or safety is available in this patient subset.

(b) (4)

Although the zoledronic acid primary fracture study (2301) enrolled subjects with CrCl between 30 and above, labeling restricts dosing to < 35 ml/min. During further review, a prior clinical pharmacology review (Lau, 8/10/2007) and submitted PK data (see below) highlighted increased renal AEs events (change in serum cr > 0.5 mg/dl) in the patients in the 30-35 ml/min group.

## Increases in serum creatinine relative to baseline 9-11 days post-infusion by baseline creatinine clearance

### Overall

Increase in serum creatinine > 0.5mg/dL (9-11 days post-infusion)						
Zoledronic acid			Placebo			
Baseline CRCL	N	n	(%)	N	n	(%)
< 30 ml/min	0	0		3	0	(0.00)
= 30 - < 35 ml/min	47	5	(10.64)	65	1	(1.54)
= 35 - < 40 ml/min	84	2	(2.38)	95	3	(3.16)
= 40 - = 50 ml/min	372	7	(1.88)	358	4	(1.12)
> 50 - < 60 ml/min	550	7	(1.27)	513	2	(0.39)
= 60 ml/min	1267	21	(1.66)	1304	9	(0.69)
<b>All Patients</b>	<b>2320</b>	<b>42</b>	<b>(1.81)</b>	<b>2338</b>	<b>19</b>	<b>(0.81)</b>

Overall for zoledronic acid-treated patients, the incidence of an increase in serum creatinine >0.5 mg/dL relative to baseline was similar in patients whose baseline calculated CrCl was <60 mL/min compared with those whose baseline calculated CrCl was =60 mL/min (21 [1.99%] of 1053 patients vs. 21 [1.66%] of 1267 patients, respectively).

PMO data from Study 2301

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Therefore, the labeling was modified to retain a creatinine clearance <35 ml/min as the cut-off (b) (4)

### Dear Healthcare Provider Letter:

The sponsor has agreed to issue a Dear Healthcare Provider Letter.

### Conclusions/Recommendations

Based on AERS reporting, the reporting rates of acute renal failure do not appear to be increasing. However, the reviewer agrees that additional safeguards could improve the safety profile of Reclast and decrease the incidence of acute renal insufficiency requiring dialysis and the occurrence of fatal outcomes.

1. Contraindication for use in patients with creatinine clearance <35 ml/min. Due to the increased risk of renal dysfunction in patients with pre-existing renal disease, after internal discussion with OSE, the warning for use in patients with creatinine clearance < 35 ml/min should be upgraded to a contraindication. At least one case report resulted in death due to renal failure in a patient who should not have received Reclast. There is some evidence in the clinical community that off-label “renal dosing” is being used. The contraindication should deter this use.
2. Expand Contraindication in those with evidence of acute renal impairment. Subjects, regardless of baseline function, who also have an acute illness involving

- fluid losses are also at increased risk for renal dysfunction. Subjects with history or physical signs suggesting dehydration, should have Reclast therapy withheld until normovolemic status has been achieved.
3. Updated Warning and Precaution for those with pre-existing renal disease (CrCl > 35). The majority of patients at risk are those with pre-existing renal disease (30-60 ml/min) or other risk factors including advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Reclast administration. Therefore, we agree with the sponsor's proposed language in the Warnings and Precautions section. In addition, drug administration should be withheld if history or physical signs suggest dehydration. However, based on the case series, acute renal failure leading to death (n=3) or dialysis (n=4) occurred in 7 subjects with GFR < 60 ml/min. When combined with other risk factors, these subjects also appear to be Reclast at higher risk. Therefore, Reclast should be used with caution in patients with underlying renal dysfunction and in those patients with multiple risk factors, including advanced age. (b) (4)
  4. (b) (4)
  5. Baseline renal function should be defined by estimating GFR or creatinine clearance. Although not perfect, the creatinine clearance by Cockcroft-Gault or MDRD approximates GFR better than serum creatinine alone. Continued monitoring of creatinine and GFR should be continued in high-risk subjects (i.e., weekly/biweekly for the first month).
  6. Assessment of fluid status and concomitant medications (diuretics, NSIADS, or other nephrotoxic drugs) should be done prior to each dose. Rehydration may be necessary. No data are available to suggest a recommended amount of volume and should be tailored to limits of any underlying disease, i.e. congestive heart failure.
  7. No dose adjustment is indicated based on baseline renal function in the postmenopausal patient population.
  8. We agree with the issuance of a Dear Healthcare Provider Letter.

**Recommended regulatory action:**

1. A new contraindication for use in patients with creatinine clearance < 35 ml/min and those with evidence of acute renal impairment.
2. An updated Warning and Precaution for those with pre-existing renal disease (CrCl > 35). Reclast should be used with caution in patients with underlying renal dysfunction, especially in patients with other risk factors. In addition, drug administration should be withheld if history or physical signs suggest dehydration.

3. The labeling proposals for the Highlights, Warning and Precautions, and Postmarketing should be approved. Additional recommended labeling changes have been negotiated with the sponsor.
4. Continued monitoring of GFR should be continued in high-risk patients.
5. Assessment of fluid status and concomitant medications (diuretics, NSIADS, or other nephrotoxic drugs) should be done prior to each dose. Rehydration may be necessary and the dose should be withheld until normovolemic status has been achieved.
6. The labeling changes should be communicated to physicians via a Drug Safety Communication or a Dear Health Care Provider Letter. The sponsor intends to issue a Dear Healthcare Provider Letter following approval of the labeling.
7. Changes should be made to the Medication Guide to highlight the risk of dialysis and death from renal insufficiency in concordance with the Physician labeling.

Marcea B. Whitaker, M.D.  
Medical Officer  
Division of Reproductive and Urologic Products

## **Appendix A: Case Review**

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	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
1	6687580-0-00-01  415141  Nurse Louisiana	(b) (6)	83/F  130 lb  baseline CrCl 56.8 (FDA)	Rheumatologic Dx?, bladder CA in situ COPD, hypothyroid, OA, HTN, spinal stenosis, glaucoma, Elev plts, Ex-tob	Reclast 5 mg IV  For Osteopenia	10-5-09/  (b) (6) Death	Lasix 20 mg, synthroid 137 mcg	Prior c/o several mo h/o of malaise/weight loss/ "feeling bad". Pre- infusion Cr 0.7. One week after infusion → decreased U/O and ankle swelling. Lasix increased to 40 mg bid. Progressed to SOB at rest. Elev plt 800k, cr > 4.0 on (b) (6) Admitted (b) (6) Renal bx → vasculitis with significant damage to glomeruli, tx with plasmapheresis, cytoxan, EF 10%. Dialysis begun. Hospice. Expired (b) (6)  Cr 0.7-> >4.0 (b) (6)	Onset- 1 week after infusion -Rheum condition not specified (underlying renal disease?) -Vasculitis not caused by Reclast -diuretics  Likely pre-exisiting renal disease- Due to underlying rheum d/o  Case not clean
2	6927711-8 Case # 7543754  Physician Alabama	(b) (6)	66/F  baseline CrCl 59	UNK	Reclast 5mg	UNK/ HO/LT Dialysis	Combivent, toprol, verapamil, Coumadin, norvasc	(b) (6) pt presented with "allergic reaction", "acute renal failure", ischemic hepatitis, elevated K+ 9.5, low sodium 131 and decreased GFR from 59 (in May ??yr) → 47. Received Dialysis. Remains hospitalized at time of report-Outcome improved	-temporal association not proven -no details/UNK medical hx  Not good case

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
3	7060177-9 Case# 7639225  Physician Ohio	(b) (6)	74/F  CrCl 46 (FDA)	Osteoporosis, HTN, PMR, Colon Ca, COPD, CVA, cardiac revasc.	Reclast 2/10/10 (1 <sup>st</sup> dose)	2/10/10  Dialysis	Lisinopril Loperyl (loperamide) simvastatin PPI (omeprazole ) prednisone 10 mg, metoprolol	Additional reports showed that fatigue/lethargy/facial edema and decreased urinary output preceded Reclast infusion by 2 weeks. (b) (6) after 1 <sup>st</sup> Reclast dose, pt experienced lethargy/anorexia and presented to ER with facial edema- "acute renal failure" was noted -Cr of 19 (baseline 1.22) Ultrasound done (?renal). Dialysis x 2 mo.	Onset 2 weeks - symptoms preceded Reclast infusion (lethargy/anorexia/facial edema)  Not good case
4	6619000-6 Case 7308623  Physician Louisiana	(b) (6)	79/F 71 kg  ?CrCl	Osteoporosis	Relcast 2/1/10 (1 <sup>st</sup> dose)	HO 2/3/10 Dialysis-> Discharged	ASA, benicar (olmesartan) , ca Vit D	Chronic diarrhea. (b) (6) after 1 <sup>st</sup> dose, subject was hospitalized with acute renal failure with complications of UTI, hypotension (requiring neosynephrine drip), and severe metabolic acidosis, diarrhea. SCr of >6.0. Dialysis Discharged (b) (6)	Onset 2 days Chronic diarrhea + sounds like urosepsis and prerenal failure but no mention of antibiotics or blood cultures  No baseline Cr reported  Not good case
5	6308476 Case 7051952  Physician Massachusetts	(b) (6)	85/F 54 kg	Osteoporosis Rheumatoid arthritis	Reclast 5 mg 6/24/09 (1 <sup>st</sup> dose)	7/1/09 "acute renal failure"	MTX weekly	h/o RA on MTX. <1 week after infusion presented with "acute renal failure" Cr. 0.7 baseline to 7.2 (b) (6)	Onset 1 week -MTX can cause severe nephropathy or renal failure. Renal dysfunction with low dose MTX is rare

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
			CrCl 49 (FDA)					BUN 109 and bone marrow suppression – Hb 8.5, WBC 0.7, plt 193k (b) (6) and mucositis, myalgias. Pt hospitalized and received dialysis.	- anemia has been reported with Reclast but not more gross myelosuppression (all cell lines affected in this case suggesting MTX effect.
6	6379032-2 Case # 7132708  Physician California	(b) (6)	62/F 72 kg  CrCl 51	Osteoporosis Pre-existing infection HTN Neurogenic bladder	Reclast 5 mg	6/15/09 (1 <sup>st</sup> dose)  Dialysis	ASA Atenolol Wellbutrin Bentyl Crestor Reglan Morphine Prednisone Zolof Zetia Levoxyl Elavil Septra sulfonamide Klonopin Imodium Albuterol Omeprazole MVI Immunosup pressants Ca/Vit D3 Fluticasone	6/1/09 Pre-tx labs: CrCl=51, Hb 10.5, GFR 44 (b) (6) (although report states 2008), pt with “acute renal failure” associated with lethargy and confusion and was hospitalized. CrCl=14.9, Hb 9.5 pH 7.17, alb 3.0, Tprot 8.7. Discharged (b) (6) 6/2009 cr 4.4 (b) (6) +urine nitrate	Onset: 1 week + temporal association - pre-existing renal dysfunction - Tprotein/alb gap of 5.7 suggesting a paraproteinemia - unsure of reason for prednisone + urine nitrate  Confounding Not a good case
7	6184225-3 Case 6977722	(b) (6)	77/F 63Kg	Osteoporosis Hypertension	Reclast 1 <sup>st</sup> dose 4/2008 2 <sup>nd</sup> dose	Dialysis and discharged	Lexapro Lovaza Zestril	(b) (6) after 2 <sup>nd</sup> infusion (b) (6) pt had N/V. Also decreased U/O,	Onset 3 dyas + temporal relationship -on HCTZ (concomitant med)

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concom.Meds	Narrative/Case Description	Comment
	Physician Michigan		CrCl 54		3/26/09		Lescol Zetia HCTZ	edema, abd discomfort, anorexia, fatigue and malaise. Admitted on (b) (6), BUN/Cr of 65/8.0 (baseline 16- 26/0.9-1.0). Dialysis, CABGx4 (b) (6) Dialysis d/c'd BUN/cr down to 20/2.84 (date UNK). Renal biopsy showed ATN	Good case but on diuretics
8	7045821-4-00-01 Triage 423247  Family member Michigan	--	63/F 202#  No baseline info	Osteoporosis DM HTN	Reclast	9/18/10  Dialysis	UNK	(b) (6) after infusion c/o flu-like sxs, body aches, h/a, SOB. Presented ot ER (b) (6) for "kidney failure" and dialysis started. Renal bx (b) (6), (b) (6). Also UTI	Onset 6 days +temporal association -no concom. Meds listed -no baseline bun/cr -bx results not provided  Contributing factor UTI  Family member report
9	ISR 6993034-4- 00-01 Triage 429815  VA	---	83/F 180.4 #  CrCl 73.5	Osteoporosis HTN DM Hypothyroid CAD Hyperlipidemi a PVD Fx	Reclast 5 mg iv	8/24/10  Dialysis	HCTZ Lotrel Metformin zantac	Admitted (b) (6) (b) (6) after infusion with dehydration and "acute renal failure". Hydrated and dialysis started. Cr 8.32 (baseline 0.75). Renal US nl . Cr down to 2.56	Onset 10 days +temporal association -HCTZ  Good case but diuretics
10	ISR 6915953-7- 00-01 Triage 426355  Family member	(b) (6)	67/F 160 #  No baseline	UNK Osteoporosis	Reclast	8/5/10  Dialysis	UNK	Presented with severe swelling, SOB, LOC, elev K+, hypotension "kidney failure" "liver damage" (b) (6) after	Onset 1 day +temporal association Limited info

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight info	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
	Alabama							infusion. Dialysis and fluids given, intubation. Elev liver enzymes. Improvement/ dialysis stopped	
11	6689049-6 Case 7315307  Physician Ohio	(b) (6)	79/Male  Stage 3 by definition	Osteoporosis CKD (Stage 3) HTN DM Afib DVT BPH Dementia Anemia Hyperlipidemia Obstructive uropathy Nephrolithiasis Pyelonephritis	Reclast 5 mg	(b) (6)  Death	Inderal Amiodarone Glucotrol Flomax Paxil Allopurionol Zocor Aricept Namenda (memantine) Digoxin Allegra Verapamil Megace Ativan Coumadin Risperdal Novulin Zofrna Morphine Ancef calan	Baseline Stage 3 CKD (baseline Cr 1.2-1.6). Admitted (b) (6) with cold purple R lower limb due to extensive DVT, metabolic acidosis, "acute renal failure" (Cr 3.7), rhabdomyolysis. Started venous-venous hemofiltration, had thrombectomy but remained oliguric Sepsis/shock	-No temporal association -underlying renal disease Other reason for renal failure- (rhadomyolysis) Sepsis  Not related, not a good case
12	6645962-7 Case 7312100  Physician Belgium	(b) (6)	80/F	Osteoporosis	Aclasta 5 mg iv -2 <sup>nd</sup> dose	1/26/10 (previously reported as 2/16/10) death	Vit D Ca	(b) (6) after 2 <sup>nd</sup> infusion (b) (6) admitted for refractory epilepsy. Renal failure noted while in ICU - Cr	- temporal relationship (weeks) (23 days) -Renal failure likely due to hypotension related to refractory epilepsy

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Meds	Narrative/Case Description	Comment
								3.0 (pre-dose Cr 1.1, 1/17/10), hypocalcemia (Ca 2.5 mg/dL [ULN 5 mg/dL]). "Renal failure" noted.  (Likely error in reported Ca range, pt received Aclasta so likely SI units should have been reported – nl range 2.1-2.6 mmol/liter)	
13	6623890-0 Case 7303949  Physician Lebanon	(b) (6)	80/F	PMO Recent Hip fx s/p recent repair h/o CRF (Cr 2.5) Atrial fib	Aclasta 5 mg iv- 1 <sup>st</sup> dose	7/1/09	UNK	In (b) (6) presented with SOB/LOC, "renal failure" followed by cardiac arrest, coma, multisystem failure and death	-temporal relationship (days to weeks) Underlying renal disease  Not good case
14	6557403-9 Case 7248147  Physician France	--	?/M	Osteoporosis CVD HTN Prostate CA DM	Aclasta 5 mg	1/6/10	Irbesartan Furosemide Plavix Crestor Diamicon (oral hypoglycem ic) Omeprazole Ideos (CaC03) Disotrine (NTG) Paracetamol	Presented with acute abdominal pain (UNK date) and hypotension. "Renal failure" and hyperkalemia noted. Pt died (b) (6) after Aclasta infusion due to intestinal infarct	Onset 3 days + temporal association -on diuretic -Better explanation: CVD on drugs for hyperlipidemia → emboli (arrhythmia/cholesterol) + ischemic vasculature  Confounding  Not a good case

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
							Vit D3 Metformin oxycontin		
15	6528359-X Case 7238330  consumer Ecuador	(b) (6)	64/?  No baseline info	Osteoporosis Gout arthritis HTN Back pain due for surgical repair	Aclasta iv	8/1/09 Death	Amlodipine Irbesartan- HCTZ Colchicine urosin	Pt had difficulty walking due to back pain. On 9/10/09, lost balance and could not stand and was hospitalized on (b) (6). Pt died (b) (6) due to "renal failure" and cardiorespiratory arrest.	-no temporal association -no labs -On HCTZ/diuretic -Missing information
16	6418607-9 Case 7161336  Physician Florida	--	?/F  No baseline info	UNK	Reclast 5 mg – 1 <sup>st</sup> infusion	8/1/2009 Death	UNK	Developed "renal failure" and died (b) (6) (b) (6) after infusion. Had "normal" creatinine prior to infusion	Onset 1 month - no temporal association - limited information
17	7035918-7 Case 7622438  US	(b) (6)	75/F	Osteoporosis Abd discomfort Cardiac operation	Reclast	12/16/09 or 12/17/09 Death	Actonel-> GI upset Boniva -> GI upset Cholesterol reducers Thyroid medication	On UNK date (approx 2 weeks) after infusion, pt was ill, couldn't eat, had aches and pains, flu-like sxs. Hospitalized (b) (6) for "acute renal failure" Died (b) (6)	+ temporal relationship (2 weeks) -acute phase reaction -limited information
18	6423985-0 Case 7117651  Physician Texas	(b) (6)	69/F	Osteoporosis RA CHF	Reclast	5/13/09 Death	Lisinopril Spironlacton e Plavix Lipitor Coumadin dipyridamol	On (b) (6) (b) (6) presented with dehydration, arthralgia, decreased U/O, and flu- like sxs. Cr. 6.9. Diagnosed with	+ temporal relationship 1week Acute phase reaction -diuretic use -pancreatitis

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
							e	“kidney failure”. CT showed pancreatitis and distended GB. Improved w/ IVF (Cr=0.78). Pt readmitted and then expired after discharge.	
19	6716482-6 Case 7352581  Physician Ohio	(b) (6)	73/F 54 kg  CrCl 42 (FDA)	Osteoporosis Osteoarthritis RA Chondrocalcinosis pyrophosphate DM HTN COPD Tob abuse	Reclast 5 mg	3/1/10 Death (b) (6)	Rituxan Nexium Herupex? Metformin Foradil (fomoterol) Arava Prednisone HCTZ Albuterol Exforge (Ca channel blocker and ARB) Januvia(sita gliptin) Tenex Vicodin Bit B Solumderol Mirapex (for parkinsons) Folate Patanese Vit C Ca ASA	Flare of RA on (b) (6), sCr 2.4 and wbc 15k w/ 14% bands. On (b) (6) 0 Cr2.3. On (b) (6) sCr 6.0. Renal biopsy showed ATN. Pt expired (b) (6) due to renal failure, sepsis and DVT. Baseline Cr 1.0 (1/1/10)	+temporal association (1 week) - Sepsis contributing factor -diuretic -underlying renal disease - Renal bx showing ATN

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
20	6248401-3 Case 7033443  Physician Florida	--	82/F 58 kg  CrCl 28.3 (FDA)	Osteoporosis/F x Insomnia Dementia Spinal laminectomy AV stenosis RBBB Vit B def Hyperlipidemi a OA HTN Gout Cataract operation Uterine prolapse/hyster ectomy	Reclast 5 mg	6/10/09	Ambient Dilaudid Namenda (memantidin e for alzheimers) Benicar Toprol Vytorin Tylenol Exelon (rivastigmin e – alzheimers) Pantoprazol e Lotrel (amolodipin e/benzapril) MVI Ca/Vit D ASA	Baseline BUN/cr 3/2009 of 29/1.4. On (b) (6), presented to ER with weakness, lethargy, anxiety, respiratory distress, tachypnea, nasal flaring, bilateral crackles, decreased appetite. Cr 17.0 and diagnosed with bradycardia, decreased LOC, and “acute renal failure”. She became hypotensive and was unresponsive. DNR status/comfort care. Pt expired	+temporal association (12 days) -known hx of AV stenosis- normal course of endstage disease -CrCl < 30 should not have received drug
21	6550825-1 Case 7189899  Physician Kentucky	(b) (6)	69/F 38kg (84 lbs)  CrCl 35 (FDA)	Osteoporosis RA Vit B12 def Scoliosis Dehydration diverticulitis	Reclast 5 mg	12/1/07 10/8/09  death	Remicade Prednisone Vit B12 advil	11 days following infusion, she developed nausea, abdominal pain, pancreatitis, UTI and “severe renal failure”, Hospitalized (b) (6) for dehydration, decreased U/O, lethargy and confusion and dialysis started. Cr 4.1, GFR 11 on (b) (6) (pre-dose Cr 0.9, GFR	+temporal association 11 days -NSAID use -pancreatitis –contributing cause

	ISR# Case# Source	Pt ID	Age/ Sex/ Weight	PMH	Drug/Dose Indication	Dates of Use/ Event Date	Concon.Med s	Narrative/Case Description	Comment
								56 on (b) (6). Decrease in H/H from 11.4 to 9.0. CT showed gallstone pancreatitis, UA showed UTI. Pt expired (b) (6) following hemorrhage causing respiratory event- thought due to "possible PE".	

The renal deterioration caused by Zometa (zoledronic acide) was multifactorial, however, acute tubular necrosis (ATN) has been described as the potential mechanism. Renal biopsy of 6 patiens iwht rneal deterioration following Zometa (multiple myeloma, etc.) showed signs of ATN tubular cell degeneration, loss of the brush border and apoptosis. In general these changes should be present in the absence of glomerular pathology, interstitial nephritis or vascular disease.

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/s/  
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MARCEA B WHITAKER  
08/31/2011

THERESA E KEHOE  
08/31/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21817/S-012**

**OTHER REVIEW(S)**

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

Date: August 8, 2011

To: Jennifer Mercier  
Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

From: Quynh-Van Tran, PharmD, BCPP  
Regulatory Review Officer  
Division of Drug Marketing, Advertising and Communications  
(DDMAC)

Subject: DDMAC Comments on the Dear Health Care Provider (DHCP)  
Letter for Reclast<sup>®</sup> (zoledronic acid) injection (NDA 21817)

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This consult is in response to DRUP's July 28, 2011, request for DDMAC's review of proposed DHCP letter for Reclast<sup>®</sup> (zoledronic acid) injection regarding the contraindication in patients with severe renal impairment.

DDMAC appreciates the opportunity to provide comments on the proposed DHCP letter. Please see attached Reclast's DHCP letter with our comments incorporated therein.

If you have any questions, please contact Quynh-Van Tran, (301) 796-0185, or [quynh-van.tran@fda.hhs.gov](mailto:quynh-van.tran@fda.hhs.gov).

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/s/  
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QUYNH-VAN TRAN  
08/08/2011

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management

**PATIENT LABELING REVIEW**

Date: July 1, 2011

To: Scott Monroe, M.D., Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Acting Team Leader, Patient Labeling Reviewer,  
**Division of Risk Management (DRISK)**

Melissa Hulett, MSBA, BSN, RN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): Reclast (zolendronic acid)

Dosage Form/Route: Injection

Application Type/Number: NDA 21-817

Supplement Number 012

TSI Number: 621

Applicant: Novartis Pharmaceuticals Corporation

OSE RCM #: 2011-1781

## 1 INTRODUCTION

On May 13, 2011 Novartis submitted a prior approval supplement [REDACTED] (b) (4) [REDACTED] for Reclast (zolendronic acid) Injection. This submission provides for the addition of safety information regarding renal impairment to the Reclast labeling.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to provide a targeted review of the renal impairment labeling for the Applicant's proposed Medication Guide (MG) for Reclast (zolendronic acid) Injection.

[REDACTED] (b) (4)

## 2 MATERIAL REVIEWED

- Draft Reclast (zolendronic acid) Injection Medication Guide (MG) submitted May 13, 2011 and received by DRISK on June 28, 2011
- Draft Reclast (zolendronic acid) Injection Prescribing Information (PI) submitted May 13, 2011, revised by the Review Division throughout the current review cycle and received by DRISK on June 28, 2011
- DDMAC review of the Reclast (zolendronic acid) Injection Medication Guide (MG) dated June 29, 2011

## 3 REVIEW METHODS

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The proposed MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated and clean versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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ROBIN E DUER  
07/01/2011

LASHAWN M GRIFFITHS  
07/01/2011

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

*Memorandum*

**Date:** June 30, 2011

**To:** Theresa Kehoe, MD – Medical Team Leader  
Jennifer Mercier – Chief, Project Management Staff  
Meredith Alpert – Safety Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

**From:** Michelle Safarik, MSPAS, PA-C – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** DDMAC comments on draft Reclast product labeling (PI)  
NDA 021817

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This consult is in response to DRUP's June 20, 2011, request for DDMAC review of updated safety information regarding renal impairment to be included in the Reclast PI and Medication Guide (Med Guide).

Comments on the proposed Med Guide were provided under separate cover on June 29, 2011. Given the requested turn-around time for this consult response, please note this review of the proposed PI focuses on the renal impairment safety update language.

Section 5.3 of the proposed PI states, "Rare reports of hospitalization and/or dialysis or (b) (4) fatal outcome occurred in patients with underlying moderate to severe renal impairment or with any of the risk factors described in this section [see *Post-Marketing Experience (6.2)*]."

Section 6.2 of the proposed PI states, (b) (4)

According to the *Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, “When an adverse reaction identified from spontaneous reporting is included in the labeling, the number of spontaneous reports ordinarily is not cited, because the number can quickly become outdated. If the number of reports is cited, the period of observation should be stated.”

We acknowledge that one cannot infer incidence rates from AERS and that currently, the post-marketing reports of these renal adverse reactions may indeed be (b) (4). However, if the number of reports does increase, we recommend deleting the word (b) (4) from the labeling.

DDMAC appreciates the opportunity to provide comments. If you have any questions, please contact Michelle Safarik at 301-796-0620 or at [michelle.safarik@fda.hhs.gov](mailto:michelle.safarik@fda.hhs.gov).

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/s/  
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MICHELLE L SAFARIK  
06/30/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

*Memorandum*

**Date:** June 29, 2011

**To:** Meredith Alpert – Safety Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

**From:** Michelle Safarik, MSPAS, PA-C – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** DDMAC comments on draft Reclast Medication Guide  
(Med Guide)  
NDA 021817

---

This consult is in response to DRUP's June 20, 2011, request for DDMAC review of updated safety information regarding renal impairment to be included in the Reclast product labeling (PI) and Med Guide.

Comments on the proposed PI will be provided under separate cover.

Our comments are provided directly below in the proposed Med Guide provided by DRUP via e-mail on June 28, 2011. DDMAC appreciates the opportunity to provide comments. If you have any questions, please contact Michelle Safarik at 301-796-0620 or at [michelle.safarik@fda.hhs.gov](mailto:michelle.safarik@fda.hhs.gov).

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/s/  
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MICHELLE L SAFARIK  
06/29/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21817/S-012**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**REQUEST FOR DDMAC LABELING REVIEW CONSULTATION**

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Jennifer Mercier DRUP
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REQUEST DATE July 28, 2011	IND NO.	NDA/BLA NO. 21187	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) – DHCP Letter
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NAME OF DRUG Reclast	PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) August 1, 2011
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NAME OF FIRM: Novartis	PDUFA Date:
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**TYPE OF LABEL TO REVIEW**

<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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**EDR link to submission:**

**Please Note:** There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, “substantially complete” labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

**COMMENTS/SPECIAL INSTRUCTIONS:**

Please see the attached DHCP letter. Please review and make any comments by the desired completion date.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND
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/s/  
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JENNIFER L MERCIER  
07/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: Janice Maniwang  <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Meredith Alpert, Division of Reproductive and Urologic Products, x61218	
REQUEST DATE June 20, 2011	TSI NO. #621	NDA/BLA NO. 20817/S-012	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Reclast	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG bisphosphonates	DESIRED COMPLETION DATE July 5, 2011
NAME OF FIRM: Novartis		PDUFA Date: November 13, 2011 (Sunday)	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> <a href="\\Cdsub1\evsprod\NDA021817\0084\m1\us">\\Cdsub1\evsprod\NDA021817\0084\m1\us</a>			
<b>Please Note:</b> There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> On May 13, 2011, Novartis submitted a Prior Approval Supplement (b) (4) (S-012). This supplement contains a revised label with changes to the Warning section on Renal Impairment (section 5.3). Revisions were also made to the Medication Guide reflecting these labeling changes. We would like to request the following 1) DDMAC review the revised labeling changes and 2) attend the July 6 labeling meeting to discuss their review.			
Labeling Meetings: July 6, 2011			
SIGNATURE OF REQUESTER: Meredith Alpert, x61218			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND	



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/s/  
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MEREDITH H ALPERT  
06/21/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **OSE/DPV II/DRISK**  
cc: Maria Wasilik

FROM (Name, Office/Division, and Phone Number of Requestor): **Meredith Alpert, Division of Reproductive and Urologic Products, x61218**

DATE  
June 3, 2011

IND NO.  
TSI 621

NDA NO.  
021817

TYPE OF DOCUMENT

DATE OF DOCUMENT

NAME OF DRUG  
Reclast

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Bisphosphonate

DESIRED COMPLETION DATE  
August 1, 2011

NAME OF FIRM: **Novartis**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** On May 13, 2011, Novartis submitted a Prior Approval Supplement (S-012). This supplement contains a revised label with changes to the Warning section on Renal Impairment (Section 5.3). Revisions were also made to the Medication Guide reflecting these labeling changes. We request the following: 1) DPV II review the text that modifies the WARNING on Renal Impairment in section 5.3 and 2) DRISK review the updated Medication Guide. The EDR link to the submission is listed below.

\\Cdsesub1\evsprod\NDA021817\0084

SIGNATURE OF REQUESTOR  
**Meredith Alpert, M.S., Acting Safety Project Manager**

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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MEREDITH H ALPERT  
06/03/2011