# PAMIDRONATE DISODIUM- pamidronate disodium injection
# Mylan Institutional LLC

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use PAMIDRONATE DISODIUM INJECTION safely and effectively. See full prescribing information for PAMIDRONATE DISODIUM INJECTION.**

**PAMIDRONATE DISODIUM injection, for intravenous use**
**Initial U.S. Approval: 1991**

## RECENT MAJOR CHANGES

Warnings and Precautions (5.2) 05/2025

## INDICATIONS AND USAGE

Pamidronate disodium is a bisphosphonate indicated for the treatment of:

- moderate or severe hypercalcemia associated with malignancy, with or without bone metastases (1.1)
- patients with moderate to severe Paget's disease of bone (1.2)
- osteolytic bone metastases of breast cancer or osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy (1.3)

Limitations of use
Safety and efficacy of pamidronate disodium in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions have not been established. (1.4)

## DOSAGE AND ADMINISTRATION

- Hypercalcemia of malignancy: 60 mg to 90 mg pamidronate disodium as a single dose infused over 2 hours to 24 hours for moderate hypercalcemia, or 90 mg as a single dose infused over 2 hours to 24 hours for severe hypercalcemia. If warranted, retreat after a minimum of 7 days. (2.1)
- Paget's disease of bone: 30 mg pamidronate disodium daily as a 4-hour infusion on 3 consecutive days. (2.2)
- Osteolytic Bone Metastases of Breast Cancer: 90 mg pamidronate disodium as a 2-hour infusion every 3 to 4 weeks. Retreat after recovery of renal function. (2.3)
- Osteolytic Bone Lesions of Multiple Myeloma: 90 mg pamidronate disodium as a 4-hour infusion once every four weeks. Retreat after recovery of renal function. (2.3)
- Administer through a separate infusion line. Do not allow pamidronate disodium infusion to come in contact with any calcium or divalent cation-containing solutions. (2.6)

## DOSAGE FORMS AND STRENGTHS

- Injection: 30 mg/10 mL (3 mg/mL) and 90 mg/10 mL (9 mg/mL) solution in single-dose vials (3)

## CONTRAINDICATIONS

Hypersensitivity to pamidronate, other bisphosphonates, or mannitol (4)

## WARNINGS AND PRECAUTIONS

- Renal failure: Do not exceed single doses of 90 mg pamidronate disodium. Assess renal function before each treatment. In patients with bone metastases with severe renal impairment, use of pamidronate disodium is not recommended. (5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)
- Electrolyte disorders (e.g., hypophosphatemia, hypokalemia, hypomagnesemia, hypocalcemia): Monitor phosphorus, potassium, magnesium, calcium and vitamin D and adequately supplement as appropriate. (5.3)
- Osteonecrosis of the jaw: Perform preventive dental procedures prior to initiating pamidronate disodium. Avoid invasive procedures if possible in patients receiving pamidronate disodium. (5.4)
- Atypical fractures of the femur can occur after minimal or no trauma. Evaluate patients with thigh or groin pain for possible fracture. (5.5)

## ADVERSE REACTIONS

Most common adverse reactions per indication:

- Hypercalcemia of malignancy (≥ 15%): Fever, nausea, infusion site reactions, hypocalcemia, hypophosphatemia (6.1)
- Paget's disease (≥ 10%): Temperature increase, hypertension, arthrosis, bone pain, headache (6.1)
- Osteolytic bone metastases of breast cancer or osteolytic lesions of multiple myeloma (≥ 30%): Skeletal pain, nausea, anemia, fever, fatigue, vomiting, dyspnea (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

## DRUG INTERACTIONS

- Nephrotoxic drugs: Use with caution. (7.1)
- Thalidomide: Increased risk of renal dysfunction in patients with multiple myeloma. (7.2)

## USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: May impair fertility. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 12/2025**

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## FULL PRESCRIBING INFORMATION: CONTENTS*

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

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Hypercalcemia of Malignancy

Pamidronate disodium is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases.

### 1.2 Paget's Disease

Pamidronate disodium is indicated for the treatment of patients with moderate to severe Paget's disease of bone.

### 1.3 Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

Pamidronate disodium is indicated in conjunction with standard antineoplastic therapy,

for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma *[see Clinical Studies (14.3)]*.

### 1.4 Limitations of Use

The safety and efficacy of pamidronate disodium in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Hypercalcemia of Malignancy

Vigorous saline hydration, should be initiated promptly along with pamidronate therapy and if possible the urine output should be about 2 L/day throughout treatment *[see Warnings and Precautions (5.2)]*.

Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment *[see Warnings and Precautions (5.1)]*. Treatment should be withheld for renal deterioration.

Moderate Hypercalcemia

The recommended dose of pamidronate disodium in moderate hypercalcemia (corrected serum calcium* of approximately 12 mg/dL to 13.5 mg/dL) is 60 mg to 90 mg given as a single-dose, intravenous infusion over 2 hours to 24 hours. Longer infusions (i.e., greater than 2 hours) may reduce the risk for renal toxicity, particularly in patients with preexisting renal impairment.

Severe Hypercalcemia

The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum calcium* > 13.5 mg/dL) is 90 mg given as a single-dose, intravenous infusion over 2 to 24 hours. Longer infusions (i.e., greater than 2 hours) may reduce the risk for renal toxicity, particularly in patients with preexisting renal insufficiency/impairment.

*Albumin-corrected serum calcium = serum calcium, mg/dL + 0.8 (4.0-serum albumin, g/dL).

Retreatment

Retreatment 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 remain normal after initial treatment. A minimum of 7 days between treatments is recommended to allow for full response to the initial dose. The dose and manner of retreatment is identical to that of the initial therapy.

### 2.2 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. When clinically indicated, patients should be retreated at the dose of initial therapy.

## 2.3 Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

Osteolytic Bone Metastases 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.

In a clinical study, renal deterioration was defined as follows:

- With normal baseline creatinine, an increase of 0.5 mg/dL.
- With abnormal baseline creatinine, an increase of 1 mg/dL.

In this clinical study, pamidronate disodium treatment was resumed only when the creatinine

returned to within 10% of the baseline value.

The optimal duration of therapy is not known; however, in two breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefits *[see Clinical Studies (14.3)]*.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of pamidronate disodium in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4-hour infusion administered every four weeks.

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to pamidronate disodium infusion.

Limited information is available on the use of pamidronate disodium in multiple myeloma patients with a serum creatinine greater than or equal to 3 mg/dL.

Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment. Treatment should be withheld for renal deterioration.

In a clinical study, renal deterioration was defined as follows:

- With normal baseline creatinine, an increase of 0.5 mg/dL.
- With abnormal baseline creatinine, an increase of 1 mg/dL.

In this clinical study, pamidronate disodium treatment was resumed only when the creatinine returned to within 10% of the baseline value.

The optimal duration of therapy is not known. However, in a study of patients with myeloma, final analysis after 21 months demonstrated overall benefits *[see Clinical Studies (14.3)]*.

## 2.5 Dilution for Administration

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 2 hours and up to 24 hours for the 60 mg and 90 mg doses. The recommended dose should be

diluted in 1000 mL of sterile 0.45% or 0.9% sodium chloride injection or 5% dextrose injection. This infusion 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 sterile 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection and administered over a 4-hour period daily for 3 consecutive days.

Osteolytic Bone Metastases of Breast Cancer

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

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection, and administered over a 4-hour period every four weeks.

### 2.6 Incompatibilities, Inspection before Use

Pamidronate disodium must not be mixed with calcium-containing infusion solutions such as Ringer's solution. Administer as a single intravenous solution and infuse using an intravenous line reserved for pamidronate alone.

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

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 30 mg/10 mL (3 mg/mL) and 90 mg/10 mL (9 mg/mL) solution in single-dose vials

## 4 CONTRAINDICATIONS

Pamidronate disodium is contraindicated in patients with hypersensitivity to pamidronate disodium, other bisphosphonates, or mannitol. Reactions to pamidronate disodium injection and to mannitol have included anaphylaxis.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Deterioration in Renal Function, Use in Patients with Renal Impairment

Bisphosphonates, such as pamidronate disodium, have been associated with renal toxicity, including focal segmental glomerulosclerosis. This toxicity has been manifested as nephritic syndrome, deterioration of renal function, and renal failure. Renal failure has been reported in patients after a single dose of pamidronate disodium. Some patients had gradual improvement in renal status after pamidronate disodium was discontinued.

Do not administer single doses of pamidronate disodium in excess of 90 mg due to the

risk of clinically significant deterioration in renal function, *[see Dosage and Administration (2.5)]*.

Assess serum creatinine prior to each treatment. Withhold treatment until renal function returns to baseline in patients who show evidence of deterioration in renal function. Do not administer pamidronate in patients with severe renal impairment for the treatment of bone metastases *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

### 5.2 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, pamidronate disodium can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In reproductive studies, administration of pamidronate to pregnant rats and rabbits at doses equivalent to 0.6 to 8.3 times the highest human recommended dose resulted in maternal toxicity and embryo-fetal effects.

Bisphosphonates, such as pamidronate disodium, are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and after pamidronate disodium treatment *[see Use in Specific Populations (8.1, 8.3)]*.

### 5.3 Electrolyte Disorders

Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5% to 17%), were reported in pamidronate disodium-treated patients. Cases of symptomatic hypocalcemia (including tetany) have been reported in association with pamidronate disodium therapy. Monitor serum levels of calcium, phosphate, magnesium, and potassium, following initiation of therapy with pamidronate disodium. If hypocalcemia occurs, short-term calcium therapy may be necessary. In the absence of hypercalcemia, supplement with oral calcium and vitamin D in order to minimize the risk of hypocalcemia.

### 5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including pamidronate disodium. Many of these patients were also receiving chemotherapy and corticosteroids, which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of ONJ with certain tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Local infection including osteomyelitis has been reported with ONJ.

Patients receiving pamidronate should maintain good oral hygiene and have a dental examination with preventive dentistry prior to initiation of treatment.

While on treatment, avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each

patient based on individual benefit/risk assessment *[see Adverse Reactions (6.2)]*.

### 5.5 Atypical Fractures of the Femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including pamidronate disodium. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to just above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. These fractures may occur after minimal or no trauma. Patients may experience thigh or groin pain weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures also has been reported. A number of case reports noted that patients were receiving treatment also with glucocorticoids (such as prednisone or dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain in the absence of trauma should be evaluated for an atypical fracture. Consider discontinuation of pamidronate disodium therapy in patients suspected to have an atypical femur fracture pending evaluation of the patient, based on an individual benefit risk assessment. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.

## 6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Deterioration in renal function *[see Warnings and Precautions (5.1)]*
- Electrolyte disorders *[see Warnings and Precautions (5.3)]*
- Osteonecrosis of the jaw *[see Warnings and Precautions (5.4)]*
- Atypical fractures of the femur *[see Warnings and Precautions (5.5)]*

### 6.1 Clinical Trials Experience

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

Hypercalcemia of Malignancy

Transient elevation of temperature by at least 1°C was noted 24 to 48 hours after administration of pamidronate disodium in 34% of patients in clinical trials. Local soft-tissue reactions (redness, swelling or induration and pain on palpation) at the site of catheter insertion were observed, most commonly in patients treated with 90 mg of pamidronate disodium. Symptomatic treatment resulted in resolution in all patients.

Cases of uveitis, iritis, scleritis, and episcleritis have been reported, including one case of scleritis and one case of uveitis upon separate rechallenges.

Five of 231 patients (2%) who received pamidronate disodium while enrolled on controlled

clinical trials for management of hypercalcemia were reported to have seizures, including two patients with pre-existing seizure disorders. One patient on the control (saline arm) also had a seizure. At least 15% of patients treated with pamidronate disodium for hypercalcemia of malignancy experienced the following adverse reactions during a clinical trial:

***General:*** Fluid overload, generalized pain

***Cardiovascular:*** Hypertension

***Gastrointestinal:*** Abdominal pain, anorexia, constipation, nausea, vomiting

***Genitourinary:*** Urinary tract infection

***Musculoskeletal:*** Bone pain

***Laboratory abnormality:*** Anemia, hypokalemia, hypomagnesemia, hypophosphatemia

Table 1 lists the adverse reactions reported during comparative, controlled trials.

**Table 1: Adverse Reactions Reported in Three U.S. Controlled Clinical Trials**

| | **Percent of Patients** | | | | |
|---|---|---|---|---|---|
| | **Pamidronate Disodium** | | | **Etidronate Disodium** | **Saline** |
| | **60 mg over 4 hr** | **60 mg over 24 hr** | **90 mg over 24 hr** | **7.5 mg/kg x 3 days** | |
| | **n = 23** | **n = 73** | **n = 17** | **n = 35** | **n = 23** |
| **General** | | | | | |
| Edema | 0 | 1 | 0 | 0 | 0 |
| Fatigue | 0 | 0 | 12 | 0 | 0 |
| Fever | 26 | 19 | 18 | 9 | 0 |
| Infusion-site reaction | 0 | 4 | 18 | 0 | 0 |
| Moniliasis | 0 | 0 | 6 | 0 | 0 |
| **Gastrointestinal** | | | | | |
| Abdominal pain | 0 | 1 | 0 | 0 | 0 |
| Anorexia | 4 | 1 | 12 | 0 | 0 |
| Constipation | 4 | 0 | 6 | 3 | 0 |
| Diarrhea | 0 | 1 | 0 | 0 | 0 |
| Dyspepsia | 4 | 0 | 0 | 0 | 0 |
| Gastrointestinal hemorrhage | 0 | 0 | 6 | 0 | 0 |
| Nausea | 4 | 0 | 18 | 6 | 0 |
| Stomatitis | 0 | 1 | 0 | 3 | 0 |
| Vomiting | 4 | 0 | 0 | 0 | 0 |
| **Respiratory** | | | | | |
| Rales | 0 | 0 | 6 | 0 | 0 |
| Rhinitis | 0 | 0 | 6 | 0 | 0 |
| Upper respiratory infection | 0 | 3 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| **CNS** | | | | | |
| Insomnia | 0 | 1 | 0 | 0 | 0 |
| Psychosis | 4 | 0 | 0 | 0 | 0 |
| Somnolence | 0 | 1 | 6 | 0 | 0 |
| **Cardiovascular** | | | | | |
| Atrial fibrillation | 0 | 0 | 6 | 0 | 4 |
| Atrial flutter | 0 | 1 | 0 | 0 | 0 |
| Cardiac failure | 0 | 1 | 0 | 0 | 0 |
| Hypertension | 0 | 0 | 6 | 0 | 4 |
| Syncope | 0 | 0 | 6 | 0 | 0 |
| Tachycardia | 0 | 0 | 6 | 0 | 4 |
| **Endocrine** | | | | | |
| Hypothyroidism | 0 | 0 | 6 | 0 | 0 |
| **Hemic and Lymphatic** | | | | | |
| Anemia | 0 | 0 | 6 | 0 | 0 |
| Leukopenia | 4 | 0 | 0 | 0 | 0 |
| Neutropenia | 0 | 1 | 0 | 0 | 0 |
| Thrombocytopenia | 0 | 1 | 0 | 0 | 0 |
| **Musculoskeletal** | | | | | |
| Myalgia | 0 | 1 | 0 | 0 | 0 |
| **Urogenital** | | | | | |
| Uremia | 4 | 0 | 0 | 0 | 0 |
| **Laboratory Abnormalities** | | | | | |
| Hypocalcemia | 0 | 1 | 12 | 0 | 0 |
| Hypokalemia | 4 | 4 | 18 | 0 | 0 |
| Hypomagnesemia | 4 | 10 | 12 | 3 | 4 |
| Hypophosphatemia | 0 | 9 | 18 | 3 | 0 |

Paget's Disease

Adverse reactions that occurred in at least 5% of patients with Paget's disease treated with

90 mg of pamidronate disodium in two clinical trials included fever, nausea, back pain, and bone pain. Dizziness, headaches, parathesias, and increased sweating were also reported and occurred more frequently than reported in patients treated with pamidronate for hypercalcemia of malignancy.

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

***Cardiovascular:*** Hypertension

***Musculoskeletal:*** Arthrosis, bone pain

***Nervous system:*** Headache

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

The most commonly reported (> 15%) adverse reactions occurred with similar frequencies in the pamidronate disodium and in the placebo group (see Table 2).

**Table 2: Commonly Reported Adverse Reactions in Three U.S. Controlled Clinical Trials**

| | Pamidronate Disodium 90 mg over 4 hours | Placebo | Pamidronate Disodium 90 mg over 2 hours | Placebo | All Pamidronate Disodium 90 mg | Placebo |
|---|---|---|---|---|---|---|
| | N = 205 % | N = 187 % | N = 367 % | N = 386 % | N = 572 % | N = 573 % |
| **General** | | | | | | |
| Asthenia | 16 | 17 | 26 | 19 | 22 | 19 |
| Fatigue | 32 | 28 | 40 | 29 | 37 | 29 |
| Fever | 39 | 38 | 38 | 32 | 39 | 34 |
| Metastases | 1 | 3 | 31 | 24 | 21 | 18 |
| Pain | 13 | 12 | 15 | 18 | 14 | 16 |
| **Digestive System** | | | | | | |
| Anorexia | 17 | 17 | 31 | 25 | 26 | 22 |
| Diarrhea | 27 | 27 | 29 | 31 | 29 | 30 |
| Dyspepsia | 18 | 13 | 18 | 15 | 23 | 18 |
| Nausea | 36 | 37 | 64 | 59 | 54 | 52 |
| Pain Abdominal | 20 | 16 | 24 | 18 | 23 | 18 |
| Vomiting | 17 | 20 | 46 | 39 | 36 | 33 |
| **Hemic and Lymphatic** | | | | | | |
| Anemia | 48 | 42 | 40 | 37 | 43 | 38 |
| Granulocytopenia | 21 | 16 | 19 | 21 | 20 | 19 |
| **Musculoskeletal System** | | | | | | |
| Arthralgias | 11 | 7 | 15 | 13 | 14 | 11 |
| Myalgia | 25 | 15 | 26 | 23 | 26 | 20 |
| Skeletal Pain | 61 | 72 | 70 | 75 | 67 | 74 |
| **CNS** | | | | | | |
| Anxiety | 8 | 9 | 18 | 17 | 14 | 14 |
| Headache | 24 | 20 | 27 | 24 | 26 | 22 |
| Insomnia | 17 | 17 | 25 | 19 | 22 | 19 |
| **Respiratory System** | | | | | | |
| Coughing | 26 | 23 | 25 | 20 | 26 | 21 |
| Dyspnea | 22 | 21 | 35 | 24 | 30 | 23 |
| Pleural Effusion | 3 | 4 | 15 | 9 | 11 | 8 |
| Sinusitis | 15 | 17 | 16 | 10 | 16 | 12 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Upper Respiratory Tract Infection | 32 | 28 | 20 | 20 | 24 | 23 |
| **Urogenital System** | | | | | | |
| Urinary Tract Infection | 16 | 9 | 20 | 18 | 19 | 16 |

In the breast cancer trials, four pamidronate disodium-related adverse reactions, interstitial pneumonitis, malaise and dyspnea, symptomatic hypocalcemia, and severe bone pain, resulted in discontinuation of therapy.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval pamidronate sodium use. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General: reactivation of Herpes simplex and Herpes zoster, influenza-like symptoms

CNS: confusion and visual hallucinations, sometimes in the presence of electrolyte imbalance

Skin: rash, pruritus

Special senses: conjunctivitis, orbital inflammation

Renal and urinary disorders: focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome; renal tubular disorders (RTD); tubulointerstitial nephritis, and glomerulonephropathies.

Laboratory abnormalities: hyperkalemia, hypernatremia, hematuria. Cases of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and anaphylactic shock. Pamidronate disodium is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates *[see Contraindications (4)]*.

Respiratory, thoracic and mediastinal disorders: adult respiratory distress syndrome (ARDS), interstitial lung disease (ILD).

Musculoskeletal and connective tissue disorders: severe, occasionally incapacitating bone, joint, and/or muscle pain.

## 7 DRUG INTERACTIONS

### 7.1 Nephrotoxic Drugs

Caution is indicated when pamidronate disodium is used with other potentially nephrotoxic drugs.

### 7.2 Thalidomide

In multiple myeloma patients, the risk of renal deterioration may be increased when

pamidronate disodium is used in combination with thalidomide.

### 7.3 Loop Diuretics

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, pamidronate disodium can cause fetal harm when administered to a pregnant woman. Available data from case reports with pamidronate disodium use in pregnant women are insufficient to inform a drug-associated risk. Administration of pamidronate to pregnant rats and rabbits resulted in maternal toxicity and embryo-fetal effects *(see Data)*.

Bisphosphonates, such as pamidronate disodium, are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and

miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

*Animal Data*

In animal reproduction studies, intravenous administration of pamidronate to pregnant rats and rabbits during the period of organogenesis resulted in maternal toxicity and embryo-fetal effects at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion.

### 8.2 Lactation

Risk Summary

There are limited data on the presence of pamidronate or its metabolites in human milk, its effects on a breastfed child, or its effects on milk production.

Pamidronate disodium binds to bone long term and may be released over periods of weeks to years. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during and after pamidronate disodium treatment.

### 8.3 Females and Males of Reproductive Potential

Pamidronate disodium can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of pamidronate disodium.

Contraception

Females

Pamidronate disodium binds to bone long term and may be released over periods of weeks to years. Advise females of reproductive potential to use effective contraception during and after pamidronate disodium treatment.

Infertility

Based on animal studies, pamidronate disodium may impair fertility in males and females of reproductive potential *[see Nonclinical Toxicology (13.1)].*

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

Of the total number of subjects in clinical studies of pamidronate disodium, approximately 20% were 65 and over, while approximately 15% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### 8.6 Patients with Renal Impairment

The renal clearance of pamidronate was reduced in patients with reduced creatinine clearance. Because pamidronate disodium is administered on a monthly basis, drug accumulation is not expected. No changes in pamidronate disodium dosing regimen are recommended for patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min). Limited pharmacokinetic data exist in patients with creatinine clearance < 30 mL/min *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

### 8.7 Patients with Hepatic Impairment

Patients with moderate hepatic impairment exhibited higher mean pamidronate AUC and $C_{max}$. Because pamidronate disodium is administered on a monthly basis, drug accumulation is not expected. No changes in pamidronate disodium dosing regimen are recommended for patients with mild to moderate hepatic impairment. Pamidronate disodium has not been studied in patients with severe hepatic impairment *[see Clinical*

*Pharmacology (12.3)]*.

## 10 OVERDOSAGE

Cases of drug overdose have been reported in hypercalcemia patients treated with total doses of 225 mg to 300 mg pamidronate disodium given over 2.5 to 4 days. All patients survived, but all developed hypocalcemia that required intravenous and/or oral administration of calcium. If overdosage occurs, treat symptomatic hypocalcemia patients with short-term intravenous calcium.

Single doses of pamidronate disodium should not exceed 90 mg, and the duration of the intravenous infusion should be no less than 2 hours *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

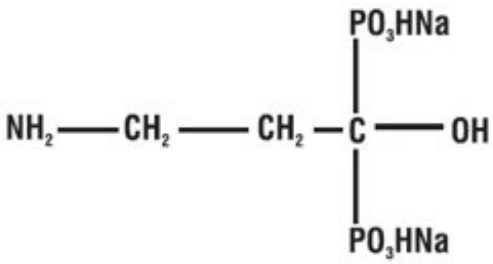
In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium/day for 3 days experienced high fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), and transient taste perversion, occurring about 6 hours after the first infusion. Fever and hypotension reversed with steroid therapy.

## 11 DESCRIPTION

Pamidronate Disodium Injection is a bisphosphonate available in 30 mg and 90 mg vials for intravenous administration. Each mL of the 30 mg/10 mL vial contains 3 mg pamidronate disodium, 47 mg mannitol; water for injection, q.s.; and phosphoric acid to adjust pH 6.0 to 7.0. Each mL of the 90 mg/10 mL vial contains, 9 mg pamidronate disodium, 37.5 mg mannitol; water for injection, q.s.; and phosphoric acid to adjust pH 6.0 to 7.0.

The pH of a 1% solution of pamidronate disodium in distilled water is approximately 8.3.

Pamidronate disodium, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, and its structural formula is:




Pamidronate disodium is a white powder. It is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2$ and its molecular weight is 279.1 (calculated as the anhydrous form).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The principal pharmacologic action of pamidronate disodium is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Pamidronate disodium adsorbs to calcium phosphate (hydroxyapatite) crystals in bone and may block dissolution of this mineral component of bone. *In vitro*, pamidronate disodium inhibited osteoclast activity. In animal studies, pamidronate disodium inhibited bone resorption, but did not inhibit bone formation and mineralization. In animal tumor models, pamidronate disodium inhibited the increased osteoclast activity induced by tumors.

### 12.2 Pharmacodynamics

Serum phosphate levels have been noted to decrease after administration of pamidronate disodium, presumably because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7 to 10 days.

Urinary calcium/creatinine and urinary hydroxyproline/creatinine ratios decrease and usually return to within or below normal after treatment with pamidronate disodium. These changes occur within the first week after treatment, as do decreases in serum calcium levels, and are consistent with an antiresorptive pharmacologic action.

### 12.3 Pharmacokinetics

Table 3 shows maximum concentration, percent of dose excreted in urine, total clearance, and renal clearance of pamidronate after an intravenous infusion of 30, 60, or 90 mg of pamidronate disodium over 4 hours and 90 mg of pamidronate disodium over 24 hours in cancer patients (n = 24) who had minimal or no bony involvement.

**Table 3: Mean (Standard Deviation, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients (n = 6 for each group)**

| Dose (infusion rate) | Maximum Concentration (mcg/mL) | Percent of dose excreted in urine | Total Clearance (mL/min) | Renal Clearance (mL/min) |
|---|---|---|---|---|
| 30 mg (4 hrs) | 0.73 (0.14, 19.1%) | 43.9 (14.0, 31.9%) | 136 (44, 32.4%) | 58 (27, 46.5%) |
| 60 mg (4 hrs) | 1.44 (0.57, 39.6%) | 47.4 (47.4, 54.4%) | 88 (56, 63.6%) | 42 (28, 66.7%) |
| 90 mg (4 hrs) | 2.61 (0.74, 28.3%) | 45.3 (25.8, 56.9%) | 103 (37, 35.9%) | 44 (16, 36.4%) |
| 90 mg (24 hrs) | 1.38 (1.97, 142.7%) | 47.5 (10.2, 21.5%) | 101 (58, 57.4%) | 52 (42, 80.8%) |

Distribution

The body retention of pamidronate was 54 ± 16% (mean ± standard deviation) of the dose over 120 hours.

Metabolism

Pamidronate is not metabolized.

Elimination

The elimination half-life is 28 ± 7 hours (mean ± standard deviation). Total and renal clearances of pamidronate were 107 ± 50 mL/min and 49 ± 28 mL/min, respectively. The rate of elimination from bone has not been determined.

After administration of 30, 60, and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate disodium over 24 hours, 46 ± 16% (mean ± standard deviation) of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose.

Specific Populations

*Renal Impairment*

The pharmacokinetics of pamidronate were studied in cancer patients (n = 19) with normal and varying degrees of renal impairment. Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. Renal clearance correlated with creatinine clearance (see Figure 1). Because pamidronate disodium is administered on a monthly basis, drug accumulation is not expected.

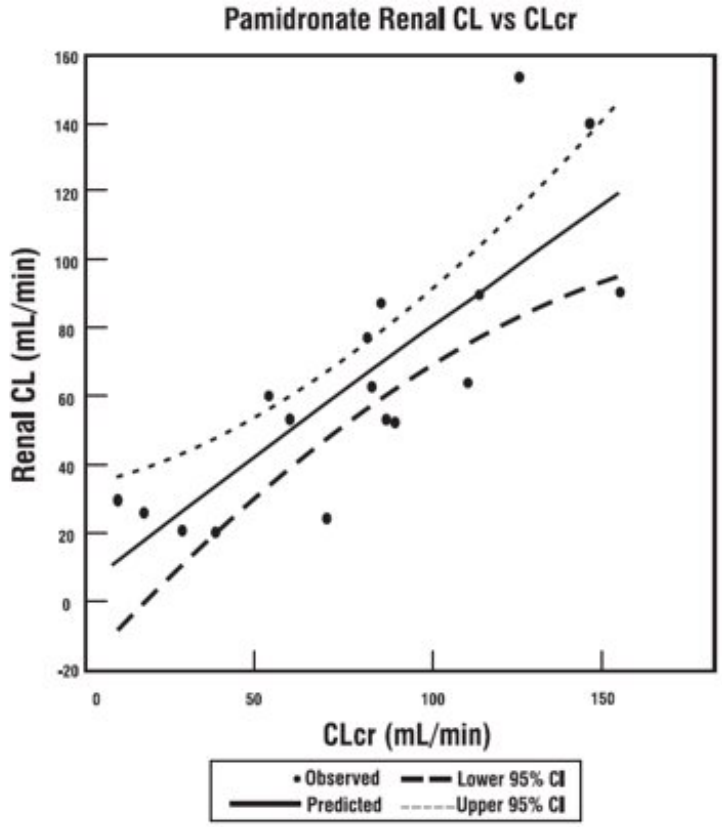



**Figure 1: Pamidronate renal clearance as a function of creatinine clearance in patients with normal and impaired renal function. The lines are the mean prediction line and**

**95% confidence intervals.**

*Hepatic Impairment*

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n = 6) and mild to moderate hepatic dysfunction (n = 7). Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. Although there was a difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (53% increase) and $C_{max}$ (29% increase), and decreased plasma clearance (33% decrease) values. Because pamidronate disodium is administered on a monthly basis, drug accumulation is not expected.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study with daily oral administration of pamidronate in rats, there was a positive dose-response relationship for benign adrenal pheochromocytoma. The lowest daily dose associated with adrenal pheochromocytoma resulted in systemic exposures that were similar to the systemic exposure achieved in patients at the intended clinical dose. Adrenal pheochromocytoma also was observed in low numbers in the control animals and is considered a relatively common spontaneous neoplasm in the rat. Pamidronate given daily by oral administration was not carcinogenic in an 80 week study in mice.

Pamidronate was not genotoxic in the Ames bacterial mutagenicity assay, nucleus-anomaly test, sister-chromatid-exchange study, and point-mutation test. Pamidronate was not genotoxic in the in vivo rat micronucleus assay.

In rats, decreased fertility occurred in first-generation offspring of parents who had received 150 mg/kg of pamidronate orally; however, this occurred only when animals were mated with members of the same dose group.

### 13.2 Animal Toxicology and/or Pharmacology

After intravenous administration of radiolabeled pamidronate in rats, approximately 50% to 60% of the compound was rapidly adsorbed by bone and slowly eliminated from the body by the kidneys. In rats given 10 mg/kg bolus injections of radiolabeled pamidronate disodium, approximately 30% of the compound was found in the liver shortly after administration and was then redistributed to bone or eliminated by the kidneys over 24 to 48 hours. Studies in rats injected with radiolabeled pamidronate disodium showed that the compound was rapidly cleared from the circulation and taken up mainly by bones, liver, spleen, teeth, and tracheal cartilage. Radioactivity was eliminated from most soft tissues within 1 to 4 days; was detectable in liver and spleen for 1 and 3 months, respectively; and remained high in bones, trachea, and teeth for 6 months after dosing. Bone uptake occurred preferentially in areas of high bone turnover. The terminal phase of elimination half-life in bone was estimated to be approximately 300 days.

## 14 CLINICAL STUDIES

### 14.1 Hypercalcemia of Malignancy

In one double-blind clinical trial, 52 patients who had hypercalcemia of malignancy received 30 mg, 60 mg, or 90 mg of pamidronate disodium as a single 24-hour intravenous infusion if their corrected serum calcium levels were ≥ 12 mg/dL after 48-hours of saline hydration (See Table 4).

**Table 4: Comparison of Calcium Normalization Following a 24-hour Infusion of Pamidronate Disodium**

| **Pamidronate Disodium** | **30 mg** | **60 mg** | **90 mg** |
|---|---|---|---|
| Mean Baseline Corrected Serum Calcium (after 48 hours saline hydration) | 13.8 mg/dL | 13.8 mg/dL | 13.3 mg/dL |
| **% Patients with Normalized Serum Calcium (N = 52)** | | | |
| Day 7 | 41% | 61% | 100% |
| Day 14 | ---- | 33% | 53% |

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of ≥ 12 mg/dL after at least 24-hours of saline hydration were randomized to receive either 60 mg of pamidronate disodium as a single 24-hour intravenous infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous infusion daily for 3 days. Results are shown in Table 5.

**Table 5: Calcium Levels, Percentage of Patients with Response over Time, and Median Duration of Response**

| | **Pamidronate Disodium 60 mg/24-hours (N = 30)** | **Etidronate Disodium 7.5 mg/kg/2-hours (N = 35)** | **P-value** |
|---|---|---|---|
| **Mean Corrected Serum Calcium Level** | | | |
| Baseline | 14.6 mg/dL | 13.8 mg/dL | |
| At Day 7 | 10.4 mg/dL | 11.2 mg/dL | |
| **% Patients with Normalized Serum Calcium Level or > 15% from Baseline** | | | |
| At Day 7 | 97% | 65% | $P < 0.01$ |
| At Day 14 | 43% | 18% | |
| **Median Duration of Response** | | | |
| | 7 days | 5 days | |

In a third multicenter, randomized, parallel, double-blind trial, 69 patients with cancer, who had a corrected serum calcium level of ≥ 12 mg/dL after 24 hours of saline hydration, received 60 mg of pamidronate disodium as a 4-or 24-hour infusion or a saline control (Table 6).

**Table 6: Comparison of Pamidronate Disodium 4-hour, 24-hours Infusion with**

**Saline Control**

| | **Pamidronate Disodium 60 mg/4 hours** | **Pamidronate Disodium 60 mg/24 hours** | **Saline Control** |
|---|---|---|---|
| Baseline Corrected Serum Calcium | 14.2 mg/dL | 13.7 mg/dL | 13.7 mg/dL |
| **% Patients with Normalized Serum Calcium (N = 69)** | | | |
| At Day 7 | 78% | 61% | 22% |
| At Day 14 | 39% | 26% | --- |
| **Median Duration of Complete Response** | | | |
| Days | 4 | 6.5 | |

In all three trials, similar response rates were observed with pamidronate disodium treatment regardless of the presence or absence of bone metastases. Concomitant administration of furosemide did not affect response rates.

Thirty-two patients who had recurrent or refractory hypercalcemia of malignancy were given a second course of 60 mg of pamidronate disodium over a 4-or 24-hour period. Of these, 41% showed a complete response and 16% showed a partial response to the retreatment, and these responders had about a 3 mg/dL fall in mean-corrected serum calcium levels 7 days after retreatment.

In a fourth multicenter, randomized, double-blind trial, 103 patients with cancer and hypercalcemia (corrected serum calcium ≥ 12 mg/dL) received 90 mg of pamidronate disodium as a 2-hour infusion. The mean baseline corrected serum calcium was 14 mg/dL.

Patients were not required to receive IV hydration prior to drug administration, but all subjects did receive at least 500 mL of IV saline hydration concomitantly with the pamidronate infusion. By day 10 after drug infusion, 70% of patients had normal corrected serum calcium levels (< 10.8 mg/dL).

### 14.2 Paget’s Disease

In a double-blind clinical trial, 64 patients with moderate to severe Paget’s disease of bone received 5 mg, 15 mg, or 30 mg of pamidronate disodium as a single 4-hour infusion daily on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 mg of pamidronate disodium.

For the 15 mg, 45 mg, and 90 mg groups, mean baseline serum alkaline phosphatase levels were 1409 U/L, 983 U/L, and 1085 U/L, and mean baseline urine hydroxyproline/creatinine ratios were 0.25, 0.19, and 0.19, respectively.

The effects of pamidronate disodium on serum alkaline phosphatase (SAP) and urine hydroxyproline/creatinine ratios (UOHP/C) are summarized in Table 7.

**Table 7: Percent of Patients with Decrease in SAP and UOHP/C**

| | **SAP** | | | **UOHP/C** | | |
|---|---|---|---|---|---|---|
| % Decrease | 15 mg | 45 mg | 90 mg | 15 mg | 45 mg | 90 mg |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥ 50 | 26% | 33% | 60% | 15% | 47% | 72% |
| ≥ 30 | 40% | 65% | 83% | 35% | 57% | 85% |

For the 15 mg, 45 mg, and 90 mg groups, median maximum percent decreases from baseline in serum alkaline phosphatase were 25%, 41%, and 57%, and urine hydroxyproline/creatinine ratios were 25%, 47%, and 61%, respectively. The median time to response (≥ 50% decrease) for serum alkaline phosphatase was approximately 1 month for the 90 mg group, and the response duration ranged from 1 to 372 days.

Twenty-five patients who had Paget's disease were retreated with 90 mg of pamidronate disodium. Of these, 44% had a ≥ 50% decrease in serum alkaline phosphatase from baseline after treatment, and 39% had a ≥ 50% decrease in urine hydroxyproline/creatinine ratio from baseline after treatment.

### 14.3 Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

*Breast Cancer*

Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of pamidronate disodium 90 mg infused over 2 hours every 3 to 4 weeks for 24 months to placebo for prevention of SREs in breast cancer patients with osteolytic bone metastases who had one or more predominantly lytic metastases of at least 1 cm in diameter. The first trial enrolled 382 patients receiving chemotherapy, of whom 185 were randomized to pamidronate disodium and 197 to placebo. The second trial enrolled 372 patients receiving hormonal therapy, of whom 182 were randomized to pamidronate disodium and 190 to placebo. All but three patients were evaluable for efficacy. Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. Therapy continued for 24 months unless patient discontinued study.

Median duration of follow-up was 13 months in patients receiving chemotherapy and 17 months in patients receiving hormone therapy. Twenty-five percent of the patients in the chemotherapy study and 37% of the patients in the hormone therapy study received pamidronate disodium for 24 months. Efficacy results are shown in Table 8:

**Table 8: Efficacy Results in Breast Cancer Patients**

| | **Breast Cancer Patients Receiving Chemotherapy** | | | | | |
|---|---|---|---|---|---|---|
| | **Any SRE** | | **Radiation** | | **Fractures** | |
| | **Pamidronate disodium** | **Placebo** | **Pamidronate disodium** | **Placebo** | **Pamidronate disodium** | **Placebo** |
| **N** | **185** | **195** | **185** | **195** | **185** | **195** |
| Skeletal Morbidity Rate (#SRE/year) Mean | 2.5 | 3.7 | 0.8 | 1.3 | 1.6 | 2.2 |
| P-Value | < .001 | | < .001* | | .018* | |
| Proportion of patients having an | 46% | 65% | 28% | 45% | 36% | 49% |

| | | | | | | |
|---|---|---|---|---|---|---|
| SRE | | | | | | |
| P-Value | < .001 | | < .001* | | .014* | |
| Median Time to SRE (months) | 13.9 | 7.0 | NR† | 14.2 | 25.8 | 13.3 |
| P-Value | < .001 | | < .001* | | .009* | |
| | **Breast Cancer Patients Receiving Hormonal Therapy** | | | | | |
| | **Any SRE** | | **Radiation** | | **Fractures** | |
| | **Pamidronate disodium** | **Placebo** | **Pamidronate disodium** | **Placebo** | **Pamidronate disodium** | **Placebo** |
| **N** | **182** | **189** | **182** | **189** | **182** | **189** |
| Skeletal Morbidity Rate (#SRE/year) Mean | 2.4 | 3.6 | 0.6 | 1.2 | 1.6 | 2.2 |
| P-Value | .021 | | .013* | | .040* | |
| Proportion of patients having an SRE | 55% | 63% | 31% | 40% | 45% | 55% |
| P-Value | .094 | | .058* | | .054* | |
| Median Time to SRE (months) | 10.9 | 7.4 | NR† | 23.4 | 20.6 | 12.8 |
| P-Value | .118 | | .016* | | .113* | |

* Fractures and radiation to bone were two of several secondary endpoints. The statistical significance of these analyses may be overestimated since numerous analyses were performed.
† NR = Not Reached

*Advanced Multiple Myeloma*

In a double-blind, randomized, placebo-controlled trial, 392 patients on therapy for advanced multiple myeloma received pamidronate disodium or placebo to determine the effect on the occurrence of skeletal-related events (SREs). SREs were defined as the occurrence of new or additional pathologic fractures, radiation therapy or surgery for bony fracture, impending fracture, or spinal cord compression. Pamidronate disodium 90 mg or placebo was administered as a 4-hour infusion every 4 weeks for 9 months. Of the 392 patients enrolled, 377 were evaluable for efficacy. Results are shown in Table 9.

**Table 9: SRE Outcomes in Multiple Myeloma**

| | **Pamidronate disodium 90 mg /4 hours (N = 196)** | **Placebo (N = 181)** | **P-value** |
|---|---|---|---|
| At 1 year<br>% of Patients with SRE | 24% | 41% | P < 0.001 |

| | | | |
|---|---|---|---|
| % with Pathological Fracture | 17% | 30% | P < 0.004 |
| % with Radiation to Bone | 14% | 21% | P < 0.049 |
| At 1.75 years (21 Months)<br>% Pathologic Vertebral Fractures | 16% | 27% | P = 0.005 |

The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the pamidronate disodium group (P = 0.001, 0.006, and 0.046, respectively). After 21 months, the proportion of patients experiencing any skeletal event remained significantly less in the pamidronate disodium group compared to the placebo group (P = 0.015). Time to first SRE was significantly longer in the pamidronate disodium group compared to placebo (P = 0.016). Survival was not different between treatment groups.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Pamidronate Disodium Injection is available as follows:

30 mg/10 mL (3 mg/mL) single-dose vial as a clear-colorless solution containing 30 mg of pamidronate disodium and 470 mg of mannitol in 10 mL water for injection.

NDC 67457-430-10
Carton of 1 single-dose vial

90 mg/10 mL (9 mg/mL) single-dose vial as a clear-colorless solution containing 90 mg of pamidronate disodium and 375 mg of mannitol in 10 mL water for injection.

NDC 67457-446-10
Carton of 1 single-dose vial

**Storage: Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].**

## 17 PATIENT COUNSELING INFORMATION

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during and after pamidronate disodium treatment *[see Use in Specific Populations (8.3)]*.
- Advise women not to breastfeed during and after pamidronate disodium treatment *[see Use in Specific Populations (8.2)]*.
- Advise males and females of reproductive potential that pamidronate may impair fertility *[see Use in Specific Populations (8.3)]*.
- Inform patients that the risk of osteonecrosis of the jaw is increased in patients undergoing invasive dental procedures. Advise patients to avoid such procedures, if possible, and to maintain good dental hygiene and routine dental care *[see Warnings and Precautions (5.4)].*
- Inform patients that atypical femur fractures have occurred in patients taking bisphosphonates. Advise patients to report any thigh or groin pain *[see Warnings and Precautions (5.5)].*

Manufactured for:
**Mylan Institutional LLC**
Morgantown, WV 26505 U.S.A.

Manufactured by:
**OneSource Specialty Pharma Limited**
(Sterile Product Division)
Bengaluru 560076, India

50107390
1200013667

Revised: 12/2025

**PRINCIPAL DISPLAY PANEL – 3 mg/mL**

**NDC 67457-430-10**

**Pamidronate Disodium Injection**

**30 mg/10 mL (3 mg/mL)**

**Sterile**

**Do not mix with calcium containing infusion solution**

**FURTHER DILUTION REQUIRED**

**For Intravenous Infusion**

**Mylan**

**Rx only**

**Single-Dose Vial**

**Each vial contains:**
**Active:** Pamidronate Disodium 30 mg

Inactives: Mannitol 470 mg; Phosphoric acid to adjust pH (6.0 to 7.0); and Water for Injection q.s to 10 mL.

**Storage: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

**Usual Dosage:** See Package Insert.

**Important: Dilution and administration differs for each indication.**

Discard unused portion.

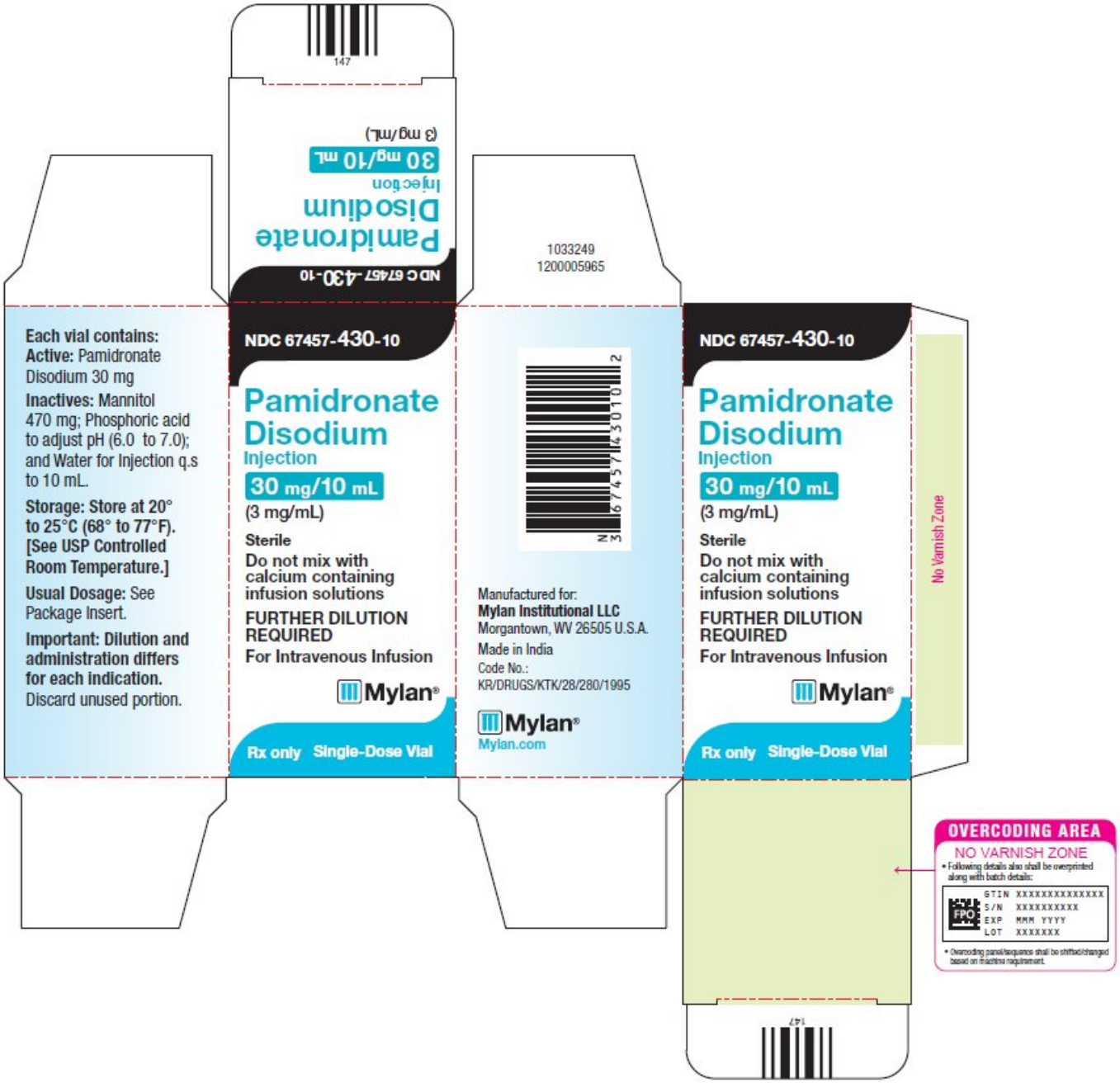
Manufactured for:
**Mylan Institutional LLC**
Morgantown, WV 26505 U.S.A.

Made in India

Code No.:

KR/DRUGS/KTK/28/280/1995

**Mylan.com**




**PRINCIPAL DISPLAY PANEL – 9 mg/mL**

**NDC 67457-446-10**

**Pamidronate Disodium Injection**

**90 mg/10 mL (9 mg/mL)**

**Sterile**

**Do not mix with calcium containing infusion solution**

**FURTHER DILUTION REQUIRED**

**For Intravenous Infusion**

**Mylan**

**Rx only**

Single-Dose Vial

**Each vial contains:**
**Active:** Pamidronate Disodium 90 mg

**Inactives:** Mannitol 375 mg; Phosphoric acid to adjust pH (6.0 to 7.0); and Water for Injection q.s to 10 mL.

**Storage: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

**Usual Dosage:** See Package Insert.

**Important: Dilution and administration differs for each indication.**

Discard unused portion.

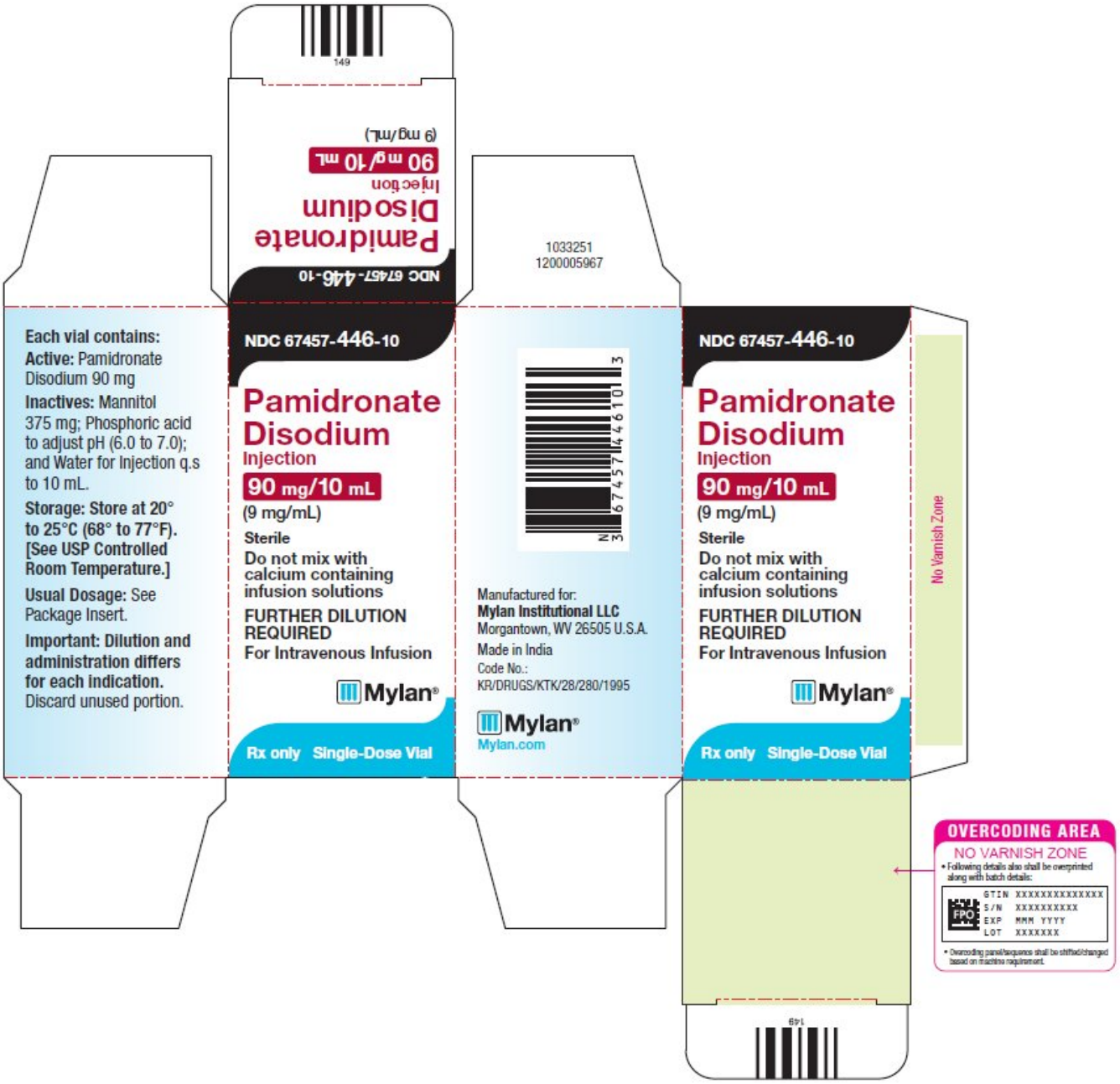
Manufactured for:
**Mylan Institutional LLC**
Morgantown, WV 26505 U.S.A.

Made in India

Code No.:

KR/DRUGS/KTK/28/280/1995

Mylan.com




# PAMIDRONATE DISODIUM

pamidronate disodium injection

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:67457-430 |
| **Route of Administration** | INTRAVENOUS | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **PAMIDRONATE DISODIUM** (UNII: 8742T8ZQZA) (PAMIDRONIC ACID - UNII:OYY3447OMC) | PAMIDRONATE DISODIUM | 3 mg in 1 mL |

| Inactive Ingredients | |
|---|---|
| **Ingredient Name** | **Strength** |
| **MANNITOL** (UNII: 3OWL53L36A) | |
| **PHOSPHORIC ACID** (UNII: E4GA8884NN) | |
| **WATER** (UNII: 059QF0KO0R) | |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start Date** | **Marketing End Date** |
| **1** | NDC:67457-430-10 | 1 in 1 CARTON | 05/10/2011 | |
| **1** | | 10 mL in 1 VIAL; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA078520 | 05/10/2011 | |

# PAMIDRONATE DISODIUM

pamidronate disodium injection

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:67457-446 |
| **Route of Administration** | INTRAVENOUS | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **PAMIDRONATE DISODIUM** (UNII: 8742T8ZQZA) (PAMIDRONIC ACID - UNII:OYY3447OMC) | PAMIDRONATE DISODIUM | 9 mg in 1 mL |

| Inactive Ingredients | |
|---|---|
| **Ingredient Name** | **Strength** |
| **MANNITOL** (UNII: 3OWL53L36A) | |
| **PHOSPHORIC ACID** (UNII: E4GA8884NN) | |
| **WATER** (UNII: 059QF0KO0R) | |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start** | **Marketing End** |

| # | Item Code | Package Description | Date | Date |
|---|---|---|---|---|
| 1 | NDC:67457-446-10 | 1 in 1 CARTON | 05/10/2011 | |
| 1 | | 10 mL in 1 VIAL; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA078520 | 05/10/2011 | |

## Labeler - Mylan Institutional LLC (790384502)

Revised: 12/2025 Mylan Institutional LLC