Product Monograph

[Pr]Pamidronate Disodium for Injection

30 mg, 90 mg

For I.V. infusion only

Bone Metabolism Regulator

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Therapeutic Classification
Bone Metabolism Regulator

Actions and Clinical Pharmacology

Pamidronate disodium belongs to a class of bisphosphonates (previously termed diphosphonate), 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 therapy is initiated, patients should be adequately rehydrated with isotonic saline (0.9%) (**see 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 may be increased, or eventually, a combination drug therapy should be considered (**see Warnings**).

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 neighboring 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 hours. Apparent steady state is therefore achieved with infusions of > 2-3 hours' duration. When infused I.V. at 60 mg over 1 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 ($t_{½\alpha}$ = 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.

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.

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 Cmax (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 funtion 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**).

Indications and Clinical Use

- **Tumor-induced hypercalcemia 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

Known or suspected hypersensitivity to Pamidronate Disodium for Injection, to any of its components (**see Composition in Pharmaceutical Information section**), or to other bisphosphonates.

Warnings

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.

Bisphosphonates, including pamidronate disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. 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)**.

As with other I.V. bisphophonates, renal monitoring is recommended, for instance,

measurement of serum creatinine prior to each dose of pamidronate disodium. Patients treated with pamidronate disodium for bone metastases should have the dose withheld if renal function has deteriorated **(see Dosage and Administration)**.

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.

Precautions

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

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.

Although pamidronate disodium is excreted unchanged by the kidney **(see Actions and Clinical Pharmacology)**, the drug has been used without apparent increase in adverse effects in patients with significantly elevated plasma creatinine levels (including patients undergoing renal replacement therapy with both hemodialysis and peritoneal dialysis). However, experience with pamidronate disodium in patients with severe renal impairment (serum creatinine >440 µmol/L, or 5 mg/dL in TIH patients; >180 µmol/L, or 2 mg/dL in multiple myeloma patients) is limited. If clinical judgment determines that the potential benefits outweigh the risk in such cases, pamidronate disodium should be used cautiously and renal function carefully monitored.

As there are no clinical data available in patients with severe hepatic insufficiency, no

specific recommendations can be given for this patient population.

Patients with Paget's disease of the bone, who are at risk of calcium or vitamin D deficiency, should be given oral calcium supplements and vitamin D to minimize the risk of hypocalcemia.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, head and neck radiotherapy, corticosteroids, poor oral hygiene).

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

Patient Monitoring

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)**

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. 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)

Drug Interactions: Pamidronate disodium has been used concomitantly with the following medications without evidence of significant adverse interactions (**see Actions and Clinical Pharmacology)**: aminoglutethimide, cisplatin, corticosteroids, cyclophosphamide, cytarabine, doxorubicin, etoposide, fluouracil, loop diuretics, megestrol, melphalan, methotrexate, mitoxantrone, paclitaxel, tamoxifen, vinblastine, vincristine, and, in patients with severe hypercalcemia, calcitonin or mithramycin.

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.

Use in Pregnancy: There is no clinical evidence to support the use of pamidronate disodium in pregnant women. Therefore, pamidronate disodium should not be administered during pregnancy except for life-threatening hypercalcemia.

In animal experiments, pamidronate was not teratogenic and did not affect general reproductive performance or fertility. In rats, prolonged parturition and reduced pup survival were probably caused by a decrease in maternal serum calcium levels. The fertility of the pups was also reduced. Pamidronate crosses the placental barrier and accumulates in fetal bone.

Lactation: There is no clinical experience with pamidronate disodium in lactating women and it is not known whether pamidronate disodium passes into breast milk. A study in lactating rats has shown that pamidronate passes into the milk. Mothers treated with pamidronate disodium should therefore not breast feed their infants.

Pediatric Use: The safety and efficacy of pamidronate disodium in children has not been established. Until further experience is gained, pamidronate disodium is only recommended for use in adult patients.

Effects on ability to drive or use machines: In rare cases, somnolence and/or dizziness may occur, in which case the patient should not drive, operate potentially dangerous machinery or engage in other activities that may be hazardous.

Adverse Reactions

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.

Adverse experiences by body system:

Frequency estimate: very common >10%, common >1-10%, uncommon >0.001-1%, rare <0.0001% - 0.001%, very rare <0.0001%, including isolated reports.

Body as a whole

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

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: muscle cramps

Gastrointestinal tract

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

Uncommon: dyspepsia

Central nervous system

Common: symptomatic hypocalcemia (paresthesia, tetany), headache, insomnia, somnolence

Uncommon: seizures, agitation, dizziness, lethargy

Very Rare: confusion, visual hallucinations

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.

Cardiovascular system

Common: hypertension

Uncommon: hypotension

Very Rare: left ventricular failure (dyspnea, pulmonary edema), congestive heart failure (edema) due to fluid overload

Respiratory system

Rare: adult respiratory distress syndrome, interstitial pneumonitis

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

Skin

Common: rash

Uncommon: pruritus

Special senses

Common: conjunctivitis

Uncommon: uveitis (iritis, iridocyclitis)

Very Rare: scleritis, episcleritis, xanthopsia

Infection

Very Rare: reactivation of Herpes simplex and Herpes zoster

Immune System

Uncommon: allergic reactions including anaphylactoid reactions, bronchospasm, dyspnoea, Quincke's (angioneurotic) oedema

Very Rare: anaphylactic shock

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

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)**. Since many patients with tumour-induced hypercalcemia have compromised renal function prior to receiving antihypercalcemia therapy **(see 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 Precautions, Patient Monitoring)**.

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 Precautions, Patient Monitoring)**.

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**
General		
Asthenia	16.4	15.4
Fatigue	30.4	35.5
Fever	35.5	30.5
Metastases	14.0	13.6
Digestive System		
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
Hemic and Lymphatic System		
Anemia	35.1	32.6
Granulocytopenia	16.8	17.3
Thrombocytopenia	11.0	13.1
Musculoskeletal System		
Myalgias	22.6	16.9
Skeletal Pain	59.4	69.1
CNS		
Headache	24.0	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-marketing Experience

A number of cases of osteonecrosis (primarily of the jaws) have been reported in association with pamidronate disodium since market introduction. Osteonecrosis of the jaws has other well documented multiple risk factors. It is not possible to determine if these events are related to pamidronate disodium or other bisphosphonates, to concomitant drugs or other therapies (e.g. chemotherapy, head and neck radiotherapy, corticosteroid), to patient's underlying disease, or to other co-morbid risk factors (e.g. anemia, infection, pre-existing oral disease).

Symptoms and Treatment of Overdosage

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 since plasma calcium levels fall progressively for several days after treatment.

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). 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 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).**

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 hypercalcemia 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. In patients receiving pamidronate disodium for bone metastases who show evidence of deterioration in renal function, pamidronate disodium 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/4h (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 Pharmacokinetics - Hepatic

impairment).

Dosing Guidelines For Tumour-Induced Hypercalcemia

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. Rehydration with normal saline before treatment is recommended (**see Precautions**). **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 derived from clinical data on uncorrected calcium values. These dose ranges also apply for calcium corrected for serum protein.

Tumour-induced hypercalcemia				
Initial Serum Calcium		**Total Dose**	**Concentration of Infusate**	**Maximum Infusion Rate**
(mmol/L)	**(mg %)**	**(mg)**	**(mg/mL)**	**(mg/h)**
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

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 may be given, according to the dosing guidelines. The limited clinical experience available to date has suggested the possibility that pamidronate disodium 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

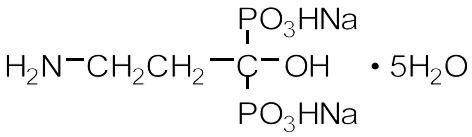
Dosing Guidelines For Paget's Disease Of Bone

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)**
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	30/60mg in ≥250-500mL	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

Pharmaceutical Information

Drug Substance



Pamidronate disodium

Chemical Name: Disodium-3-amino-1-hydroxypropylidene-1,1-bisphosphonate

Empirical Formula: $C_3H_9NO_7P_2Na_2$

Molecular Weight: 279.04

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.

Composition

Pamidronate Disodium for Injection 30 mg/vial:

Each vial of sterile lyophilized powder contains anhydrous pamidronate disodium (30 mg) and mannitol (470 mg). Phosphoric acid is employed to adjust the pH to 6.3.

Pamidronate Disodium for Injection 90 mg/vial:

Each vial of sterile lyophilized powder contains anhydrous pamidronate disodium (90 mg) and mannitol (375 mg). Phosphoric acid is employed to adjust the pH to 6.3.

These preparations contain **NO** preservatives.

Stability And Storage Recommendations

Protect vials from heat (i.e., store below 30°C).

Reconstitution Of Lyophilized Vials

Each vial of sterile lyophilized powder should be reconstituted with Sterile Water for Injection prior to dilution as given in the following table:

RECONSTITUTION TABLE

Vial size	Volume of diluent to be added to the vial	Approximate available volume	Nominal Concentration
30 mg/10 mL vial	10 mL	10 mL	3 mg/mL
60 mg/10 mL vial	10 mL	10 mL	6 mg/mL
90 mg/10 mL vial	10 mL	10 mL	9 mg/mL

Dilution Of Reconstituted Solution For I.V. Infusion:

Reconstituted solutions that have been prepared with Sterile Water for Injection should be further diluted with either 0.9% w/v sodium chloride or 5% w/v glucose

solution prior to intravenous infusion administration. The reconstituted solution is chemically and physically stable for 24 hours at room temperature. However, from a microbiological point of view, it is preferable to use the product immediately after aseptic reconstitution and dilution.

If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between reconstitution, dilution and end of administration must not exceed 24 hours.

All parenteral products should be visually inspected for particulate matter and discoloration prior to administration. Any solution found to have particulate matter or discoloration should be discarded.

Incompatibilities

Pamidronate forms complexes with divalent cations. For this reason, Pamidronate Disodium for Injection reconstituted solution must not be mixed with calcium-containing intravenous solutions such as Ringer's solution. Pamidronate Disodium for Injection reconstituted solution should be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution. Studies with containers and infusion sets/devices for infusion made of glass, polyethylene and polyvinylchloride have been shown to be compatible with diluted Pamidronate Disodium for Injection solution.

Availability of Dosage Forms

[Pr]Pamidronate Disodium for Injection 30 mg vials:

Each vial of white to practically white lyophilisate contains pamidronate disodium (30 mg). Available in cartons of 1 vial.

[Pr]Pamidronate Disodium for Injection 90 mg vials:

Each vial of white to practically white lyophilisate contains pamidronate disodium (90 mg). Available in cartons of 1 vial.

Information to the Consumer

Please read this information carefully before starting treatment with [Pr]Pamidronate Disodium for Injection. If you have further questions, ask your doctor, pharmacist or nurse.

What Is Pamidronate Disodium for Injection?

Pamidronate Disodium for Injection contains an active ingredient called pamidronate disodium. It is available as a powder in vials. One vial contains 30 mg or 90 mg of pamidronate disodium. Pamidronate Disodium for Injection is given as an infusion into a vein after appropriate dilution.

Pamidronate disodium belongs to a group of medicines called bisphosphonates which strongly bind to the bone and slow down the rate of bone change. They are used to reduce the amount of calcium in the blood of some patients who have too much calcium in their blood circulation. Pamidronate disodium can also be used in other conditions with increased bone change or pain.

What Does Pamidronate Disodium for Injection Do?

Pamidronate Disodium for Injection is used to treat:

- the increased amount of calcium in the blood (hypercalcemia) in certain conditions
- bone tumours resulting from the spread of tumours at other sites and multiple myeloma
- Paget's disease of bone in patients with symptoms.

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; 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 *What Side Effects Can Pamidronate Disodium for Injection Have?*)

You should not be given Pamidronate Disodium for Injection if you have previously had an allergic reaction to pamidronate disodium or other bisphosphonates.

Before starting treatment with Pamidronate Disodium for Injection tell your doctor

- if you have a heart, liver or kidney problem
- if you suffer from calcium or vitamin D deficiency (for example owing to your diet or as a result of digestive problems).
- if you have any dental problems or any dental procedures planned in the future.

Further Safety Measures

It is important that your doctor checks your progress at regular intervals. He or she may want to take repeated blood tests, especially after starting your treatment with Pamidronate Disodium for Injection.

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.

Other Medicines Or Substances That May Interfere With The Action Of Pamidronate Disodium for Injection

Before starting Pamidronate Disodium for Injection treatment, talk to your doctor about any other medicines that you are using or intend to use. It is especially important that your doctor knows if you are being treated with another bisphosphonate, calcitonin, calcium tablets, or vitamin supplements.

Pregnancy Or Breast-Feeding

You should tell your doctor if you are pregnant, breast-feeding, or planning to become pregnant. Pamidronate Disodium for Injection should not be given during pregnancy except in special situations and only after a careful discussion with the doctor. Mothers treated with Pamidronate Disodium for Injection should not breast-feed their babies.

Use In Children And Elderly Patients

So far children have not been treated with pamidronate disodium. Until further experience is gained, Pamidronate Disodium for Injection is only recommended for use in adult patients.

Elderly patients may be treated with Pamidronate Disodium for Injection, provided that they do not have a serious heart, liver or kidney problem.

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.

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. This is usually 30-90 mg for patients with increased blood calcium and 90 mg every 3-4 weeks for patients with tumours which have spread to the bone or multiple myeloma. Patients with Paget's disease of bone usually receive between 30-60 mg in one infusion. An infusion may last one or more hours, depending on the dose given. Your doctor will decide how many infusions you need and how often you should receive them.

What Side Effects Can Pamidronate Disodium for Injection Have?

Like all medicines, Pamidronate Disodium for Injection may have, in addition to its beneficial effects, some unwanted effects. The most common side effects are: short-lasting fever and flu-like condition with chills, sometimes together with a feeling of tiredness and general discomfort.

Less common side effects include: short-lasting muscle or joint pain, muscle cramps, pain, redness and swelling at the site of infusion, indigestion, nausea, vomiting, abdominal pain, constipation, diarrhea, loss of appetite, headache, dizziness, sleepiness, tiredness, confusion, agitation, skin rash, itching, eye irritation.

Other side effects not listed above may also occur in some patients. Eye pain, redness, photophobia, excessive tearing or decreased vision should be reported to your physician as they may indicate more serious eye complications which have been associated with pamidronate disodium.

Some patients have reported problems with their jaw bones while receiving cancer treatments that include pamidronate disodium. Dental hygiene is an important element of your overall cancer 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.

Further Information

Expiry Date

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.

Storage Conditions

Protect vials from heat (store below 30°C). **Keep this medicine out of the reach of children.**

Other Important Information

This medicine has been prescribed for your current medical problem only. Do not give it to other people.

Pharmacology

Animal Pharmacology

Subcutaneous administration of pamidronate disodium to rats reduced urinary hydroxyproline excretion within 2-8 days starting at 0.16 µmol/kg/day and reaching a maximum at 16 µmol/kg/day. At higher doses (>40 µmol/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 I.P.) 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, S.C. administration of 16 µmol/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 µg/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 S.C. Similarly, pamidronate disodium reduced hypercalcemia of malignancy in rats bearing Walker 256 carcinosarcoma tumours. 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 3.0% 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 I.V., 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.

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.

Tumour-induced Hypercalcemia: Pamidronate disodium lowered plasma calcium between 3 to 7 days following the initiation of treatment irrespective of the tumour 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 >4.0 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 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 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 groups. The proportion of patients experiencing an SRE was significantly smaller, and the time to first SRE was significantly longer in pamidronate disodium-treated multiple myeloma and breast cancer + chemotherapy patients. The same trend was seen in the hormonally-treated breast cancer patients. Fewer pamidronate disodium-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 or placebo in addition to their underlying antimyeloma therapy to determine the effect of pamidronate disodium 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 or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 pamidronate disodium, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the pamidronate disodium group (24% vs 41%, $p<0.001$), and the mean skeletal

morbidity rate (#SRE/year) was significantly smaller for pamidronate disodium 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 group ($p=0.001$, 0.006, and 0.046, respectively). Moreover, fewer pamidronate disodium 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 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-treated patients.

After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the pamidronate disodium 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 patients vs placebo patients ($p=.008$), and time to first SRE was significantly longer in the pamidronate disodium group compared to placebo ($p=0.016$). Fewer pamidronate disodium 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 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 whic was at least 1 cm in diameter. In one trial patients were receiving hormonal therapy

patients 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 received either 90 mg of pamidronate disodium (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 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 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 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 significantly greater for pamidronate disodium patients compared to placebo patients (p=0.049 and 0.016, respectively).

Bone lesion partial response, assessed radiologically, was 30% for the pamidronate disodium 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 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 (*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 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 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 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 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 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 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 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 I.V. at 15 mg/2 hours daily for 5 consecutive days (N=12). ALP normalized in 4 patients. Five patients required retreatment 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 (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% patients.

In a larger, open clinical trial of similar design, patients were also stratified according to initial ALP. However, those with ALP <500 (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% 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 50-60% patients.

Toxicology

Acute Toxicity

In acute toxicity studies, pamidronate disodium was better tolerated when administered as a short-term I.V. infusion or I.P. than as a bolus I.V. dose, presumably because of lower plasma concentrations. In mice, the I.V. bolus and I.P. 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 I.V. dose and >40 mg/kg when administered as an I.V. infusion.

Subacute And Chronic Toxicity

Pamidronate disodium has been administered to mice, rats, rabbits and dogs for

≤3 months by intermittent I.V. infusion or a bolus I.V. dose. Repeat dose animal studies demonstrate that intermittent administration of pamidronate disodium by I.V. infusion is better tolerated than the bolus I.V. 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 I.V. 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 I.V. 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.

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 (2500 µg/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 ≤1000 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 tumours than those fed *ad libitum*. In this study, the incidence of liver tumours 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 tumours in female Wistar rats administered 1000 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 tumours are of biological or clinical significance.

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