

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-113

FINAL PRINTED LABELING

WARNINGS

In both rats and dogs, hyperphosphatemia has been associated with intravenous (bolus and infusion) administration of pamidronate disodium. Two 7-day intravenous infusion studies were conducted in the dog wherein pamidronate disodium was given for 1, 4, or 24 hours at doses of 1 to 20 mg/kg for up to 7 days. In the first study, the compound was well tolerated at 3 mg/kg (1.7 x highest recommended human dose (HRHD) for a single intravenous infusion) when administered for 4 or 24 hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occurred when 1 mg/kg was infused for 1 hour and at doses of 2 to 10 mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 1 hour. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at 24 mg/kg after each infusion dose. Pamidronate disodium injection was given to rats at doses of 2, 4, and 20 mg/kg and to dogs at doses of 2, 4, 8, and 20 mg/kg as a 1-hour infusion, once a week, for 3 months followed by a 1-month recovery period. In rats, hyperphosphatemia was observed at all mg/kg and included increased BUN and creatinine levels and tubular degeneration and necrosis. These findings were still present at 20 mg/kg at the end of the recovery period. In dogs, hyperphosphatemia and renal tubular necrosis occurred at 20 mg/kg at the 1-hour infusion of elevated BUN and creatinine levels at 2 mg/kg and renal tubular degeneration at 24 mg/kg. The kidney changes were partially reversible at 8 mg/kg, in both studies, and the dose level that produced no adverse renal effects was considered to be 2 mg/kg (1.1 x HRHD for a single intravenous infusion).

Patients who receive an intravenous infusion of pamidronate disodium should have periodic evaluations of standard laboratory and clinical parameters of renal function. Studies conducted by young rats have reported the disruption of renal tubule formation following single- and multiple-dose administration of bisphosphonates. The clinical significance of these findings is unknown.

PRECAUTIONS

General
Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, and potassium, should be carefully monitored following initiation of therapy with pamidronate disodium. Cases of symptomatic hypophosphatemia (12%), hypocalcemia (7%), hypomagnesemia (11%), and hypokalemia (15% to 17%), were reported in pamidronate disodium-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with pamidronate disodium therapy. If hypocalcemia occurs, short-term calcium therapy may be necessary. In Pamidronate's clinical trial, 17% of patients treated with 90 mg of pamidronate disodium showed serum calcium levels below 8 mg/dL.

Pamidronate disodium has not been tested in patients who have class II or III renal impairment (creatinine ≥ 1.5 mg/dL), and in low multiple myeloma patients with serum creatinine ≥ 3 mg/dL. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics.) Clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

Laboratory Tests
Serum calcium, electrolytes, phosphate, magnesium and creatinine, and CBC, differential, and hematology/hematology must be closely monitored in patients treated with pamidronate disodium. Patients who have preexisting azotemia, hypocalcemia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment.

Drug Interactions
Concomitant administration of a loop diuretic had no effect on the calcium-lowering action of pamidronate disodium.

Concomitantly Administered Agents
In a (Q4 week) carcinogenicity study (daily oral administration) in rats, there was a positive dose response relationship for benign adrenal pheochromocytoma in males (P < 0.0001). Although this condition was also observed in females, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited and bioavailability of pamidronate disodium in rats, the lowest daily dose associated with adrenal pheochromocytoma was similar to the labeled clinical dose. Adrenal pheochromocytoma was also observed in low numbers in the control animals and in 4 out of 10 rats in the study. Pamidronate disodium (daily oral administration) was not carcinogenic in the 60-week study in mice.

Pamidronate disodium was nonmutagenic in the *in vitro* mutagenicity assays: Ames test, *Salmonella* and *Escherichia coli*-microsome test, nucleoside-analog test, sister-chromatid-exchange test, protein-mutagenicity test, and micronucleus test in the rat.

In rats, decreased fertility occurred in first-generation offspring of parents who received 150 mg/kg of pamidronate disodium orally; however, this occurred only when parents were mated with members of the same dose group. Pamidronate disodium has not been administered intravenously in such a study.

Pregnancy: Postpartum Effects: Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women.

Prone to hypocalcemia studies conducted in rats and rabbits indicated that pamidronate disodium produces moderate toxicity and embryofetal effects when given during organogenesis at doses of 0.5 to 8.3 times the highest recommended human dose for a single intravenous infusion. As it has been shown that pamidronate disodium can cross the placenta in rats and has produced marked maternal and embryofetal effects in rats and rabbits, it should not be given to women during pregnancy.

Nursing Mothers
It is not known whether pamidronate disodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pamidronate disodium is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of pamidronate disodium in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Studies
Hypercalcemia of Malignancy
Transient mild elevations of temperature by at least 1°C was noted 24 to 48 hours after administration of pamidronate disodium in 24% of patients in clinical trials. In the same trial, 18% of patients had a temperature elevation of at least 1°C 24 to 48 hours after treatment.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (18%) in patients treated with 90 mg of pamidronate disodium. Symptomatic treatment resulted in rapid resolution in all patients.

Have cases of urticaria, hives, scurfs, and urticaria have been reported, including one case of urticaria and one case of urticaria upon separate occasions.

Five of 221 patients (2%) who received pamidronate disodium during the four U.S. controlled hypercalcemia clinical studies were reported to have had seizures. 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the same trial 1 patient (4%) had a seizure.

At least 15% of patients treated with pamidronate disodium for hypercalcemia of malignancy also experienced the following adverse events during a clinical trial:

General: Headache, pruritus, pain
Cardiovascular: Hypertension
Gastrointestinal: Abdominal pain, anorexia, constipation, nausea, vomiting
Genitourinary: Urinary tract infection
Musculoskeletal: Bone pain
Laboratory abnormalities: Anemia, hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia

Many of these adverse experiences may have been related to the underlying disease state.

The following table lists the adverse experiences considered to be treatment-related during comparative, controlled U.S. trials.

	Treatment-Related Adverse Experiences Reported in Three U.S. Controlled Clinical Trials				Saline
	30 mg over 4 hr n=23	90 mg over 24 hr n=73	90 mg over 24 hr n=17	90 mg over 24 hr n=35	
General					
Headache	0	1	0	0	0
Fatigue	0	0	12	0	0
Fever	26	19	18	8	0
Fluid overload	0	0	0	0	0
Infection-site reaction	0	4	18	0	3
Headache	0	0	8	0	2
Rigors	0	0	0	0	4
Gastrointestinal					
Abdominal pain	0	1	0	0	0
Anorexia	4	1	12	0	0
Constipation	0	0	6	2	0
Diarrhea	0	1	0	0	0
Dyspepsia	4	0	0	0	0
Gastrointestinal hemorrhage	0	0	6	0	0
Nausea	0	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	2	0	0	0
Respiratory					
Dyspnea	0	0	0	3	0
Rhinitis	0	0	0	0	0
Rhinitis	0	0	0	0	0
Upper respiratory infection	0	3	0	0	0
CNS					
Seizure	0	0	0	0	4
Convulsions	0	0	0	0	0
Hypocalcemia	0	1	0	0	0
Hypomagnesemia	0	0	0	0	4
Psychosis	4	0	0	0	0
Convulsions	0	1	0	0	0
Taste perversion	0	0	0	3	0
Cardiovascular					
Arrhythmia	0	0	0	0	4
Arrhythmia	0	1	0	0	0
Cardiac failure	0	0	0	0	0
Hypertension	0	0	6	0	4
Syncope	0	0	0	0	0
Tachycardia	0	0	0	0	4
Endocrine					
Hypoparathyroidism	0	0	6	0	0
Muscle and lymphatic					
Anemia	4	0	6	0	0
Leukopenia	4	0	0	0	0
Neutropenia	0	1	0	0	0
Thrombocytopenia	0	1	0	0	0
Bleeding/thrombotic					
Myeloma	0	1	0	0	0
Urinary					
Urinary	4	0	0	0	0
Laboratory Abnormalities					
Hypocalcemia	0	1	12	0	0
Hypocalcemia	4	4	18	0	0
Hypomagnesemia	0	0	12	2	4
Hypophosphatemia	0	0	18	2	0
Abnormal liver function	0	0	0	2	0

Pamidronate Disodium
Transient mild elevation of temperature $>1^\circ\text{C}$ above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of pamidronate disodium in clinical trials.

Drug-related musculoskeletal pain and nervous system symptoms (dyspnea, head-ache, paresthesia, increased sweating) were more common in patients with Paget's disease treated with 90 mg of pamidronate disodium than in patients with hypercalcemia of malignancy treated with the same dose.

Adverse experiences considered to be related to trial drug, which occurred in at least 5% of patients with Paget's disease treated with 90 mg of pamidronate disodium in two U.S. clinical trials, were fever, nausea, back pain, and bone pain.

At least 10% of all pamidronate disodium-treated patients with Paget's disease also experienced the following adverse experiences during clinical trial:

Cardiovascular: Hypertension
Musculoskeletal: Arthritis, bone pain
Nervous system: Headache

Most of these adverse experiences may have been related to the underlying disease state.

Delayed Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

The most commonly reported ($>15\%$) adverse experiences occurred with either pamidronate disodium or placebo treatment groups, and most of these adverse experiences may have been related to the underlying disease state or cancer therapy.

Summary of Reported Adverse Experiences in Three U.S. Controlled Clinical Trials

	Pamidronate Disodium 90 mg		Pamidronate Disodium 90 mg		All Pamidronate Disodium	
	30 mg over 4 hr n=23	90 mg over 24 hr n=73	30 mg over 4 hr n=17	90 mg over 24 hr n=35	30 mg over 4 hr n=23	90 mg over 24 hr n=73
General						
Headache	16.1	17.1	25.6	19.2	22.2	18.5
Fatigue	31.7	28.3	40.3	26.8	37.2	29.0
Fever	38.5	38.0	38.1	32.1	36.5	34.0
Metastases	1.0	3.0	31.3	24.4	20.5	17.5
Fluid overload	13.2	11.8	15.0	16.1	14.3	16.1
Cardiovascular						
Anorexia	17.1	17.1	31.1	24.9	26.0	22.3
Constipation	28.3	31.7	36.0	36.8	33.2	35.1
Diarrhea	29.8	28.8	29.4	30.8	28.8	29.7
Dyspepsia	17.4	18.3	18.2	15.0	22.6	17.6
Nausea	35.6	37.4	43.8	58.1	53.5	51.8
Pain Abdominal	19.5	16.0	24.3	19.1	22.6	17.5
Vomiting	16.6	19.8	48.3	28.1	35.7	32.8
Muscle and lymphatic						
Anemia	47.8	41.7	39.5	36.8	42.5	38.4
Granulocytopenia	20.5	15.6	19.3	20.5	19.8	18.8
Thrombocytopenia	16.6	17.1	12.5	14.0	14.0	15.0
Bleeding/thrombotic						
Arteriosclerosis	10.7	7.0	15.3	12.7	13.6	10.8
Myeloma	25.4	15.0	26.4	22.5	26.0	20.1
Stroke	61.0	71.7	70.0	75.4	66.8	74.0
CNS						
Seizure	7.8	9.1	18.0	16.8	14.3	14.3
Anxiety	24.4	19.8	27.2	23.6	26.2	23.3
Insomnia	17.1	17.2	25.1	19.4	22.2	19.0
Respiratory						
Coughing	26.3	22.5	26.3	19.7	25.7	20.8
Dyspnea	22.0	21.4	35.1	24.4	30.4	22.4
Pneumonia	2.9	4.3	15.0	9.1	10.7	7.5
Sinusitis	14.6	16.8	16.1	10.4	15.6	12.0
Upper respiratory tract infection	32.2	28.2	19.6	20.2	24.1	22.9
Urinary						
Urinary tract infection	15.6	9.1	29.2	17.8	18.5	15.6

Of the conditions commonly associated with chemotherapy, the frequency of vomiting, anorexia, and nausea were slightly more common in the pamidronate disodium patients whereas constipation and diarrhea occurred at a frequency similar to that in placebo patients. In the breast cancer trials, mild elevations of serum creatinine occurred in 13.5% of pamidronate disodium patients and 12.2% of placebo patients. Mild and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of pamidronate disodium-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia for pamidronate disodium-treated patients were 2.2%, 10.5%, 1.7%, and 4.4%, respectively, and for placebo-treated patients were 1.2%, 12%, 1.7%, and 4.5%, respectively. In previous hypercalcemia of malignancy trials, patients treated with pamidronate disodium (90 or 30 mg over 24 hours) developed electrolyte abnormalities more frequently (see ADVERSE REACTIONS, Hypercalcemia of Malignancy).

Arterial and venous thromboses were reported slightly more frequently in the pamidronate disodium group than in the placebo group (13.6% and 29% vs 10.8% and 25.1%, respectively).

In multiple myeloma patients, there were two pamidronate disodium-related serious and unexpected adverse experiences. Four of these were reported during the 12-month extension of the multiple myeloma trial. Three of the reports were of worsening renal function developing in patients with preexisting multiple myeloma or multiple myeloma-associated amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a patient receiving pamidronate disodium and acute promyelocytic leukemia. One pamidronate disodium-treated patient experienced an allergic reaction characterized by urticaria and hives upon, very rare, and occurred within 24 hours after the sixth infusion. In the breast cancer trials, there were two pamidronate disodium-related adverse experiences, all moderate to severe, that caused a patient to discontinue participation in the trial. One was due to interstitial pneumonitis, another to nausea and dyspnea. One pamidronate disodium patient discontinued the trial due to a symptomatic hypocalcemia. Another pamidronate disodium patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

Postmarketing Experience
Rare instances of allergic manifestations have been reported, including hypersensitivity, dyspnea, or angioedema, and very rarely, anaphylactic shock. Pamidronate disodium is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates (see CONTRAINDICATIONS).

OVERDOSEAGE

There have been several cases of drug misadministration of intravenous pamidronate disodium in hypercalcemia patients with total doses of 225 mg to 300 mg given over 2 to 12 to 4 days. All of these patients survived, but they experienced hypocalcemia that required intravenous and/or oral administration of calcium.

In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium over 3 days experienced high fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), and transient loss of consciousness, noted about 6 hours after the first infusion. The fever and hypotension were rapidly corrected with steroids.

If overdose occurs, symptomatic hypocalcemia could also result; such patients should be treated with short-term intravenous calcium.

DOSE AND ADMINISTRATION

Hypercalcemia of Malignancy
Consideration should be given to the severity of as well as the symptoms of hypercalcemia. Vigorous saline hydration alone may be sufficient for treating mild, asymptomatic hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure in hypercalcemia treated with pamidronate disodium. The use of glucocorticoid therapy may be helpful.

Hypercalcemia of Malignancy
The recommended dose of pamidronate disodium injection in moderate hypercalcemia (corrected serum calcium >12 mg/dL) is 90 mg. The 90 mg dose is given as an initial, SINGLE DOSE, intravenous infusion over 24 hours. The 90 mg dose must be given by an initial, SINGLE DOSE, intravenous infusion over 24 hours.

Severe Hypercalcemia
The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum calcium >13.5 mg/dL) is 90 mg. The 90 mg dose must be given by an initial, SINGLE DOSE, intravenous infusion over 24 hours.

*Adverse-corrected serum calcium (CCA, mg/dL) = serum calcium, mg/dL, ± 0.8 (4.0 serum albumin, g/dL).

Rehydration
A limited number of patients have received more than one treatment with pamidronate disodium for hypercalcemia. Rehydration with pamidronate disodium, in patients who show complete or partial response initially, may be carried out if serum calcium does not return to normal or remains elevated after initial treatment. It is recommended that a minimum of 7 days elapse before rehydration, to allow for full response to the initial dose. The dose and manner of rehydration is identical to that of the initial therapy.

Paget's Disease
The recommended dose of pamidronate disodium in patients with moderate to severe Paget's disease of bone is 30 mg daily, administered as a 4-hour infusion on 3 consecutive days for a total dose of 90 mg.

Rehydration
A limited number of patients with Paget's disease have received more than one treatment of pamidronate disodium in clinical trials. When clinically indicated, patients should be rehydrated at the dose of initial therapy.

Delayed Bone Lesions of Breast Cancer
The recommended dose of pamidronate disodium in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4-hour infusion given over 3 to 4 weeks.

Patients with marked Brucella-sensu parvulus and dehydration should receive adequate hydration prior to pamidronate disodium infusion.

Unlabeled information is available on the use of pamidronate disodium in multiple myeloma patients with a serum creatinine ≥ 3 mg/dL.

The optimal duration of therapy is not yet known, however. In a study of patients with myeloma, final analysis after 21 months demonstrated overall benefit (see CLINICAL TRIALS section).

Osteolytic Bone Lesions of Breast Cancer
The recommended dose of pamidronate disodium in patients with osteolytic bone metastases is 90 mg administered over a 2-hour infusion given every 3 to 4 weeks.

Pamidronate disodium has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotrexate, mitomycin, vinorelbine, desferrioxamine, prednisone, halothane, vincristine, regimast, and tamoxifen. It has been given less frequently with asparagin, cyclosporin, cytarabine, dacarbazine, and methoprednisone. The optimal duration of therapy is not known. However, in breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefit (see CLINICAL TRIALS section).

Preparation of Solution

Hypercalcemia of Malignancy
The daily dose must be administered as an intravenous infusion over at least 4 hours for the 90 mg dose, and over 24 hours for the 30 mg dose. The recommended dose should be diluted in 1000 mL of 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection. This solution is stable for up to 24 hours at room temperature.

Paget's Disease
The recommended daily dose of 30 mg should be diluted in 500 mL of 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection, and administered over a 4-hour period for 3 consecutive days.

Delayed Bone Lesions of Breast Cancer
The recommended dose of 90 mg should be diluted in 250 mL of 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection, and administered over a 2-hour period every 3 to 4 weeks.

Osteolytic Bone Lesions of Multiple Myeloma
The recommended dose of 90 mg should be diluted in 500 mL of 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection and administered over a 4-hour period on a monthly basis.

Pamidronate disodium must not be mixed with solution-containing infusion solutions, such as Ringer's solution, and should be given in a single intravenous infusion and then separately from all other drugs.

After Pamidronate drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Pamidronate Disodium Injection is supplied in single dose, flip-top vials as a clear, colorless solution containing Pamidronate Disodium 3 mg/mL, and 9 mg/mL, as follows:

30 mg (300-004-01), 30 mg in 10 mL, individually boxed.

90 mg (300-005-01), 90 mg in 10 mL, individually boxed.

Store at 25°C (77°F).

Manufactured by: Bedford LaboratoriesTM

Bedford, OH 44148

August 2001

Manufactured by: Bedford Laboratories, Inc.

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PMD-AQ-P01