

**Pamidronate** Disodium for Injection  
**Bone Metabolism Regulator**

**SUMMARY PRODUCT INFORMATION**

Route of Administration	Dosage Form/Strength	Clinically Relevant 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**

- **Tumour-induced hypercalcaemia following adequate saline rehydration.** Prior to treatment with Pamidronate Disodium for Injection, 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, to any of its components (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**), or to other bisphosphonates;
- ◆ in pregnancy;
- ◆ in breast-feeding women.

**WARNINGS AND PRECAUTIONS**

**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 should not be given together with other bisphosphonates to treat hypercalcaemia since the combined effects of these agents are unknown.

Pamidronate disodium 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 tumour-induced hypercalcaemia 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). 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 patients treated with zoledronic acid (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 Machines**

In rare cases, 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 hypocalcaemia 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 hypocalcaemia.

**Lytic bone metastases or multiple myeloma:**

In the absence of hypercalcaemia, 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 hypocalcaemia. In the event that hypercalcaemia develops, calcium and Vitamin D supplements should be discontinued immediately.

**Hepatic/Biliary/Pancreatic**

There are no clinical data available in patients with severe hepatic insufficiency.

**Musculoskeletal Pain**

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports occur rarely. This category of drugs includes pamidronate disodium for injection. 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.

**Osteonecrosis of the Jaw (ONJ):**

Osteonecrosis of the jaw (ONJ) has been reported in cancer patients treated with bisphosphonates, including pamidronate disodium for injection. Although no causal relationship has been established, there is an association between bisphosphonate use and the development of ONJ. Postmarketing experience suggests a greater frequency of reports of ONJ based on tumour 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. Cancer patients 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. Cancer 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, these 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 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.

**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 (some with fatal outcome) has 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 should not exceed 90 mg, and the recommended infusion time should be observed (see **DOSAGE AND ADMINISTRATION**).

Pamidronate Disodium for Injection is excreted intact primarily via the kidney (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**), thus the risk of renal adverse reactions may be greater in patients with impaired renal function.

As with other i.v. bisphosphonates, renal monitoring is recommended; for instance, measurement of serum creatinine prior to each dose of pamidronate disodium for injection. Experience with pamidronate disodium for injection in patients with severe renal impairment (serum creatinine > 440 µmol/L in TIH patients; > 180 µmol/L in multiple myeloma patients) is limited. If clinical judgement 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 bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see **DOSAGE AND ADMINISTRATION**).

### Special Populations

#### 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.

There are no adequate and well-controlled studies in pregnant women and no clinical evidence to support the use of pamidronate disodium for injection in pregnant women. 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 is no clinical experience with 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.

#### Pediatrics:

The safety and efficacy of pamidronate disodium for injection in children have not been established. Until further experience is gained, Pamidronate Disodium for Injection is only recommended for use in adult patients.

### 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 tumour-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.

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy with pamidronate disodium for injection. Patients with anemia, leukopenia or thrombocytopenia should have regular hematology assessments. 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 tumour-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 Experiences by Body System:

##### Biochemical Changes:

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

##### Blood:

Common: anemia, thrombocytopenia, lymphocytopenia  
Very rare: leukopenia  
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.

##### Body as a Whole:

Very common: fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue, and flushes

##### Cardiovascular System:

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 patients treated with zoledronic acid (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.  
Common: hypertension  
Uncommon: hypotension  
Very rare: left ventricular failure (dyspnea, pulmonary edema), congestive heart failure (edema) due to fluid overload

##### Central Nervous System:

Common: symptomatic hypocalcemia (paresthesia, tetany), headache, insomnia, somnolence  
Uncommon: seizures, agitation, dizziness, lethargy  
Very rare: confusion, visual hallucinations

##### Gastrointestinal Tract:

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

##### Immune System:

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

##### Infection:

Very rare: reactivation of Herpes simplex and Herpes zoster

##### Local Reactions:

Common: reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis)

##### Musculoskeletal System:

Common: transient bone pain, arthralgia, myalgia, generalized pain  
Uncommon: osteonecrosis of the jaw (ONJ), muscle cramps

##### Renal System:

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

##### Respiratory System:

Rare: adult respiratory distress syndrome, interstitial pneumonitis

##### Skin:

Common: rash  
Uncommon: pruritus

##### Special Senses:

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

*Many of these adverse events may have been related to the underlying disease.*

### Tumour-induced Hypercalcemia and Paget's Disease

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

Adverse Experiences	Tumour-induced Hypercalcemia	Paget's Disease
No. of patients	n = 910	n = 395
	(%)	(%)
Fever	6.9	8.9
Headache	0.0	4.8
Hypocalcemia	3.2	0.8
Influenza-like symptoms	0.0	11.9
Infusion site reaction	1.7	1.8
Malaise	0.0	5.8
Myalgia	0.0	2.0
Nausea	0.9	2.0
Pain (bone)	0.0	8.9
Pain (unspecified)	0.0	7.9
Rigors	0.0	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 tumour-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 i.v. bisphosphonates, renal monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

### Bone Metastases and Multiple Myeloma

The most commonly reported adverse experiences 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 Experiences in Three Controlled Trials (regardless of causality)		
Bone Metastases and Multiple Myeloma Patients		
Adverse Event	Pamidronate Disodium 90 mg	Placebo
	n = 572	n = 573
<b>General</b>		
Asthenia	16.4	15.4
Fatigue	30.4	35.5
Fever	35.5	30.5
Metastases	14.0	13.6
<b>Digestive System</b>		
Anorexia	20.8	18.0
Constipation	27.6	30.9
Diarrhea	24.3	26.2
Dyspepsia	13.6	12.4
Nausea	48.4	46.4
Pain (Abdominal)	17.3	14.0
Vomiting	30.9	28.1
<b>Hemic and Lymphatic Systems</b>		
Anemia	35.1	32.6
Granulocytopenia	16.8	17.3
Thrombocytopenia	11.0	13.1
<b>Musculoskeletal System</b>		
Myalgias	22.6	16.9
Skeletal Pain	59.4	69.1
<b>CNS</b>		
Headache	24.0	19.7
Insomnia	18.2	17.3

Commonly Reported Adverse Experiences in Three Controlled Trials (regardless of causality)		
Bone Metastases and Multiple Myeloma Patients		
Adverse Event	Pamidronate Disodium 90 mg	Placebo
	n = 572	n = 573
<b>Respiratory System</b>		
Coughing	21.2	18.8
Dyspnea	23.3	18.7
Upper Respiratory Infection	19.8	20.9
<b>Urogenital System</b>		
Urinary Tract Infection	14.5	10.8

### Postmarket Adverse Drug Reactions

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. 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.

The following adverse reactions have been reported in postmarketing use:

**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; **Renal:** focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome; **Laboratory abnormalities:** hyperkalemia, hypernatremia, hematuria. Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and, very rarely, anaphylactic shock.

### DRUG INTERACTIONS

#### Drug-Drug Interactions

Drug interaction studies with pamidronate disodium for injection in humans have not been conducted.

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 recommendations differ for tumour-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 tumour-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).**

#### Dilution of Pamidronate Disodium for Injection for IV 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 - 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, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portions.

#### Incompatibilities

Pamidronate Disodium for Injection must not be mixed with calcium-containing infusion solutions, such as Ringer's solution.

### 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 tumour-induced hypercalcaemia where the benefit outweighs the potential risk.

As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, 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 1.0 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**).

### Recommended Dose and Dosage Adjustment

#### Dosing Guidelines for Tumour-Induced Hypercalcaemia:

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

In tumour-induced hypercalcaemia, 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 hypercalcaemia of malignancy may not reflect the severity of hypercalcaemia, 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 hypercalcaemia may be asymptomatic, moderate to severe hypercalcaemia 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 hypercalcaemia 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 hypercalcaemia. However, when symptoms of hypercalcaemia 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 hypercalcaemia 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.

Tumour-Induced Hypercalcaemia				
Initial Serum Calcium		Total Dose (mg)	Concentration of Infusate (mg/mL)	Maximum Infusion Rate (mg/h)
(mmol/L)	(mg %)			
Up to 3.0	Up to 12.0	30	30 mg/125 mL	22.5 mg/h
3.0 - 3.5	12.0 - 14.0	30 or 60*	30 mg/125 mL 60 mg/250 mL	22.5 mg/h 22.5 mg/h
3.5 - 4.0	14.0 - 16.0	60* or 90	60 mg/250 mL 90 mg/500 mL	22.5 mg/h 22.5 mg/h
> 4.0	> 16.0	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 hypercalcaemia 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-weekly 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 either 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 D5W. 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)
<b>Regimen 1</b> <b>Total dose</b> <b>180 mg</b>	30 mg once weekly for 6 weeks	30 mg in ≥ 250 - 500 mL	15 mg/h
<b>Regimen 2</b> <b>Total dose</b> <b>210 mg</b>	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
<b>Retreatment Regimen</b> <b>Total dose</b> <b>180 mg</b>	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.

### OVERDOSAGE

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

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

### 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.

#### **Tumour-induced Hypercalcemia**

In tumour-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 tumour-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 isotonic saline (0.9%) (see **WARNINGS AND PRECAUTIONS**). 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 tumour-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 i.v. 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 tumour-induced hypercalcemia is limited. In general, with retreatment, 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 tumour cells secrete paracrine factors which stimulate neighbouring osteoclasts to resorb bone. By inhibiting osteoclast function, bisphosphonates interrupt the cascade of events which lead to tumour-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 remodeling, 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**

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 hour. Apparent steady state is therefore achieved with infusions of more than 2 to 3 hours' duration. When infused i.v. 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.

As pamidronate has a strong affinity for calcified tissues, total elimination is not observed within the time frame of experimental studies.

After an i.v. 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.

Urinary elimination is biphasic ( $t_{1/2\alpha} = 1.6$  h;  $t_{1/2\beta} = 27.2$  h). The apparent renal clearance is about 54 mL/min, and there is a tendency for renal clearance to correlate with creatinine clearance.

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.

#### **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 AUC (39.7%) and  $C_{max}$  (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**).

Hepatic and metabolic clearance of pamidronate disodium are insignificant. Pamidronate disodium thus displays little potential for drug interactions at either the metabolic or protein binding level.

##### **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**).

#### **STORAGE AND STABILITY**

Protect vials from heat. Store at room temperature (15 - 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.

**AVAILABILITY OF DOSAGE FORMS**

**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.

**PHARMACEUTICAL PARTNERS OF CANADA INC.**  
Richmond Hill, ON L4B 3P6

 1-877-821-7724