PRODUCT MONOGRAPH

[Pr]PAMIDRONATE DISODIUM FOR INJECTION

(pamidronate disodium)

3 mg / mL, 6 mg / mL and 9 mg / mL

Solution for Injection

For Intravenous Infusion Only

Bone Metabolism Regulator

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[Pr]PAMIDRONATE DISODIUM FOR INJECTION

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Nonmedicinal Ingredients
Intravenous (slow infusion only)	Solution for Injection 3 mg / mL Solution for Injection 6 mg / mL Solution for Injection 9 mg / mL	Mannitol, USP Phosphoric Acid, NF Sodium Hydroxide, NF Water for Injection, USP

INDICATIONS AND CLINICAL USE

- **Tumor-induced hypercalcemia following adequate saline rehydration.**
  Prior to treatment with Pamidronate Disodium for Injection (pamidronate disodium), renal excretion of excess calcium should be promoted by restoring and maintaining adequate fluid balance and urine output.
- **Conditions associated with increased osteoclast activity: predominantly lytic bone metastases and multiple myeloma.**
- **Symptomatic Paget's disease of bone.**

CONTRAINDICATIONS

Pamidronate Disodium for Injection is contraindicated in:

- Patients with known or suspected hypersensitivity to Pamidronate Disodium for Injection (pamidronate disodium), to any of its excipients (see DOSAGE FORMS, COMPOSITION AND PACKAGING), or to other bisphosphonates.
- Pregnancy.
- Breast-feeding women.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The following are serious adverse events:
  - Osteonecrosis of the jaw (ONJ) (see WARNINGS AND PRECAUTIONS, General).
  - Deterioration in renal function (see WARNINGS AND PRECAUTIONS, Renal).

- Pamidronate Disodium for Injection should not be administered to patients with severe renal impairment except in cases of life-threatening tumor-induced hypercalcemia (see WARNINGS AND PRECAUTIONS, Special populations, Renal Impairment and DOSAGE AND ADMINISTRATION).

- Single doses of Pamidronate Disodium for Injection should not exceed 90 mg and the recommended infusion time should be observed (see WARNINGS AND PREACAUTIONS, Renal and DOSAGE AND ADMINISTRATION).

General

Pamidronate Disodium for Injection must never be given as a bolus injection since severe local reactions and thrombophlebitis may result from high local concentrations.

Pamidronate Disodium for Injection **should always be diluted and administered as a slow intravenous infusion (see DOSAGE AND ADMINISTRATION). Regardless of the volume of solution in which Pamidronate Disodium for Injection is diluted, slow intravenous infusion is absolutely necessary for safety.**

Pamidronate Disodium for Injection should not be given together with other bisphosphonates to treat hypercalcemia since the combined effects of these agents are unknown.

Pamidronate Disodium for Injection should not be mixed with calcium-containing intravenous infusions.

Patients must be assessed prior to and during administration of Pamidronate Disodium for Injection to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

It is essential in the initial treatment of tumor-induced hypercalcemia that intravenous rehydration be instituted to restore urine output. Patients should be hydrated adequately throughout treatment, but overhydration must be avoided.

Cardiovascular

In patients with cardiac disease, especially in the elderly, additional saline overload may precipitate cardiac failure (left ventricular failure or congestive heart failure). Therefore, overhydration should be avoided especially in patients at risk of cardiac failure. Fever (influenza-like symptoms) may also contribute to this deterioration.

Atrial fibrillation: When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Previously, it has been observed in a clinical trial investigating patients with postmenopausal osteoporosis, that zoledronic acid-treated patients (5 mg) had an increased rate of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism of this increased incidence of atrial fibrillation in isolated studies with some bisphosphonates, including pamidronate disodium, is unknown.

Effects on Ability to Drive or Use Machinery

Somnolence and/or dizziness may occur following Pamidronate Disodium for Injection infusion, in which case the patient should not drive, operate potentially dangerous machinery or engage in other activities that may be hazardous because of decreased alertness.

Endocrine and Metabolism

Paget's Disease:

Pre-existing hypocalcemia must be treated by adequate intake of calcium and Vitamin D before initiating Pamidronate Disodium for Injection. Other disturbances of mineral metabolism (e.g., parathyroidectomy resulting in partial or complete hypoparathyroidism) must also be effectively managed. It is recommended that patients with Paget's disease of bone have their serum calcium levels assessed before and during treatment with Pamidronate Disodium for Injection (e.g. as part of their annual examination). All patients should be counselled regarding the importance of calcium and Vitamin D supplementation in maintaining serum calcium levels and on the symptoms of hypocalcemia.

Lytic Bone Metastases or Multiple Myeloma:

In the absence of hypercalcemia, patients who are at risk of calcium or Vitamin D deficiency should be given oral calcium and Vitamin D supplementation in order to minimize the risk of hypocalcemia. In the event that hypercalcemia develops, calcium and Vitamin D supplements should be discontinued immediately.

Hematologic

In clinical trials for patients with multiple myeloma and metastatic breast cancer, patients treated with pamidronate disodium had a higher number of anemia, leukopenia and thrombocytopenia adverse events than placebo-treated patients. Therefore, patients with pre-existing anemia, leukopenia, or thrombocytopenia should have regular hematology assessments.

Hepatic/Biliary/Pancreatic

There are no clinical data available in patients with severe hepatic impairment. Therefore, caution should be exercised when Pamidronate Disodium for Injection is given to these patients (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates, including pamidronate disodium. The time to onset of symptoms varied from one day to several months after starting the drug. Most

patients had relief of symptoms after stopping treatment. A subset of patients had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate.

Ophthalmologic

Ocular disturbances (conjunctivitis, uveitis, episcleritis and orbital inflammation) have been reported with bisphosphonate therapy, including pamidronate disodium. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. Treatment with Pamidronate Disodium for Injection may need to be discontinued.

Osteonecrosis of the Jaw (ONJ):

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including Pamidronate Disodium for Injection. The majority of reports have occurred in cancer patients treated with bisphosphonates; however, some cases have been reported in patients receiving bisphosphonates for Paget's disease. Although no causal relationship has been established, there is an association between bisphosphonate use and the development of ONJ. Post-marketing experience suggests a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma) and dental status (dental extractions, periodontal disease and local trauma including poorly fitting dentures); these are associated with a greater risk of developing ONJ. Patients with cancer also receive other treatments that may play a role in the development of ONJ, such as chemotherapy and glucocorticosteroids. Many patients had signs of local infection including osteomyelitis.

Presentation of ONJ may include altered local sensation (hyperesthesia or numbness), maxillofacial pain, “toothaches”, denture sore spots, loose teeth, exposed bone in the oral cavity, impaired healing, recurrent or persistent soft tissue infection in the oral cavity and marked oral odour. The onset can be from months to years after commencing bisphosphonate therapy. Patients should maintain good oral hygiene; it is recommended that advanced cancer patients be encouraged to have an oral examination of both hard and soft tissues, with preventive dentistry prior to treatment with bisphosphonates, and that such assessments continue at regularly scheduled intervals after bisphosphonate therapy is initiated. While on bisphosphonate treatment, patients should avoid invasive dental procedures if possible. Biopsies are not recommended unless metastasis to the jaw is suspected. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there is 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.

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

The following should be considered when evaluating a patient’s risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds)
- Route of administration (higher risk for parenteral administration)
- Cumulative dose of bone resorption therapy
- Co-morbid conditions (e.g. anemia, coagulopathies) and smoking

- Periodontal disease, poorly fitting dentures, history of dental disease.

Temporary interruption of Pamidronate Disodium for Injection treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of external auditory canal

Cases of osteonecrosis of the external auditory canal have been reported predominantly in adult cancer patients treated with long-term bisphosphonates, including pamidronate disodium.

Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving Pamidronate Disodium for Injection who present with ear symptoms including chronic ear infections.

Atypical Fractures of the Femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. Reports of atypical femoral fracture have also been received in patients treated with pamidronate disodium. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore, the contralateral femur should be examined in pamidronate disodium-treated patients, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of pamidronate disodium for injection therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During Pamidronate Disodium for Injection treatment, patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Renal

Bisphosphonates, including pamidronate disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Renal deterioration, progression to renal failure and dialysis (some with fatal outcome) have been reported very rarely in patients after the initial dose or a single dose of pamidronate disodium for injection. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with pamidronate disodium for injection in patients with multiple myeloma.

Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of Pamidronate Disodium for Injection should not exceed 90 mg, and the recommended infusion time should be observed (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women:
There are no adequate studies that support the use of pamidronate disodium for injection in pregnant women. It has been shown that pamidronate disodium for injection can cross the placenta in rats and has produced marked maternal and embryo/fetal adverse effects in rats and rabbits (see TOXICOLOGY, Reproductive Toxicity). When administered during organogenesis in animals, pamidronate disodium can cause bone mineralization defects. Therefore, Pamidronate Disodium for Injection should not be used during pregnancy (see CONTRAINDICATIONS).

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 very limited 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 versus oral) on this risk has not been established.

Nursing Women:
There are no adequate studies that support the use of pamidronate disodium for injection in lactating women. A study in lactating rats has shown that pamidronate passes into the milk. Mothers treated with Pamidronate Disodium for Injection should therefore not breast-feed their infants (see CONTRAINDICATIONS).

Women of Child-Bearing Potential
Women of child-bearing potential must use highly effective contraception during treatment.

Fertility:
There are no data available.

Pediatrics:
There are no adequate studies that support the use of pamidronate disodium for injection in children. Pamidronate Disodium for Injection is not recommended for use in children.

Renal Impairment:
Pamidronate disodium is excreted intact primarily via the kidney (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics), thus the risk of adverse reactions may be greater in patients with impaired renal function. Single doses of Pamidronate Disodium for Injection should not exceed 90 mg and the recommended infusion time should be observed (see DOSAGE AND ADMINISTRATION).

As with other intravenous bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Pamidronate Disodium for Injection. Experience with pamidronate disodium in patients with severe renal impairment (serum creatinine >440 mcmol/L in TIH patients; >180 mcmol/L in multiple myeloma patients) is limited. If clinical judgment determines that the potential benefits outweigh the risk in such cases, Pamidronate Disodium for Injection should be used cautiously and renal function carefully monitored. Patients treated with pamidronate disodium for injection for bone metastases or multiple myeloma should have their dose withheld if renal function has deteriorated (see DOSAGE AND ADMINISTRATION - Renal Impairment).

Monitoring and Laboratory Tests

Patients should have standard serum creatinine and clinical renal function parameters periodically evaluated. Patients receiving frequent pamidronate disodium infusions over a prolonged period of time, and those with pre-existing renal disease or a predisposition to renal impairment (e.g., patients with multiple myeloma and/or tumor-induced hypercalcemia) should have evaluations of standard laboratory and clinical parameters of renal function prior to each dose of pamidronate disodium. Fluid balance (urine output, daily weights) should also be followed carefully. If there is deterioration of renal function during pamidronate disodium therapy, the infusion must be stopped (see WARNINGS AND PRECAUTIONS, Renal).
Pamidronate disodium is excreted intact primarily via the kidney, thus the risk of renal adverse reactions may be greater in patients with impaired renal function.

Patients with anemia, leukopenia or thrombocytopenia should have regular hematology assessments.

Serum electrolytes, calcium, phosphate and magnesium should be monitored following initiation of therapy with Pamidronate Disodium for Injection. Occasional cases of mild, transient hypocalcemia, usually asymptomatic, have been reported. Symptomatic hypocalcemia occurs rarely and can be reversed with calcium gluconate. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcemia due to relative hypoparathyroidism.

In tumor-induced hypercalcemia, either ionized calcium or total serum calcium corrected (adjusted) for albumin should be monitored during treatment with pamidronate disodium. Serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since hypoalbuminemia is commonly present. Corrected serum calcium values should be calculated using established algorithms, such as:

$$cCa = tCa + (0.02 \times [40 - ALB])$$

where:
cCa = adjusted calcium concentration (mmol/L)
tCa = measured total calcium concentration (mmol/L)
ALB = measured albumin concentration (g/L)

Although mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia is usually associated with a variety of signs and symptoms, and can be life-threatening if not promptly recognized and treated. Individuals at risk and their caregivers should be made aware

that signs and symptoms of hypercalcemia include: lethargy, fatigue, confusion, loss of appetite, nausea and vomiting, constipation, excessive thirst and urination. Measures such as maintaining mobility and ensuring adequate hydration could diminish the symptoms of hypercalcemia. However, when symptoms of hypercalcemia are detected, it is important to seek medical assistance promptly.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions with pamidronate disodium are usually mild and transient. The most common adverse reactions are influenza-like symptoms and mild fever (an increase in body temperature of > 1 °C, which may last up to 48 hours). Fever usually resolves spontaneously and does not require treatment. Acute "influenza-like" reactions usually occur only with the first pamidronate disodium infusion. The tables below show the incidence of the more commonly observed adverse effects overall and by indication.

Clinical Trial Adverse Drug Reactions

Adverse drug reactions from clinical trials are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, <1/100); rare (≥1/10 000, <1/1 000); very rare (<1/10 000), including isolated reports.

Infections and infestations:
Very rare: reactivation of Herpes simplex and Herpes zoster.

Blood and lymphatic system disorders:
Common: anemia, thrombocytopenia, lymphocytopenia, granulocytopenia.
One case of acute lymphoblastic leukemia has been reported in a patient with Paget's disease. The causal relationship to the treatment or the underlying disease is unknown.

Immune system disorders:
Uncommon: allergic reactions including anaphylactoid reactions, bronchospasm, dyspnea, Quincke's (angioneurotic) edema.
Very rare: anaphylactic shock.

Metabolism and nutrition disorders:
Very common: hypocalcemia, hypophosphatemia.
Common: hypokalemia, hypomagnesemia, increase in serum creatinine.
Uncommon: abnormal liver function tests, increase in serum urea.
Very rare: hyperkalemia, hypernatremia.

Nervous system disorders:
Common: symptomatic hypocalcemia (tetany, paresthesia), headache, insomnia, somnolence.
Uncommon: seizures, pseudotumor cerebri, lethargy, agitation, dizziness.
Very rare: confusion, visual hallucinations.

Eye disorders:
Common: conjunctivitis.
Uncommon: uveitis (iritis, iridocyclitis).
Very rare: scleritis, episcleritis, xanthopsia.

Ear disorders:
Osteonecrosis of the external auditory canal.

Cardiac disorders:
Common: Atrial fibrillation.
Very rare: left ventricular failure (dyspnea, pulmonary edema), congestive heart failure (edema) due to fluid overload.

Vascular disorders:
Common: hypertension.
Uncommon: hypotension.

Gastrointestinal disorders:
Common: nausea, vomiting, anorexia, abdominal pain, diarrhea, constipation, gastritis.
Uncommon: dyspepsia.

Skin and subcutaneous disorders:
Common: rash.
Uncommon: pruritus.

Musculoskeletal and connective tissue disorders:
Common: transient bone pain, arthralgia, myalgia, generalized pain.
Uncommon: osteonecrosis of the jaw (ONJ), muscle cramps.

Renal and urinary disorders:
Uncommon: acute renal failure.
Rare: focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome.
Very rare: hematuria, deterioration of pre-existing renal disease.

General disorders and administration site conditions:
Very common: fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue, and flushes.
Common: reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis.

Tumor-induced Hypercalcemia and Paget's Disease

Adverse events considered to be related to pamidronate disodium occurring in ≥ 1% of patients in the specified indication:

Adverse Events	Tumor-induced Hypercalcemia	Paget's Disease
No. of patients	**n = 910**	**n = 395**
	(%)	(%)
Fever	6.9	8.9
Headache	0	4.8
Hypocalcemia	3.2	0.8
Influenza-like symptoms	0	11.9
Infusion site reaction	1.7	1.8
Malaise	0	5.8
Myalgia	0	2
Nausea	0.9	2
Pain (bone)	0	8.9
Pain (unspecified)	0	7.9
Rigors	0	2.8

Bisphosphonates, including pamidronate disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure (see WARNINGS AND PRECAUTIONS). Since many patients with tumor-induced hypercalcemia have compromised renal function prior to receiving antihypercalcemia therapy (see WARNINGS AND PRECAUTIONS), it is difficult to estimate the role of individual bisphosphonates in subsequent changes in renal function. Deterioration of renal function (elevation of serum creatinine of > 20% above baseline), which could not be readily explained in terms of pre-existing renal disease, prior nephrotoxic chemotherapies or compromised intravascular volume status has been noted in 7 cases of 404 patients treated with pamidronate disodium where these data have been reported. As with other intravenous bisphosphonates, renal monitoring is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Bone Metastases and Multiple Myeloma

The most commonly reported adverse events regardless of relationship to therapy are shown in the table below.

Deterioration of renal function (including renal failure) has been associated with bisphosphonates including pamidronate disodium. Renal monitoring is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Commonly Reported Adverse Events in Three Controlled Trials (regardless of causality)		
Bone Metastases and Multiple Myeloma Patients		
Adverse Event	**Pamidronate Disodium 90 mg**	**Placebo**
	n = 572	**n = 573**
General		
Asthenia	16.4	15.4
Fatigue	30.4	35.5
Fever	35.5	30.5
Metastases	14	13.6
Digestive System		
Anorexia	20.8	18
Constipation	27.6	30.9
Diarrhea	24.3	26.2
Dyspepsia	13.6	12.4
Nausea	48.4	46.4
Pain (Abdominal)	17.3	14
Vomiting	30.9	28.1
Hemic and Lymphatic Systems		
Anemia	35.1	32.6
Granulocytopenia	16.8	17.3
Thrombocytopenia	11	13.1
Musculoskeletal System		
Myalgias	22.6	16.9
Skeletal Pain	59.4	69.1
CNS		
Headache	24	19.7
Insomnia	18.2	17.3
Respiratory System		
Coughing	21.2	18.8
Dyspnea	23.3	18.7
Upper Respiratory Infection	19.8	20.9
Urogenital System		
Urinary Tract Infection	14.5	10.8

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported in post-marketing use:

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

Musculoskeletal and connective tissue disorders: severe and occasionally incapacitating bone, joint, and/or muscle pain, osteonecrosis of the jaw (ONJ), atypical subtrochanteric and diaphyseal femoral fractures;

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

Skin: rash, pruritus;

Eye disorders: conjunctivitis, scleritis, orbital inflammation;

Renal and urinary disorders: renal tubular disorders (RTD), tubulointerstitial nephritis, glomerulonephropathies;

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

Laboratory abnormalities: hyperkalemia, hypernatremia, hematuria. Instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and anaphylactic shock.

Description of Selected Adverse Drug Reactions

Atrial fibrillation: When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Previously, it has been observed in a clinical trial investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased rate of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%).The mechanism of this increased incidence of atrial fibrillation in isolated studies with some bisphosphonates, including pamidronate disodium, is unknown.

Osteonecrosis of the jaw: Cases of osteonecrosis of the jaw (ONJ) are uncommon, although data suggest a higher number of reported cases in certain cancers, such as advanced breast cancer and multiple myeloma. Some cases have been reported in patients receiving pamidronate for Paget's disease. The majority of reported cases of ONJ are associated with invasive dental procedures (such as tooth extraction or dental surgery and local trauma including poorly fitting dentures) or periodontal disease. Many patients had signs of local infection including osteomyelitis.

DRUG INTERACTIONS

Drug-Drug Interactions

Drug interaction studies with pamidronate disodium for injection in humans have not been conducted. Since hepatic and metabolic clearances of pamidronate disodium are minor, pamidronate disodium displays little potential for drug-drug interactions at either the metabolic or protein-binding level (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics and DETAILED PHARMACOLOGY – Animal Pharmacology).

The concomitant use of pamidronate disodium for injection and calcitonin may result in significant hypocalcemia due to a synergistic effect that produces a more rapid fall in serum calcium.

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

In multiple myeloma patients, the risk of renal dysfunction may be increased when pamidronate disodium is used in combination with thalidomide.

Pamidronate Disodium for Injection should not be used in combination with other bisphosphonates.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing recommendations differ for tumor-induced hypercalcemia, lytic bone metastases and multiple myeloma, and Paget's disease. For patients suffering from TIH and multiple myeloma, see the TIH dosage guidelines.

Pamidronate Disodium for Injection must never be given as a bolus injection (see WARNINGS AND PRECAUTIONS**).** Pamidronate Disodium for Injection should be administered in a compatible calcium-free intravenous solution (e.g., sterile normal saline or dextrose 5% in water). Pamidronate Disodium for Injection should be infused slowly.

To minimize local reactions the cannula should be carefully inserted in a relatively large vein.

The infusion rate should never exceed 60 mg/h (1 mg/min), and the concentration of Pamidronate Disodium for Injection in the infusion solution should not exceed 90 mg/250 mL. A dose of 90 mg should normally be administered as a 2-hour infusion in 250 mL infusion solution. **However, in patients with multiple myeloma and in patients with tumor-induced hypercalcemia, it is recommended not to exceed 90 mg in 500 mL over 4 hours (i.e., an infusion rate of 22.5 mg/h).**

Renal Impairment

Pamidronate Disodium for Injection should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumor-induced hypercalcemia where the benefit outweighs the potential risk.

As with other intravenous bisphosphonates, renal monitoring is recommended, such as the measurement of serum creatinine prior to each dose of Pamidronate Disodium for Injection. In patients receiving Pamidronate Disodium for Injection for bone metastases or multiple myeloma who show evidence of deterioration in renal function, Pamidronate Disodium for Injection treatment should be withheld until renal function returns to within 10% of the baseline value.

This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL.
- For patients with abnormal baseline creatinine, increase of 1 mg/dL.

A pharmacokinetic study conducted in patients with cancer and normal or impaired renal function indicates that the dose adjustment is not necessary in mild (creatinine clearance 61 – 90 mL/min) to moderate renal impairment (creatinine clearance 30 – 60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4 h (approximately 20 – 22 mg/h).

Hepatic Impairment

A pharmacokinetic study indicates that no dose adjustment is necessary in patients with mild to moderate abnormal hepatic function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment). Pamidronate disodium for injection has not been studied in patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS). Therefore, caution should be exercised when Pamidronate Disodium for Injection is given to patients with severe hepatic impairment.

Recommended Dose and Dosage Adjustment

Dosing Guidelines for Tumor-Induced Hypercalcemia:

Patients must be adequately rehydrated prior to and during administration of Pamidronate Disodium for Injection.

In tumor-induced hypercalcemia, either ionized calcium or total serum calcium corrected (adjusted) for albumin should be monitored during treatment with Pamidronate Disodium for Injection. Serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since hypoalbuminemia is commonly present. Corrected serum calcium values should be calculated using established algorithms, such as:

$$cCa = tCa + (0.02 \times [40 - ALB])$$

where:
cCa = adjusted calcium concentration (mmol/L)
tCa = measured total calcium concentration (mmol/L)
ALB = measured albumin concentration (g/L)

Although mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia usually associated with a variety of signs and symptoms, and can be life-threatening if not promptly recognized and treated. Individuals at risk and their caregivers should be made aware that signs and symptoms of hypercalcemia include: lethargy, fatigue, confusion, loss of appetite, nausea and vomiting, constipation, excessive thirst and urination. Measures such as maintaining mobility and ensuring adequate hydration could diminish the symptoms of hypercalcemia. However, when symptoms of hypercalcemia are detected, it is important to seek medical assistance promptly.

The recommended total dose of Pamidronate Disodium for Injection for a treatment course depends upon initial plasma calcium levels. Doses should be adapted to the degree of severity of

hypercalcemia, to ensure normalization of plasma calcium and to optimize the duration of response. **A dose of 90 mg should be administered in 500 mL of infusion solution. The infusion rate should not exceed 22.5 mg/hour.**

The total dose for a treatment course may be given as a single infusion or in multiple infusions spread over 2 – 4 consecutive days. The **maximum dose** of Pamidronate Disodium for Injection per treatment course is 90 mg whether for initial or repeat treatment courses. Higher doses have not been associated with increased clinical effect.

The following table presents dosing guidelines for Pamidronate Disodium for Injection derived from clinical data on uncorrected calcium values. These dose ranges also apply for calcium corrected for serum protein.

Tumor-Induced Hypercalcemia				
Initial Serum Calcium		**Total Dose (mg)**	**Concentration of Infusate (mg/mL)**	**Maximum Infusion Rate (mg/h)**
(mmol/L)	**(mg %)**			
Up to 3	Up to 12	30	30 mg/125 mL	22.5 mg/h
3 – 3.5	12 – 14	30 or 60*	30 mg/125 mL 60 mg/250 mL	22.5 mg/h 22.5 mg/h
3.5 – 4	14 – 16	60* or 90	60 mg/250 mL 90 mg/500 mL	22.5 mg/h 22.5 mg/h
> 4	> 16	90	90 mg/500 mL	22.5 mg/h

* Two vials of 30 mg each may be used.

Decreases in serum calcium levels are generally observed within 24 – 48 hours after drug administration, with maximum lowering occurring by 3 – 7 days. If hypercalcemia recurs, or if plasma calcium does not decrease within 2 days, repeat infusions of Pamidronate Disodium for Injection may be given according to the dosing guidelines. The limited clinical experience available to date has suggested the possibility that Pamidronate Disodium for Injection may produce a weaker therapeutic response with repeat treatment in patients with advanced cancer.

Dosing Guidelines for Bone Metastases and Multiple Myeloma:
The recommended dose of Pamidronate Disodium for Injection for the treatment of predominantly lytic bone metastases and multiple myeloma is 90 mg administered as a single infusion every 4 weeks. In patients with bone metastases who receive chemotherapy at 3-week intervals, Pamidronate Disodium for Injection 90 mg may also be given every 3 weeks. A dose of 90 mg should normally be administered as a 2-hour infusion in 250 mL of infusion solution. However, in patients with multiple myeloma, it is recommended not to exceed 90 mg in 500 mL over 4 hours.

Radiotherapy is the treatment of choice for patients with solitary lesions in weight-bearing bones.

Bone Metastases		
Disease State	**Dosing Schedule**	**Concentration of Infusate (mg/mL)**
Bone metastases	90 mg/2 hours every 3*- 4 weeks	90 mg/250 mL
Multiple myeloma	90 mg/4 hours every 4 weeks	90 mg/500 mL

* For patients receiving chemotherapy every 3 weeks

Dosing Guidelines for Paget's Disease of Bone:
The recommended total dose of Pamidronate Disodium for Injection for a treatment course is 180 – 210 mg. This may be administered as 6 doses of 30 mg once a week (total dose 180 mg). Alternatively, 3 doses of 60 mg may be administered every second week, but treatment should be initiated with a 30 mg dose (total dose 210 mg) as influenza-like reactions are common only with the first infusion. Each dose of 30 mg or 60 mg should be diluted in at least 250 mL or 500 mL, respectively, of normal saline or 5% dextrose in water. An infusion rate of 15 mg per hour is recommended. This regimen, omitting the initial dose, can be repeated after 6 months until remission of disease is achieved, and when relapse occurs (see table below).

Paget's Disease			
Recommended total dose/treatment course : 180 – 210 mg			
Regimen	**Dosing Schedule**	**Concentration of Infusate (mg/mL)**	**Infusion Rate (mg/h)**
Regimen 1 **Total dose 180 mg**	30 mg once weekly for 6 weeks	30 mg in ≥ 250 – 500 mL	15 mg/h
Regimen 2 **Total dose 210 mg**	Infusions administered every 2 weeks; initial dose (week 1) = 30 mg; subsequent doses (weeks 3, 5 & 7) = 60 mg	30/60 mg* in ≥ 250 – 500 mL	15 mg/h
Retreatment Regimen **Total dose 180 mg**	60 mg every 2 weeks for a total of 3 infusions.	60 mg* in 500 mL	15 mg/h

* Two vials of 30 mg each may be used.

Administration
Dilution of Pamidronate Disodium for Injection for Intravenous Infusion
Pamidronate Disodium for Injection should be further diluted with either 0.9% w/v sodium chloride or 5% w/v dextrose injection prior to intravenous infusion administration. Diluted solutions prepared in this manner should be used within 24 hours from dilution when stored at room temperature (15 °C – 30 °C) due to the possibility of microbial contamination during preparation. Discard the unused portion.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration,

whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portions.

Incompatibilities
Pamidronate forms complexes with divalent cations. For this reason, Pamidronate Disodium for Injection must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Ringer's solution.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Patients who have received doses higher than those recommended should be carefully monitored. Clinically significant hypocalcemia with paresthesia, tetany and hypotension may be reversed by an infusion of calcium gluconate. Acute hypocalcemia is not expected to occur with Pamidronate Disodium for Injection since plasma calcium levels fall progressively for several days after treatment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Pamidronate disodium belongs to a class of bisphosphonates (previously termed diphosphonates), which inhibit bone resorption. The therapeutic activity of pamidronate disodium is attributable to its potent anti-osteoclastic activity on bone. In animal studies, at therapeutic doses, pamidronate disodium inhibits bone resorption apparently without inhibiting bone formation and mineralization.

The predominant means by which pamidronate disodium reduces bone turnover both *in vitro* and *in vivo* appears to be through the local, direct antiresorptive effect of bone-bound bisphosphonate. Pamidronate disodium binds to calcium phosphate (hydroxyapatite) crystals and directly inhibits the formation and dissolution of this bone mineral component *in vitro*. *In vitro* studies indicate that pamidronate disodium is a potent inhibitor of osteoclastic bone resorption. Pamidronate disodium also suppresses the migration of osteoclast precursors onto the bone and their subsequent transformation into the mature resorbing osteoclast.

Tumor-induced Hypercalcemia
In tumor-induced hypercalcemia, pamidronate disodium normalizes plasma calcium between 3 and 7 days following the initiation of treatment irrespective of the type of malignancy or presence of detectable metastases. This effect is dependent on initial calcium levels.

Pamidronate disodium improves symptoms associated with hypercalcemia, e.g. anorexia, nausea, vomiting and diminished mental status.

The kidneys play a prominent role in calcium homeostasis. In addition to skeletal osteolysis, renal dysfunction contributes to the pathogenesis of tumor-induced hypercalcemia. When diagnosed, most hypercalcemic patients are significantly dehydrated. Elevated plasma calcium antagonizes antidiuretic hormone-induced renal concentration, and thus results in polyuria and excessive fluid loss. Hydration status is further compromised by reduced fluid intake due to nausea, vomiting and diminished mental status. Furthermore, dehydration often leads to a fall in glomerular filtration rate (GFR).

Before Pamidronate Disodium for Injection therapy is initiated, patients should be adequately rehydrated with 0.9% sodium chloride injection (see WARNINGS AND PRECAUTIONS, General). Normalization of plasma calcium levels by pamidronate disodium in adequately hydrated patients may also normalize plasma parathyroid hormone (PTH) which is suppressed by hypercalcemia.

The duration of normocalcemia following pamidronate disodium treatment varies in patients with tumor-induced hypercalcemia because of early mortality, and the heterogeneity of diseases and cancer therapies. In general, recurrences tend to occur preferentially after treatment with lower doses: at doses of 30 mg or less, plasma calcium levels tend to increase after approximately 1 week, while at high doses (total treatment doses of 45 – 90 mg) plasma calcium levels remained normal for at least 2 weeks and up to several months. One study has shown a clear relationship between recurrence rates and pamidronate disodium dose: in patients treated with single intravenous infusions of 30, 45, 60, and 90 mg pamidronate disodium, recurrence rates were lower for the higher dose group 9 months after initial treatment. In patients in whom the underlying disease is well controlled by cancer therapy, the duration of response tends to be more prolonged.

Clinical experience with pamidronate disodium in relapsed tumor-induced hypercalcemia is limited. In general, with re-treatment, the response is similar to that with the first pamidronate disodium treatment, unless the cancer has progressed significantly. Therefore, pamidronate disodium treatment appears effective for recurrent hypercalcemia at doses established for the initial treatment course (see DOSAGE AND ADMINISTRATION). The mechanisms underlying possible decreased effects of repeat treatment with pamidronate disodium in advanced cancer are unknown.

In severe forms of hypercalcemia, the dose of Pamidronate Disodium for Injection may be increased, or eventually, a combination drug therapy should be considered (see WARNINGS AND PRECAUTIONS).

Bone Metastases and Multiple Myeloma

Lytic bone metastases in cancer patients are caused by increased osteoclast activity. Metastatic tumor cells secrete paracrine factors which stimulate neighbouring osteoclasts to resorb bone. By inhibiting osteoclast function, bisphosphonates interrupt the cascade of events which lead to tumor-induced osteolysis. Lytic bone destruction causes significant complications and associated morbidity.

Clinical trials in patients with predominantly lytic bone metastases or multiple myeloma showed that pamidronate disodium prevented or delayed skeletal-related events, (SREs: hypercalcemia, pathologic fractures, radiation therapy to bone, orthopedic surgery, spinal cord compression) and decreased bone pain. When used in combination with standard anticancer treatment, pamidronate disodium led to a delay in progression of bone metastases. In addition, osteolytic bone metastases which have proved refractory to cytotoxic and hormonal therapy may show radiological evidence of disease stabilization or sclerosis.

A significant reduction in bone pain was also demonstrated, which in some patients led to decreased analgesic intake and increased mobility. Greater deteriorations in ECOG performance status and Spitzer quality of life scores were seen in the placebo patients compared to pamidronate disodium-treated patients.

Paget's Disease
Paget's disease of bone, which is characterized by local areas of increased bone resorption and formation with qualitative changes in remodelling, responds well to treatment with pamidronate disodium. Repeated infusions of pamidronate disodium do not lead to reduced efficacy. In addition, patients resistant to etidronate and calcitonin respond well to pamidronate disodium infusions. In long-term follow-up to clinical trials, bone fracture rate does not appear to be increased following treatment with pamidronate disodium relative to the normally occurring rate in patients with Paget's disease.

Clinical and biochemical remission of Paget's disease has been demonstrated by bone scintigraphy, by decreases in urinary hydroxyproline and serum alkaline phosphatase, and by symptomatic improvement. Bone scans show that pamidronate disodium reduces the number of bones and the percent of the skeleton affected and that bone scintigraphy significantly improves. Bone biopsies consistently show histological and histomorphometric improvement indicating the reversal of the disease process. Symptoms improve even in those with severe disease.

Pharmacokinetics

General characteristics: Pamidronate has a strong affinity for calcified tissues and total elimination is not observed within the time frame of experimental studies.

Absorption: Pamidronate disodium is given by intravenous infusion. By definition, absorption is complete by the end of the infusion.

Distribution: Plasma concentrations of pamidronate rise rapidly after infusion is started and fall rapidly when the infusion is stopped. The apparent plasma half-life is about 0.8 hours. Apparent steady state is therefore achieved with infusions of more than about 2 to 3 hours duration. When infused intravenously at 60 mg over one hour, the peak plasma concentration is about 10 nmol/mL and the apparent total plasma clearance is about 180 mL/min.

Pamidronate disodium binding to human serum proteins is relatively low (about 54%) but increases to approximately 5 mmol when exogenous 95% calcium is added to human plasma.

Biotransformation/Metabolism: Hepatic and metabolic clearances of pamidronate disodium are minor.

Elimination: Urinary elimination is biphasic ($t_{½\alpha}$ = 1.6 h; $t_{½\beta}$ = 27.2 h). The apparent renal clearance is about 54 mL/min, and there is a tendency for renal clearance to correlate with creatinine clearance.

After an intravenous infusion, about 20 – 55% of the dose is recovered in the urine within 72 hours as unchanged pamidronate, the majority being excreted within the first 24 hours. Pamidronate does not appear to be metabolized, and the remaining fraction of the dose is retained in the body (within the time frame of the studies). The percentage of the dose retained is independent of both the dose (range 15 – 180 mg) and the infusion rate (range 1.25 – 60 mg/h).

Retention is similar after each dose of pamidronate disodium. Thus, accumulation in bone is not capacity-limited and is dependent solely on the cumulative dose.

Special Populations and Conditions

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 = 9). Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. Although there was a statistically significant 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 area under the curve (AUC: 39.7%) and maximum concentration (C_{max}: 28.6%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 – 36 hours after drug infusion. 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 abnormal hepatic function (see DOSAGE AND ADMINISTRATION).

Renal Impairment
A pharmacokinetic study conducted in patients with cancer showed no differences in plasma AUC of pamidronate between patients with normal renal function and patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 mL/min), the AUC of pamidronate was approximately 3 times higher than in patients with normal renal function (creatinine clearance > 90 mL/min) (see DOSAGE AND ADMINISTRATION).

Geriatrics
No data are available in this population.

Pediatrics
No data are available in this population.

STORAGE AND STABILITY

Protect vials from heat. Store at room temperature (15 °C – 30 °C).

Pamidronate Disodium for Injection must be kept out of reach and sight of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Pamidronate Disodium for Injection 3 mg / mL
Each vial contains 3 mg / mL Pamidronate disodium (formed from 2.53 mg pamidronic acid and 0.86 mg sodium hydroxide); Mannitol, USP, 47 mg / mL; Water for Injection, USP; and for pH adjustment Phosphoric Acid, NF.

Pamidronate Disodium for Injection 6 mg / mL
Each vial contains 6 mg / mL Pamidronate disodium (formed from 5.05 mg pamidronic acid and 1.72 mg sodium hydroxide); Mannitol, USP, 40 mg / mL; Water for Injection, USP; and for pH adjustment Phosphoric Acid, NF.

Pamidronate Disodium for Injection 9 mg / mL
Each vial contains 9 mg / mL Pamidronate disodium (formed from 7.58 mg pamidronic acid and 2.58 mg sodium hydroxide); Mannitol, USP, 37.50 mg / mL; Water for Injection, USP; and for pH adjustment Phosphoric Acid, NF.

Pamidronate Disodium for Injection is available as follows:

Pamidronate Disodium for Injection 3 mg / mL
Product Code 452000: 10 mL plastic single-dose vials packaged individually

Pamidronate Disodium for Injection 6 mg / mL
Product Code 452005: 10 mL plastic single-dose vials packaged individually

Pamidronate Disodium for Injection 9 mg / mL
Product Code 452010: 10 mL plastic single-dose vials packaged individually

Discard the unused portion.

Vial stoppers do not contain natural rubber latex.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

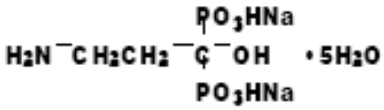
Proper name: Pamidronate Disodium

Chemical name: Disodium-3-amino-l-hydroxypropylidene-1,1-bisphosphonate

Molecular formula and molecular mass: $C_3H_9NO_7P_2Na_2 \bullet 5H_2O$

369.1 g / mol

Structural formula:



Pamidronate disodium (prepared *in situ* from pamidronic acid)

Physicochemical properties

Description: Colourless, crystalline powder

Solubility: Soluble in water or 2N sodium hydroxide, poorly soluble in 0.1N hydrochloric acid and 0.1N acetic acid and insoluble in organic solvents

pH: The pH of a 1% solution in water is approximately 8.2.

CLINICAL TRIALS

The potent inhibitory effect of pamidronate disodium on bone resorption has been demonstrated in clinical studies which have shown pamidronate disodium to be highly effective in the treatment of malignant hypercalcemia, bone metastases and Paget's disease of the bone.

Tumor-Induced Hypercalcemia

Pamidronate disodium lowered plasma calcium between 3 to 7 days following the initiation of treatment irrespective of the tumor type or presence of detectable bone metastases. In controlled clinical trials, pamidronate disodium was infused at up to 15 mg per hour for doses up to 60 mg whereas 90 mg was infused over 24 hours.

Normalization of plasma calcium levels was accompanied by a decrease in urinary calcium levels to normal, and in some cases, to below normal levels. Since it has been reported that calcium absorption from the kidney and gut are not increased by pamidronate disodium

administration, the decreases in urinary calcium observed can be regarded as solely reflecting inhibition of bone resorption rather than effects on the kidney and gut.

Normalization of plasma calcium, including transient hypocalcemia, is dependent on the initial levels of plasma calcium and the dose of pamidronate disodium selected. Severe hypercalcemia (plasma calcium > 4 mmol/L) required higher doses of pamidronate disodium for normalization than moderate hypercalcemia. However, treatment of moderate hypercalcemia with high doses of pamidronate disodium (60 to 90 mg) can lead to transient hypocalcemia. A single infusion of 90 mg is indicated only for cases of severe hypercalcemia.

Several changes in biochemical parameters occur secondary to the normalization of plasma calcium which reflect the antiresorptive activity of pamidronate disodium. Parathyroid hormone levels, which are usually suppressed in hypercalcemia of malignancy, typically recover after treatment with pamidronate disodium. This is considered to be a physiological response to lowering of blood calcium levels. Previously suppressed parathyroid hormone levels have not been observed to increase above the upper limits of normal.

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 the antiresorptive pharmacologic action of pamidronate disodium.

The decrease in urinary phosphate excretion despite a rise in glomerular filtration rate (GFR) after pamidronate disodium administration suggests a positive phosphorus balance. This effect may be related to increased phosphate uptake into bone since the lowering of phosphate excretion occurred after reductions in plasma calcium, plasma phosphate and urinary hydroxyproline. Phosphate levels usually returned to normal within 7 – 10 days. The ratio of plasma phosphate to the renal phosphate threshold ($TmPO_4$/GFR) is also decreased with pamidronate disodium treatment, probably reflecting a rise in PTH secretion due to the sharp fall in plasma calcium.

Pamidronate disodium had no consistent effects on plasma magnesium levels, thus confirming the absence of effect of pamidronate disodium on magnesium metabolism.

Bone Metastases and Multiple Myeloma

Three large Phase III trials, one in multiple myeloma and two in breast cancer (one versus standard chemotherapy and one versus hormonal therapy) showed that 90 mg Pamidronate Disodium for Injection infused every 3 – 4 weeks significantly decreased the skeletal morbidity rate (number of SREs/year) in all patient groups (see below for a more detailed description of the results). Skeletal-related events (SREs) were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Radiation to bone was also significantly lower in all pamidronate disodium for injection groups. The proportion of patients experiencing an SRE was significantly smaller, and the time to first SRE was significantly longer in pamidronate disodium for injection-treated multiple myeloma and breast cancer + chemotherapy patients. The same trend was seen in the hormonally-treated breast

cancer patients. Fewer pamidronate disodium for injection-treated multiple myeloma patients suffered vertebral pathologic fractures.

Multiple Myeloma

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myeloma were enrolled to receive pamidronate disodium for injection or placebo in addition to their underlying anti-myeloma therapy to determine the effect of pamidronate disodium for injection on the occurrence of skeletal-related events (SREs). SREs were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Patients received either 90 mg of pamidronate disodium for injection or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 pamidronate disodium for injection, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the pamidronate disodium for injection group (24% vs 41%, $p < 0.001$), and the mean skeletal morbidity rate (# SRE/year) was significantly smaller for pamidronate disodium for injection patients than for placebo patients (mean: 1.1 vs 2.1, $p < 0.02$). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the pamidronate disodium for injection group ($p = 0.001$, 0.006, and 0.046, respectively). Moreover, fewer pamidronate disodium for injection patients suffered any pathologic fracture (17% vs 30%, $p = 0.004$) or needed radiation to bone (14% vs 22%, $p = 0.049$).

In addition, decreases in pain scores from baseline occurred at the last measurement for those pamidronate disodium for injection patients with pain at baseline ($p = 0.026$) but not in the placebo group. At the last measurement, a worsening from baseline was observed in the placebo group for the Spitzer quality of life variable ($p < 0.001$) and ECOG performance status ($p < 0.011$) while there was no significant deterioration from baseline in these parameters observed in pamidronate disodium for injection-treated patients.

After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the pamidronate disodium for injection group than the placebo group ($p = 0.015$). In addition, the mean skeletal morbidity rate (# SRE/year) was 1.3 vs 2.2 for pamidronate disodium for injection patients vs. placebo patients ($p = 0.008$), and time to first SRE was significantly longer in the pamidronate disodium for injection group compared to placebo ($p = 0.016$). Fewer pamidronate disodium for injection patients suffered vertebral pathologic fractures (16% vs 27%, $p = 0.005$). Survival of all patients was not different between treatment groups.

Bone Metastases

Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of pamidronate disodium for injection infused over two hours every three to four weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had at least two lytic metastases, one of which was at least 1 cm in diameter. In one trial, patients were receiving hormonal therapy, and in the second, patients were being treated with chemotherapy at trial entry.

Breast Cancer Patients Receiving Hormonal Therapy

372 patients receiving hormonal therapy were randomized to receive either 90 mg of pamidronate disodium for injection (182) or placebo (190), each given as a two-hour infusion at intervals of three to four weeks for 24 months. The proportion of patients developing an SRE was smaller in the pamidronate disodium for injection treatment group than in the placebo treatment group throughout the trial (3, 6, 9, 12, 15, 18, 21 and 24 months). At the end of the 24 monthly cycles of the trial, the proportion of patients having an SRE (+HCM) was significantly lower for pamidronate disodium for injection patients than for placebo patients (56% vs 67%, $p = 0.027$) and the mean skeletal morbidity rate (# SRE/year) was significantly smaller for pamidronate disodium for injection patients than for placebo patients (mean: 2.4 vs 3.8, $p = 0.008$). The median time to the first SRE (+HCM) and for radiation to bone is significantly greater for pamidronate disodium for injection patients compared to placebo patients ($p = 0.049$ and 0.016, respectively).

Bone lesion partial response, assessed radiologically, was 30% for the pamidronate disodium for injection group and 24% for the placebo group ($p = 0.202$). In addition, pain and analgesic scores increased significantly less ($p = 0.007$, and $p < 0.001$, respectively) from baseline in the pamidronate disodium for injection group than in the placebo group at last measurement.

Breast Cancer Patients Receiving Chemotherapy

382 patients receiving chemotherapy were randomized to receive either 90 mg of pamidronate disodium for injection ($n = 185$) or placebo ($n = 197$), each given as a two-hour infusion at intervals of three to four weeks for 24 months. The proportion of patients developing any SRE was significantly lower on pamidronate disodium for injection than on placebo at 15 months, 18 months, 21 months and 24 months. At the end of the 24 monthly cycles of the trial, the proportion of patients having any SRE (+HCM) was significantly lower for pamidronate disodium for injection patients than for placebo patients (50% vs. 70%, $p < 0.001$) and the mean skeletal morbidity rate (# SRE/year) was significantly smaller for pamidronate disodium for injection patients than for placebo patients (mean: 2.6 vs 4.3, $p < 0.001$). The times to the first SRE occurrence, any pathologic fracture, non-vertebral pathologic fracture, and radiation to bone was statistically significantly shorter for placebo compared to pamidronate disodium for injection patients ($p < 0.001$, 0.009, 0.001, and 0.001, respectively).

Bone lesion complete and partial response, assessed radiologically, was significantly higher in pamidronate disodium for injection vs placebo breast cancer patients receiving chemotherapy (34% vs 19%, $p = 0.002$). In addition, pain and analgesic scores increased significantly less ($p = 0.050$ and $p = 0.009$, respectively) from baseline in the pamidronate disodium for injection group than in the placebo group at last measurement. In both treatment groups, the ECOG performance status worsened from baseline to endpoint, but the worsening was significantly ($p = 0.002$) larger in the placebo group than in the pamidronate disodium for injection group.

Paget's Disease

A clear dose response was demonstrated in a randomized, double-blind clinical trial in which patients received a single dose of pamidronate disodium ($n = 64$). A single infusion of pamidronate disodium 15 mg was not effective; 90 mg was most effective. A 50% fall from baseline was achieved in both ALP (alkaline phosphatase) and OHP:Cr

(hydroxyproline:creatinine ratio) in > 20% of patients with both 45 and 90 mg pamidronate disodium ($p < 0.05$).

In a multiple-dose infusion study, pamidronate disodium was infused intravenously at 15 mg/2 hours daily for 5 consecutive days (n = 12). ALP normalized in 4 patients. Five patients required re-treatment within 6 months and 6 patients after 6 months.

In an open clinical trial, patients were stratified according to initial ALP. Those with ALP < 500 I.U./L (Group A; n = 65) or > 500 I.U./L (Group B; n = 11) were administered 180 – 195 mg or 360 – 375 mg pamidronate disodium, respectively, as 30 mg weekly infusions. In Group A, ALP normalized in 80% and OHP:Cr in 88% patients. In addition, bone scan results significantly improved. The duration of remission was 543 and 388 days, respectively. In Group B, ALP and OHP:Cr were reduced 80% and 73%, respectively. These patients had particularly severe disease and only 25% remitted on the basis of OHP:Cr and the median duration of remission was relatively short (52 days). In both groups, there were subjective clinical improvements in over 50% of patients.

In a larger, open clinical trial of similar design, patients were also stratified according to initial ALP. However, those with ALP < 500 I.U./L (Group A; n = 159) or > 500 I.U./L (Group B; n = 52) were administered 210 mg or 390 mg pamidronate disodium, respectively, as infusions of 30 mg initially then 60 mg every 2 weeks. In Group A, ALP normalized in 81% and OHP:Cr in 93% of patients. In addition, bone scan results significantly improved (scintigraphic index, % of skeleton affected and number of bones affected). The median duration of remission was 780 and 494 days, respectively. In Group B, results were similar to those achieved in the previous study. Symptom evaluation demonstrated improvement in 50 to 60% of patients.

DETAILED PHARMACOLOGY

Animal Pharmacology

Subcutaneous administration of pamidronate disodium to rats reduced urinary hydroxyproline excretion within 2 – 8 days starting at 0.16 mcmol/kg/day and reaching a maximum at 16 mcmol/kg/day. At higher doses (> 40 mcmol/kg/day) pamidronate disodium inhibited bone mineralization as assessed by the molar ratio of calcium to hydroxyproline in metaphyseal bone. Doses below this level reduced bone alkaline phosphatase activity, hydroxyproline synthesis and calcium content. These changes in bone apposition parameters required at least 23 days exposure for a maximal effect, compared to 8 days for effects on bone resorption. Thus, pamidronate disodium inhibits bone resorption in rats at doses several-fold lower than those that affect bone growth and mineralization.

Low doses of pamidronate disodium increased both elastic and ultimate bone strength in the rat, whereas high doses (> 14 mg/kg/day intraperitoneally) produced opposite effects. The latter doses were far above those required to completely suppress calcium mobilization in rats.

In dogs, long-term intermittent treatment with pamidronate disodium retains structural integrity in cortical and vertebral bone. Intermittent oral pamidronate disodium treatment for 12 weeks caused no changes in the mechanical properties of cortical femoral bone but trabecular bone showed a significant increase in compressive stiffness and torsional strength.

In mice, subcutaneous administration of 16 mcmol/kg (4.5 mg/kg) pamidronate disodium for 7 days increased tibial growth plate width without concomitant effects on longitudinal growth.

The intermittent administration of pamidronate disodium to animals was also effective in inhibiting bone resorption. In 10-week old pigs, administration of 1.6 mcg/kg/day pamidronate disodium for 5 out of 21 days produced a significant inhibition of bone resorption that was equivalent to that produced with a continuous 60-day dosing regimen. In mice, once weekly treatment for 1 year augmented diaphyseal wall thickness and the number of persisting trabeculae. This effect was mainly achieved by a suppression of endosteal bone resorption, which occurs during the retrogressive phase of C57BL/Silberberg mice aged more than 4 months. Bones of treated mice also demonstrated a higher femoral calcium content and ash weight, and increased resistance to fracture stress in comparison to untreated controls.

As a result of hormonal regulation, pamidronate disodium does not significantly affect serum calcium in normal, healthy animals. Under various experimental conditions however, changes in serum calcium values will reflect the effects of pamidronate disodium on bone metabolism. In thyroid-parathyroidectomized rats, the 1,25(OH)2 vitamin D3-stimulated mobilization of calcium from bone was inhibited by pamidronate disodium at daily doses of 0.02 – 0.6 mg/kg subcutaneously. Similarly, pamidronate disodium reduced hypercalcemia of malignancy in rats bearing Walker 256 carcinosarcoma tumors. Mice bearing 5T2 myelomas had fewer skeletal lesions if treated with pamidronate disodium, although the myeloma itself was unaffected by pamidronate disodium treatment.

Twenty-four hours after single intravenous administration of 10 mg/kg to growing rats, approximately 50% of the dose is retained in bone, 0.1% in blood, 1.1% in spleen and 30% in liver. Pamidronate disodium is also stored in tracheal cartilage of rats. The percent uptake into the liver increases with dose, ranging from 3 % at 0.01 mg/kg, to 30% at 10 mg/kg doses. Levels accumulated in liver at 10 mg/kg gradually decline during the 2 weeks after administration, with redistribution and uptake into bone, or elimination by the kidneys over 24 – 48 hours.

Pamidronate disodium does not undergo significant metabolism in the rat: at 10 mg/kg intravenously, approximately 20% of the dose is excreted unchanged in the urine by 24 hours. Bile accounts for less than 0.1% of the administered dose. The biological half-life of pamidronate disodium in rats has been estimated to be approximately 300 days.

A preferential uptake and prolonged storage of ^{14}C-pamidronate disodium in bone is also observed in dogs following single intravenous administration. Radioactivity is detectable in blood only up to 72 hours.

Human Pharmacology

Pamidronate disodium is a second-generation bisphosphonate. These agents are synthetic analogues of pyrophosphate and specifically inhibit bone resorption. First generation compounds such as 1-hydroxyethylidene-1,1-biphosphonic acid (HEBP or etidronate disodium) block resorption but may also inhibit bone mineralization. Pamidronate disodium, a second generation bisphosphonate, inhibits bone resorption at doses that do not appear to affect the mineralization of newly-formed osteoid tissue and thus constitutes a rational treatment for pathological bone resorption. The predominant mode of action appears to be a local, direct effect; bisphosphonates complex tightly to, and inhibit the formation and dissolution of, hydroxyapatite crystals.

TOXICOLOGY

Acute Toxicity

In acute toxicity studies, pamidronate disodium was better tolerated when administered as a short-term intravenous infusion or intraperitoneally than as a bolus intravenous dose, presumably because of lower plasma concentrations. In mice, the intravenous bolus and intraperitoneal LD_{50} of pamidronate disodium were 20.3 mg/kg and 40 mg/kg respectively; in rats 80 mg/kg and 65 mg/kg, and in rabbits, 18.5 mg/kg and 190 mg/kg. In dogs, the LD_{50} was > 10 mg/kg for a bolus intravenous dose and > 40 mg/kg when administered as an intravenous infusion.

Subacute and Chronic Toxicity

Pamidronate disodium has been administered to mice, rats, rabbits and dogs for 3 months by intermittent intravenous infusion or a bolus intravenous dose. Repeat dose animal studies demonstrate that intermittent administration of pamidronate disodium by intravenous infusion is better tolerated than the bolus intravenous route. Dose- and regimen-dependent nephropathy occurred in all species except the mouse. These studies indicate that adverse effects with pamidronate disodium correlate strongly with peak plasma concentration. It should therefore be administered intermittently by slow infusion; daily intravenous administration, especially as a bolus, should be avoided.

The no-toxic effect level for rats and dogs administered 2, 6 or 20 mg/kg by intravenous infusion for 1 hour weekly for 3 months was 2 mg/kg for both species. In all dose groups in the dog, but only at the highest dose in the rat, pharmacological effects were evident as non-reversible, dose-related increase in primary spongy bone formation with a widened metaphyses, increased calcification and impaired remodeling with no impairment of mineralization. This was accompanied by reduced AP and serum phosphate. The major target organ for toxic effects was the kidney, but following high intravenous doses, especially those administered as a bolus, inflammation/degeneration was also observed in the stomach and the lung, and to a lesser extent in the spleen, liver and heart.

Reproductive Toxicity

Pamidronate crosses the placenta barrier readily and accumulates primarily in the fetal bones in rats. Reproductive toxicological studies conducted in rats and rabbits by peroral or intravenous administration at dose levels comparable to human therapeutic dose revealed that pamidronate causes the following adverse events and developmental abnormalities: reduced fertility in both sexes and the first generation of the offspring, distress and prolongation of parturition process

with fatal outcome, marked increases in resorption, pre- and post-implantation losses, reduced number of viable pups born, delayed skeletal maturation and ossification, shortening of long bones and visceral and external abnormalities (dilated and kinked ureters, displaced testes, shortened body, curved or hooked joints, mal-rotated hind limbs, subcutaneous hemorrhage and edema, etc.).

A study in lactating rats has shown that pamidronate passes into the milk.

Carcinogenesis and Mutagenesis

Mutagenic potential was assessed by three different methods both *in vitro* (Ames test, point mutation test, and a cytogenetic test) and *in vivo* (nucleus anomaly test, sister chromatid exchange study and a micronucleus test). There was no evidence of mutagenic potential *in vivo*. *In vitro* tests were also negative apart from a slight increase in the number of chromosome aberrations in Chinese hamster ovary cells at the highest concentration only (2 500 mcg/mL).

Carcinogenic potential was assessed in both mice and rats treated with pamidronate disodium ≤ 40 mg/kg/day and ≤ 75 mg/kg/day, respectively, by gavage for 2 years. These studies repeated earlier studies completed in the 1970's, in which pamidronate disodium ≤ 1 000 mg/kg was added to the food supply. From these studies, pamidronate disodium does not appear to have carcinogenic potential.

The only unexpected finding in these repeat carcinogenicity studies was hydrocephaly observed in the mouse study. This event occurred at all dose levels, and was probably caused by changes in cranial bones as a result of the pharmacological activity of the compound in the young, growing animals. It is not thought to be of relevance in adult patients in whom bone growth is complete.

In mice receiving pamidronate disodium ≤ 40 mg/kg daily, there was dose-dependent reduction in the incidence of neoplasms, which was attributed to pamidronate disodium-related decreases in food consumption; mice fed a restricted diet have been shown to develop fewer tumors than those fed *ad libitum*. In this study, the incidence of liver tumors was reduced relative to control animals. In female mice fed with pamidronate disodium 879 mg/kg/day in the diet, the incidence of benign hepatomas was increased relative to control animals.

In both rat carcinogenicity studies, the incidence of neoplastic lesions was within the range observed with historical controls, apart from a slight increase in intestinal leiomyomas observed in females in one study only. Intestinal leiomyomas occur spontaneously in 0.44% Wistar rats (range 0 – 2%) used as controls in carcinogenicity studies. The mean incidence of these tumors in female Wistar rats administered 1 000 mg/kg/day in the diet was 1.2% (range 0 – 3.7%). As no intestinal leiomyomas were observed in female rats in the other rat study, it is unlikely that these benign, non-fatal tumors are of biological or clinical significance.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrPAMIDRONATE DISODIUM FOR INJECTION

Read this carefully before you start taking **Pamidronate Disodium for Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Pamidronate Disodium for Injection**.

Serious Warnings and Precautions
Possible serious side effects with the use of pamidronate disodium include: • Osteonecrosis of the jaw (ONJ) (a severe bone disease that affects the jaw). • Worsening of kidney function. Pamidronate Disodium for Injection should not be given to patients with severely reduced kidney function. • Single doses of Pamidronate Disodium for Injection should not exceed 90 mg and must be given at the recommended infusion rates.

What is Pamidronate Disodium for Injection used for:
Pamidronate Disodium for Injection is used to treat:
- High calcium levels in the blood due to cancer (tumor induced hypercalcemia);
- Bone tumors resulting from the spread of tumors at other sites and multiple myeloma;
- Paget's disease of bone in patients with symptoms.

How does Pamidronate Disodium for Injection work?
Pamidronate Disodium for Injection is a bisphosphonate which strongly binds to the bone and slows down the rate of bone change. This helps to reduce the amount of calcium in the blood and bone loss.

What are the ingredients in Pamidronate Disodium for Injection
Medicinal Ingredients: Pamidronate Disodium
Non-medicinal ingredients: Mannitol, Phosphoric Acid, Sodium Hydroxide, and Water for Injection

Pamidronate Disodium for Injection comes in the following dosage forms:
Solution
Pamidronate Disodium for Injection is available as 3 mg / mL, 6 mg / mL, and 9 mg / mL strengths in 10 mL plastic single-dose vials packaged individually.

Vial stoppers do not contain any natural rubber latex.

Pamidronate Disodium for Injection is given as an infusion into a vein after appropriate dilution.

Do not use Pamidronate Disodium for Injection if:
- you are allergic to Pamidronate Disodium for Injection or other bisphosphonates;
- you are pregnant;
- you are breast-feeding.

If this applies to you, **tell your doctor before being given Pamidronate Disodium for Injection.** If you think you may be allergic, ask your doctor for advice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Pamidronate Disodium for Injection. Talk about any health conditions or problems you may have, including if you:

- have a heart, liver or kidney problem;
- suffer from calcium or Vitamin D deficiency (for example owing to your diet or as a result of digestive problems);
- have any dental problems or any dental procedures planned in the future;
- had or have pain, swelling or numbness of the jaw or a "heavy jaw feeling" or loosening of a tooth;
- have an eye problem;
- have an ear problem
- have sores in the mouth. This can lead to osteonecrosis of the jaw. Your doctor may check if you:
    - smoke
    - have or have had teeth and /or gum disease
    - have dentures that do not fit well
    - have other relevant medical conditions at the same time such as a low red blood cell count (called anemia) or if your blood can not form clots in the normal way.

Your doctor may tell you to stop taking Pamidronate Disodium for Injection until all sores in your mouth are healed.

Other warnings that you should know:

Before starting treatment with Pamidronate Disodium for Injection
Be sure that you have discussed Pamidronate Disodium for Injection treatment with your doctor. You may only be given Pamidronate Disodium for Injection after a full medical examination. Your doctor may also request a dental examination with any necessary preventive dentistry carried out prior to treatment with Pamidronate Disodium for Injection. This may be required since some patients have experienced side effects following dental procedures (such as tooth extraction) while on treatment with Pamidronate Disodium for Injection; as well, since patients with dental infections or periodontal disease (disease affecting surrounding tissues of a tooth) may be at increased risk of problems with their jaw bones following dental procedures (such as tooth extraction) while on treatment with Pamidronate Disodium for Injection (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

During treatment with Pamidronate Disodium for Injection
Ensure sufficient intake of liquids prior to infusions as directed by your doctor as this will help to prevent dehydration.

Your treatment may need to be supplemented with calcium and Vitamin D to prevent low calcium levels.

It is important that your doctor checks your progress at regular intervals. Since bisphosphonates (the class of drugs to which Pamidronate Disodium for Injection belongs) may cause damage to the kidneys (worsening of kidney function including kidney failure and death have been reported very rarely with the use of Pamidronate Disodium for Injection), he or she may want to take repeated blood tests, especially after starting your treatment with Pamidronate Disodium for Injection and before each additional dose.

Your doctor may also want to take other repeated blood tests if you have low level of white blood cells, red blood cells and/or platelets.

Tooth Extraction and Other Dental Procedures
If possible, you should not undergo tooth extraction or other dental procedures (excluding regular dental cleaning) while you are receiving treatment with Pamidronate Disodium for Injection. Please consult your doctor if a dental procedure (excluding regular dental cleaning) is required while you are receiving treatment with Pamidronate Disodium for Injection. It is important to maintain good dental hygiene; regularly scheduled dental examinations are recommended.

Pregnancy or Breast-Feeding
You should tell your doctor if you:
- are pregnant, or planning to become pregnant before you receive Pamidronate Disodium for Injection. Pamidronate Disodium for Injection should not be given during pregnancy.

- are breast-feeding or intend to breast-feed. Mothers treated with Pamidronate Disodium for Injection should not breast-feed their babies.

Women of Child-bearing Potential
You must use highly effective contraception during treatment.

Use in Children, Adolescents and Elderly Patients
Pamidronate Disodium for Injection has not been adequately studied in children or adolescents. Until further experience is gained, Pamidronate Disodium for Injection is only recommended for use in adult patients.
Elderly patients at the age of 65 years or older may be safely treated with Pamidronate Disodium for Injection, provided that they do not have a serious heart, liver or kidney problem. Ask your doctor if you have any questions about this.

If You Drive a Vehicle or Use Machinery
Pamidronate Disodium for Injection may cause some patients to become sleepy or dizzy, especially immediately after the infusion. If this happens you should not drive or use machinery or perform other tasks that need full attention.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Pamidronate Disodium for Injection:
Other bisphosphonates, calcitonin, thalidomide, or vitamin supplements.

How to take Pamidronate Disodium for Injection:
Pamidronate Disodium for Injection can be given only by slow infusion into a vein. The dose will be decided by your doctor.

Usual dose:
Tumor-induced hypercalcemia: 30-90 mg
Bone tumors or multiple myeloma: 90 mg every 3-4 weeks
Paget's disease: 30-60 mg in one infusion

An infusion may last one or more hours, depending on the dose given and the condition of your kidney. You may receive additional saline solution for re-hydration.

Overdose:

If you think you have taken too much Pamidronate Disodium for Injection, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using Pamidronate Disodium for Injection?
These are not all the possible side effects you may feel when taking Pamidronate Disodium for Injection. If you experience any side effects not listed here, contact your healthcare professional.

Very common side effects:
These side effects may affect more than 1 in 10 patients.
- short-lasting fever and flu-like condition with chills, sometimes together with a feeling of tiredness and general discomfort;
- low level of calcium and phosphate in blood;
- tiredness, lack of energy.

If any of these affects you severely, **tell your doctor.**

Common side effects:

These side effects may affect between 1 and 10 in every 100 patients.

- Low level of red blood cells
- Low level of white blood cells
- Low level of platelets (cells in the blood that help stop bleeding)
- Headache
- Sleep disturbances
- Eye irritation
- High blood pressure
- Irregular heart rhythm (atrial fibrillation)
- Vomiting
- Loss of appetite
- Abdominal pain
- Diarrhea
- Constipation
- Stomach pain
- Sickness (nausea)
- Skin rash
- Generalised pain
- Low levels of potassium and magnesium in the blood
- Short-lasting muscle or joint pain

If any of these affects you severely, **tell your doctor.**

Uncommon side effects:
These side effects may affect between 1 and 10 in every 1 000 patients.
- Agitation
- Muscle cramps
- Low blood pressure
- Itching
- Abnormal liver function test
- Problems with jaw bones (osteonecrosis of the jaw)

If any of these affects you severely, **tell your doctor.**

The following side effects have been reported in some patients taking pamidronate disodium:

- Painful red eye and/or swollen eye, painful eyeball, photophobia, excessive tearing or decreased vision. You should report these to your doctor as they may indicate more serious complications.
- Problems with jaw bones (osteonecrosis of the jaw). Dental hygiene is an important element of your overall patient care and is important in possibly decreasing the chances of this type of problem occurring. Removable dentures should fit properly and should be removed at night. Please consult with your doctor if you experience pain in your mouth, teeth or jaw, or if your gums or mouth heals poorly. Any non-healing of a dental extraction site or chronic dental infection should be assessed. If you notice any other effects, tell your doctor immediately. In addition, if possible you should not undergo tooth extraction or other dental procedures (excluding regular dental cleaning) while on therapy with Pamidronate Disodium for Injection. Please consult your doctor if a dental procedure (excluding regular dental cleaning) is required while you are receiving treatment with Pamidronate Disodium for Injection (see**Other warnings that you should know**: Tooth Extraction and Other Dental Procedures).

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Common			
• Low level of blood platelets which, if severe, may cause spontaneous bleeding and bruising			√
• Low level of white blood cells which, if severe, may cause fever, mouth ulcers, infections of the throat, ears, skin, or lungs (pneumonia)			√
• Tingling or numbness and muscle spasms and twitching, symptoms of low level of calcium			√
• Irregular heart rhythm (atrial fibrillation)			√
Uncommon			
• Severe allergic reaction which causes difficulty in breathing, swollen lips and tongue or a sudden fall in blood pressure			√
• Osteonecrosis of the jaw (numbness or feeling of heaviness in the jaw, poor healing of the gums especially after dental work, loose teeth, exposed bone in mouth, pain in the mouth, teeth or jaw, swelling or gum infections, bad breath)			√
• Osteonecrosis of the external auditory canal (chronic ear infections, ear pain, discharge from the ear)			√
• Seizures			√
• Pseudotumor cerebri (moderate to severe headaches, ringing in ears, nausea, vomiting, dizziness, blurred or dim vision, brief episodes of blindness, double vision, seeing light flashes, neck shoulder or back pain)			√
• Kidney failure (changes in urine color or absence of urine production, changes in kidney function laboratory tests, lower back pain, fatigue, nausea, loss of appetite)			√
• Kidney damage, including deterioration of pre-existing renal disease			√
Rare			
• Protein in urine			√
Very Rare			
• Anaphylactic shock			√
• Blood in urine			√
• Heart disease characterized by breathlessness and fluid retention in the body			√
• Reactivation of Herpes simplex and Herpes zoster			√
• Confusion, visual hallucinations			√
• High level of sodium and potassium in the blood			√
Unknown			
• Painful eyeball and/or swollen eyes			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Pamidronate Disodium for Injection should be stored between 15 °C – 30 °C and protected from heat. Store in the original package.

Keep this medicine out of reach and sight of children and pets.

Pamidronate Disodium for Injection should not be used after the expiry date shown on the package label. Remember to take back any unused medicine to your pharmacist.

If you want more information about Pamidronate Disodium for Injection:

- Talk to your healthcare professional

- Find the full Prescribing Information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); Fresenius Kabi Canada's website (http://www.fresenius-kabi.com/en-ca/), or by calling 1-877-821-7724.

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