

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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LABELING



Reclast[®]

(zoledronic acid) Injection

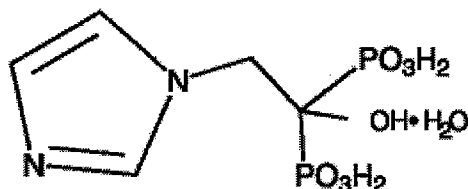
Solution for Intravenous Infusion

Rx only

Prescribing Information

DESCRIPTION

Reclast[®] contains zoledronic acid which in solution is available as zoledronate at physiological pH. Zoledronate is a bisphosphonate that inhibits osteoclast-mediated bone resorption. The parent compound from which zoledronate is prepared is zoledronic acid monohydrate which 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 with the molecular formula of $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and a molar mass of 290.1 g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.

Reclast[®] (zoledronic acid) 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:* mannitol, USP, as bulking agent, and sodium citrate, USP, as buffering agent, water for injection, USP. Zoledronic acid is marketed for oncology indications under the brand name Zometa[®] (zoledronic acid) Injection 4 mg concentrate for intravenous infusion.

CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

Reclast (zoledronic acid) Injection belongs to the bisphosphonate class 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 as other bisphosphonates, localizes preferentially at sites of high bone turnover. The main

molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other inhibitory mechanisms. The relatively long duration of action of zoledronic acid is attributable to its strong binding affinity to bone mineral. Histomorphometric data from rat and monkey studies showed a dose-dependent reduction in osteoclastic bone resorption and bone turnover.

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by irregular osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

Pharmacokinetics

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

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) 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 ± 0.30 and 1.16 ± 0.36 , respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <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 ($\pm$ s.d.) $39 \pm 16\%$ 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 ± 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 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

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

Pediatrics: Pharmacokinetic data in pediatric patients are not available.

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

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid. Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation, and in animal studies $< 3\%$ of the administered dose was recovered in the feces. This suggests no relevant role of liver function in the pharmacokinetics of zoledronic acid and no required dosage adjustment.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with normal renal function (creatinine clearance > 80 mL/min, N=37), patients with mild renal impairment (creatinine clearance = 50-80 mL/min, N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (creatinine clearance = 30-50 mL/min, N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of > 30 mL/min. Reclast (zoledronic acid) is not recommended for patients with severe renal impairment (creatinine clearance < 35 mL/min) due to lack of adequate clinical experience in this population. (See PRECAUTIONS.)

CLINICAL STUDIES

Paget's Disease of the Bone

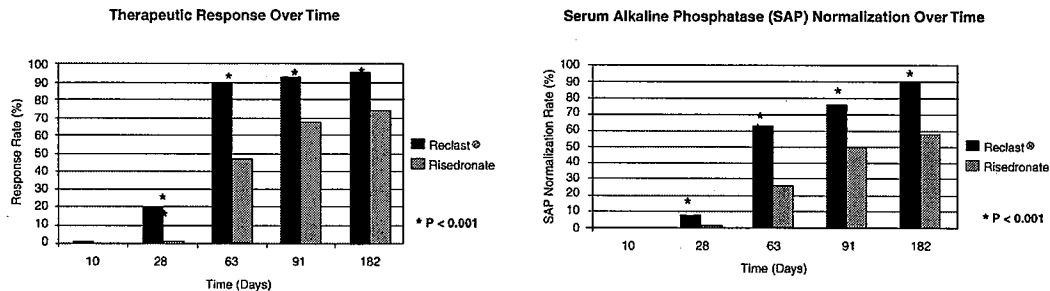
Reclast® (zoledronic acid) Injection was studied in male and female patients with moderate to severe disease (serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry), with confirmed Paget's disease of bone. Diagnosis was confirmed 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 [PINP]) and resorption (serum CTx 1 [cross-linked C-telopeptides of type I collagen] and urine α -CTx).

The 6-month combined data from both trials showed that, 96% (169/176) of Reclast-treated patients achieved a therapeutic response as compared with 74% (127/171) of patients treated with risedronate. Most Reclast patients achieved a therapeutic response by the Day 63 visit. In addition, at 6 months, 89% (156/176) of Reclast-treated patients achieved normalization of SAP levels, compared to 58% (99/171) of patients treated with risedronate ($p < 0.0001$) (see Figure 1).

Figure 1. 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 (see Table 1). 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, $\geq$ 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.

ANIMAL PHARMACOLOGY

Zoledronic acid is a potent inhibitor of osteoclastic bone resorption. In the ovariectomized rat, single iv doses of zoledronic acid of 4-500 μ g/kg (<0.1 to 3.5 times human exposure at the 5 mg intravenous dose, based on mg/m² comparison) suppressed bone turnover and protected against trabecular bone loss, cortical thinning and the reduction in vertebral and femoral bone strength in a dose-dependent manner. At a dose equivalent to human exposure at the 5 mg intravenous dose, the effect persisted for 8 months, which corresponds to approximately 8 remodeling cycles or 3 years in humans.

In ovariectomized rats and monkeys, weekly treatment with zoledronic acid dose-dependently suppressed bone turnover and prevented the decrease in cancellous and cortical BMD and bone strength, at yearly cumulative doses up to 3.5 times the intravenous human dose of 5 mg, based on mg/m² comparison. Bone tissue was normal and there was no evidence of a mineralization defect, no accumulation of osteoid, and no woven bone.

INDICATIONS AND USAGE

Paget's Disease

Reclast[®] (zoledronic acid) Injection is indicated for the 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, to induce remission (normalization of serum alkaline phosphatase).

CONTRAINDICATIONS

- Hypocalcemia
- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy and lactation

WARNINGS

A single dose of Reclast[®] (zoledronic acid) Injection should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.

Hypocalcemia may occur with Reclast therapy. To reduce the risk of hypocalcemia, all patients 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 (see PRECAUTIONS).

Reclast may cause fetal harm when administered to a pregnant woman. 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.. (See PRECAUTIONS, Pregnancy Category D.)

PRECAUTIONS

General

Reclast[®] (zoledronic acid) Injection contains the same active ingredient found in Zometa, used for oncology indications, and a patient already being treated with Zometa should not be treated with Reclast.

Mineral Metabolism

Reclast may cause hypocalcemia. Pre-existing hypocalcemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Reclast. (See CONTRAINDICATIONS.) Disturbances of calcium and mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine) must be effectively treated and clinical monitoring of calcium and mineral levels is highly recommended for these patients.

To reduce the risk of hypocalcemia, all patients 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 , ADVERSE REACTIONS, Laboratory Findings and Information For Patients.)

Renal Insufficiency

Reclast is not recommended for use in patients with severe renal impairment (creatinine clearance <35mL/min) due to lack of adequate clinical experience in this population. (See DOSAGE AND ADMINISTRATION.)

To prevent renal dysfunction, patients, especially those receiving diuretic therapy, should be appropriately hydrated prior to administration of Reclast. (See DOSAGE AND ADMINISTRATION.)

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates including zoledronic acid. Dental surgery may exacerbate the condition. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. 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.

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates, including Reclast.

Information for Patients

Physicians should instruct their patients to read the Patient Information before starting therapy with Reclast, solution for intravenous infusion. Patients should be made aware that Reclast contains the same active ingredient (zoledronic acid) found in Zometa[®], and that patients already being treated with Zometa should not be treated with Reclast.

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

Reclast should not be given if the patient is pregnant or plans to become pregnant, or if they are breast-feeding. (See CONTRAINDICATIONS and WARNINGS.)

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.

In Paget's disease, bone breaks down too much and the new bone made is not normal. Because most people do not get enough calcium and vitamin D in their diet, it is important that patients take calcium and vitamin D supplementation (for example, tablets) as directed by their doctor. 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 keep blood calcium at a healthy level. This is especially important for the two weeks after getting Reclast.

Reclast is given as a single 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 patients should eat and drink normally, which includes drinking at least 2 glasses of fluid such as water within a few hours prior to the Reclast infusion, as directed by their doctor. (See PRECAUTIONS.)

Patients should also be aware of the most common side effects of therapy. Patients may experience one or more side effects that could include: fever and chills; muscle, bone or joint pain; nausea; fatigue; and headache. Most of these side effects are mild to moderate and occur within 3 days after taking Reclast. They usually go away within 4 days after they start. Patients should consult their physician if they have questions. Some patients may experience low blood calcium after getting Reclast. Symptoms from low blood calcium are uncommon but may include numbness or tingling sensations (especially in the area around the mouth), or muscle spasms. Patients should consult their physician immediately if they develop these symptoms. (See ADVERSE REACTIONS.)

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

Drug Interactions

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

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This has not been reported in zoledronic acid clinical trials. Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcemia. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Two-year oral carcinogenicity studies were conducted in mice and rats. Rats were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg. No increased incidence of tumors was observed (at doses ≤ 0.1 times the human intravenous dose of 5 mg, based on a comparison of relative body surface areas). Mice were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥ 0.002 times the human intravenous dose of 5 mg, based on mg/m² comparison). Rats were given daily oral doses of zoledronate of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤ 0.1 times the human intravenous dose of 5 mg, based on mg/m² comparison).

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.

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

AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

Pregnancy Category D

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of 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, the particular bisphosphonate used, and the route of administration (intravenous vs oral) on this risk has not been established.

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥ 0.3 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (≥ 0.1 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given daily subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg during gestation, adverse fetal effects were observed in the mid- and high-dose groups (about 2 and 4 times human systemic exposure following a 5 mg intravenous dose, based on AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (about 1.2 times the anticipated human systemic exposure, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg during gestation (at doses ≤ 0.4 times human systemic exposure following a 5 mg intravenous dose, based on mg/m² comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥ 0.04 times the human 5 mg intravenous dose, based on mg/m² comparison). Adverse maternal effects were associated with drug-induced hypocalcemia. (See CONTRAINDICATIONS and WARNINGS.)

Labor and Delivery

Reclast should not be administered to women during labor and delivery.

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.

Pediatric Use

The safety and effectiveness of Reclast in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

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[®] (zoledronic acid) Injection 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. Consistent with intravenous administration of bisphosphonates.

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 1.

Table 1: Adverse Reactions Reported in at Least 2% of Paget's Patients Receiving Reclast (Single 5-mg IV Infusion) or Risedronate (Oral 30 mg Daily for 2 Months) Over a 6-Month Follow-Up Period

	5 mg IV Reclast®	30 mg/day x 2 Months risedronate
	%	%
System Organ Class	(N = 177)	(N = 172)
Infections and Infestations		
Influenza	7	5
Metabolism and Nutrition Disorders		
Hypocalcemia	3	1
Anorexia	2	2
Nervous System Disorders		
Headache	11	10
Dizziness	9	4
Lethargy	5	1
Paraesthesia	2	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	5	1
Gastrointestinal Disorders		
Nausea	9	6
Diarrhea	6	6
Constipation	6	5
Dyspepsia	5	4
Abdominal distension	2	1
Abdominal pain	2	2
Vomiting	2	2
Abdominal pain upper	1	2
Skin and Subcutaneous Tissue Disorders		
Rash	3	2
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	9	11

Bone Pain	9	5
Myalgia	7	4
Back pain	4	7
Musculoskeletal stiffness	2	1
General Disorders and Administrative Site Conditions		
Influenza-Like Illness	11	6
Pyrexia	9	2
Fatigue	8	4
Rigors	8	1
Pain	5	4
Peripheral edema	3	1
Asthenia	2	1

Laboratory Findings

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

Renal Dysfunction

Treatment with intravenous bisphosphonates has been associated with renal dysfunction manifested as deterioration in renal function (i.e., increased serum creatinine) and in rare cases, acute renal failure. Renal dysfunction has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g., oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration, etc), the majority of whom received a 4-mg dose every 3-4 weeks, but it has been observed in patients after a single administration. In clinical trials in Paget's disease there is no evidence of renal deterioration following a single 5-mg 15-minute infusion.

Acute Phase Reaction

Reclast has been associated with the signs and symptoms of acute phase reaction, influenza-like illness, pyrexia, myalgia, arthralgia, and bone pain. Symptoms usually occur within the first 3 days following Reclast administration. One or more of these events which were suspected to be related to drug were reported in 25% of patients in the Reclast-treated group compared to 8% in the risedronate-treated group. The majority of these symptoms resolved within 4 days of onset.

Ocular Adverse Events

Cases of iritis/uveitis/episcleritis have been reported in patients treated with bisphosphonates, although no cases were reported in the Paget's disease clinical studies. Conjunctivitis has been reported in patients treated with Reclast.

Injection Site Reactions

Local reactions at the infusion site such as redness, swelling and/or pain has been observed infrequently following the administration of zoledronic acid. No cases were reported in the Paget's disease clinical trials.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported with Reclast (see PRECAUTIONS).

Bronchoconstriction in Aspirin Sensitive Asthma Patients

While not observed in clinical trials with Reclast there have been previous reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

OVERDOSAGE

There is no experience of acute overdose with Reclast® (zoledronic acid) Injection. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant 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 WARNINGS and DOSAGE AND ADMINISTRATION.)

DOSAGE AND ADMINISTRATION

Treatment of Paget's Disease of Bone

The recommended dose is 5 mg of Reclast® (zoledronic acid) Injection in 100 mL ready to infuse solution administered intravenously via a vented infusion line.

Patients must be appropriately hydrated prior to administration of Reclast, this is especially important for patients receiving diuretic therapy (see PRECAUTIONS). Reclast can be dosed without regard to meals.

The infusion time must not be less than 15 minutes (see WARNINGS) given over a constant infusion rate.

To reduce the risk of hypocalcemia, all patients 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 PRECAUTIONS.)

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

The recommended dose in patients with creatinine clearance >35mL/min is 5 mg of Reclast (zoledronic acid) infused over no less than 15 minutes at a constant infusion rate. (See WARNINGS, PRECAUTIONS, Renal Insufficiency.)

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.

HOW SUPPLIED

Reclast® (zoledronic acid) Injection, solution for intravenous infusion, is available as a sterile solution at a pH between 6.0 to 7.0. Each plastic bottle contains 5.330 mg zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis, 4950 mg of mannitol, USP, and 30 mg of sodium citrate, USP, and 100mL water for injection, USP.

5 mg/100 mL Bottle.....NDC 0078-0435-61

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

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

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

Storage

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

For more information visit www.reclast.com or call 1-866-732-5278.

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PATIENT INFORMATION

Reclast[®]

(zoledronic acid) Injection

Solution for Intravenous Infusion

(pronounced RE-klast)

Rx only

Read this information carefully before you get Reclast Injection. Because there may be new information, read the patient leaflet each time you get another dose. This leaflet does not replace talking with your doctor. Only your doctor can prescribe Reclast Injection for you. If you have any questions about Reclast Injection, ask your doctor.

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

Reclast contains the same active ingredient (zoledronic acid) found in Zometa[®] Injection. If you are already being treated with Zometa Injection, you should not receive Reclast Injection.

It is important to drink fluids before getting Reclast, and to take 1500 mg of calcium and 800 IU of vitamin D daily, especially during the first 2 weeks after getting Reclast.

Patients with severe kidney problems should not receive Reclast Injection.

What is Reclast?

Reclast is a medicine to treat adults with Paget's disease of bone.

What is Paget's disease of bone?

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

How does Reclast work?

Reclast attaches to bone and keeps it from breaking down too much. A single dose works fast and keeps working to make your bones stronger again.

Who should not get Reclast?

You should not get Reclast if:

- Your blood calcium level is too low.
- You have severe kidney problems
- You are pregnant or plan to become pregnant. Reclast may harm your unborn baby.
- You are breast-feeding. It is not known if Reclast could pass through your breast milk into your baby.

- You are allergic to anything in Reclast (the active ingredient is zoledronic acid), or other ingredients in Reclast. There is a list of inactive ingredients in Reclast at the end of this leaflet.

What should I tell my doctor before getting Reclast?

Tell your doctor about all your medical conditions. It is important to tell your doctor if:

- You have kidney problems.
- You have a history of low blood calcium
- You are unable to take daily calcium and vitamin D supplements.
- You had parathyroid or thyroid surgery (these glands are located in your neck).
- You have a malabsorption syndrome
- You had sections of your intestine removed.
- You have asthma (wheezing) from taking aspirin.

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, herbal remedies, and vitamins. Keep a list of them to show your doctor.

Your doctor needs to know if you are taking any drugs that could harm your kidneys. Give your doctor a list of all your medicines. Your doctor will know if any of your medicines could harm your kidneys.

Your doctor needs to know if you are taking Zometa (zoledronic acid). If you are taking Zometa, you should not take Reclast

You may have experienced side effects to other bisphosphonates such as headache, upset stomach, etc. These are not considered allergic reactions. Consult with your physician if you have questions regarding allergies and side effects.

How will I get Reclast?

- To prevent low blood calcium, it is important to take calcium and vitamin D supplements (for example, tablets) as directed by your doctor. After getting Reclast all patients with Paget's disease should take 1500 mg of calcium a day in divided doses (for example, 750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D a day to keep your blood calcium at a healthy level. It is especially important to take the calcium and Vitamin D supplements during the first 2 weeks after getting Reclast.
- On the day of your treatment, you should eat and drink normally, which includes drinking at least 2 glasses of fluid (such as water), as directed by your doctor before receiving Reclast.
- Reclast is given intravenously (in your vein) by a nurse or doctor. It takes at least 15 minutes to get your medicine.
- Because Reclast works for a long time, you may not need another dose of Reclast for a year or longer.

How do I know Reclast is still working?

Your doctor can check Paget's disease with a simple blood test.

What are the possible side effects of Reclast?

Patients may get one or more side effects. The most common side effects are mild to moderate and happen within 3 days after you get Reclast. They usually go away within 4 days after they start and could include:

- fever and chills
- pain in your muscles, bones or joints
- nausea
- fatigue
- headache

Skin reactions such as redness, swelling and/or pain at the infusion site may occur. Bisphosphonates (the group of drugs that Reclast belongs to) may cause swelling, redness and itching to the eyes or eye sensitivity to light.

If you have questions about these side effects, talk to your doctor.

Some patients may experience low blood calcium after getting Reclast. Symptoms of low blood calcium may include numbness or tingling sensations (especially in the area around the mouth) or muscle spasms. Contact your doctor immediately if you notice any of these symptoms after getting Reclast.

There have been reports, primarily in patients treated with bisphosphonates for other illnesses, of persistent pain and/or non-healing sore of the mouth or jaw. If you experience these symptoms tell your doctor or dentist.

Inactive ingredients: mannitol, USP, sodium citrate, USP, and water for injection, USP.

General information about Reclast

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet is a summary of the most important information about Reclast.

For more information, ask your doctor or visit www.reclast.com or call 1-866-732-5278

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