CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-841

FINAL PRINTED LABELING

Pamidronate Disodium Injection

JUN 27 2002

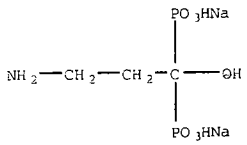
Faulding

For Intravenous Infusion
Rx only
Prescribing Information

APPROVED

DESCRIPTION

Pamidronate Disodium, is a bone-resorption inhibitor available in 30-mg, 60-mg, or 90-mg vials for intravenous administration. The pamidronate disodium obtained by combining pamidronic acid and sodium hydroxide is provided in a sterile, ready to use solution for injection.. Each mL of the 30 mg vial contains: 3 mg Pamidronate Disodium; 47 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. Each mL of the 60 mg vial contains: 6 mg Pamidronate Disodium; 40 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. Each mL of the 90 mg vial contains: 9 mg Pamidronate Disodium; 37.5 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. The pH of a 1 % solution of pamidronate disodium in distilled water is approximately 8.3. Pamidronate, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, and its structural formula is



Pamidronate disodium is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2$ and its molecular weight is 279.1 (calculated as the anhydrous form).
Inactive Ingredients. Mannitol, phosphoric acid (for adjustment to pH range of 6.0 - 7.0) and water for injection.

CLINICAL PHARMACOLOGY

The principal pharmacologic action of pamidronate is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Pamidronate adsorbs to calcium phosphate (hydroxyapatite) crystals in bone and may directly block dissolution of this mineral component of bone. *In vitro* studies also suggest that inhibition of osteoclast activity contributes to inhibition of bone resorption. In animal studies, at doses recommended for the treatment of hypercalcemia, Pamidronate inhibits bone resorption apparently without inhibiting bone formation and mineralization. Of relevance to the treatment of hypercalcemia of malignancy is the finding that pamidronate inhibits the accelerated bone resorption that results from osteoclast hyperactivity induced by various tumors in animal studies.

Pharmacokinetics

Cancer patients (n=24) who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of pamidronate disodium over 4 hours and 90 mg of pamidronate disodium over 24 hours (Table 1).

Distribution

The mean ± SD body retention of pamidronate was calculated to be 54 ± 16% of the dose over 120 hours.

Metabolism

Pamidronate is not metabolized and is exclusively eliminated by renal excretion.

Excretion

After administration of 30, 60, and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate disodium over 24 hours, an overall mean ± SD of 46 ± 16% of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean ±SD elimination half-life is 28 ± 7 hours. Mean ±SD total and renal clearances of pamidronate were 107 ± 50 mL/min and 49 ± 28 mL/min, respectively. The rate of elimination from bone has not been determined.

Special Populations

There are no data available on the effects of age, gender, or race on the pharmacokinetics of pamidronate.

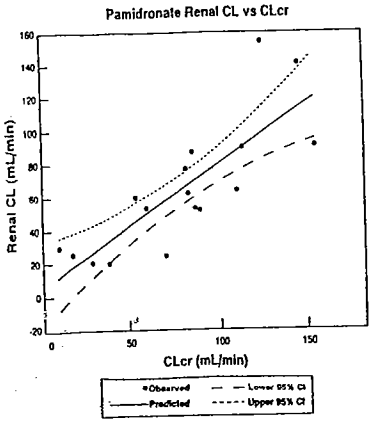
Pediatric

Pamidronate is not labelled for use in the pediatric population.

Renal Insufficiency

The pharmacokinetics of pamidronate were studied in cancer patients (n=19) with normal and varying degrees of renal impairment. Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. The renal clearance of pamidronate in patients was found to closely correlate with creatinine clearance (see Figure 1). A trend toward a lower percentage of drug excreted unchanged in urine was observed in renally impaired patients. Adverse experiences noted were not found to be related to changes in renal clearance of pamidronate. Given the recommended dose, 90 mg infused over 4 hours, excessive accumulation of pamidronate disodium in renally impaired patients is not anticipated if pamidronate is administered on a monthly basis.

Figure 1: Pamidronate renal clearance as a function of creatinine clearance in patients with normal and impaired renal function.
The lines are the mean prediction line and 95% confidence intervals.



Hepatic Insufficiency
There are no human pharmacokinetic data for pamidronate in patients who have hepatic insufficiency.
Drug-Drug Interactions
There are no human pharmacokinetic data for drug interactions with pamidronate.

Table 1

Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients (n=6 for each group)

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

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

Pharmacodynamics

Serum phosphate levels have been noted to decrease after administration of pamidronate, presumably because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7-10 days.
Urinary calcium/creatinine and urinary hydroxyproline/creatinine ratios decrease and usually return to within or below normal after treatment with pamidronate. These changes occur within the first week after treatment, as do decreases in serum calcium levels, and are consistent with an antiresorptive pharmacologic action.

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.
Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanism involved.
In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.
Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.
Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE and ADMINISTRATION).

In a third multicenter, randomized, parallel double-blind trial, a group of 69 cancer p... or 24-hour infusion, which was compared to a saline treatment group. Patients who had ... eligible for this trial.
The mean baseline-corrected serum calcium levels for pamidronate disodium 60-mg 4-hc... 14.2 mg/dL, 13.7 mg/dL, and 13.7 mg/dL, respectively.
By day 7 after initiation of treatment, 78%, 61%, and 22% of the patients had normal-cor... and saline infusion, respectively. At day 14, 39% of the patients in the pamidronate disod... 60-mg 24-hour infusion group had normal-corrected serum calcium levels or maintenanc...
For responders, the median duration of complete responses was 4 days and 6.5 days for ... 24-hour infusion, respectively.
In all three trials, patients treated with pamidronate had similar response rates in the pre... not affect response rates.
Thirty-two patients who had recurrent refractory hypercalcemia of malignancy were give... these, 41% showed a complete response and 16% showed a partial response to the retre... calcium levels 7 days after retreatment.
Unlike pamidronate disodium 60 mg, the drug has not been investigated in a controlled c...

Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic disease characterized by ch... affecting one or more bones. These changes result in thickened but weakened bones tha... fractures, neurological disorders resulting from cranial and spinal nerve entrapment and ... bone, increased serum alkaline phosphatase levels (reflecting increased bone formation)...

Clinical Trials

In one double-blind clinical trial, 64 patients with moderate to severe Paget's disease of ... single 4-hour infusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 m...
The mean baseline serum alkaline phosphatase levels were 1409 U/L, 983 U/L, and 1085 ... 0.19 for the 15-mg, 45-mg, and 90-mg groups, respectively.
The effects of pamidronate on serum alkaline phosphatase (SAP) and urine hydroxy- pre...

Percent of Patients with Significa...

	SAP		
% Decrease	15 mg	45 mg	9
≥50	26	33	
≥30	40	65	

The median maximum percent decreases from baseline in serum alkaline phosphatase a... 61% for the 15-mg, 45-mg, and 90-mg groups, respectively. The median time to respon... 90-mg group, and the response duration ranged from 1 to 372 days.
No statistically significant differences between treatment groups, or statistically signific... global evaluation in the 45-mg and 90-mg groups. Improvement in radiologic lesions oc...
Twenty-five patients who had Paget's disease were retreated with 90 mg of pamidronat... baseline after treatment, and 39% had a ≥50% decrease in urine hydroxyproline/creatir...

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Mye...

Osteolytic bone metastases commonly occur in patients with multiple myeloma or breast ca... possess an extraordinary affinity for bone. The distribution of osteolytic bone metastases ir... rather than the appendicular skeleton, although lesions in the proximal femur and humerus ... flow possibly assists attachment of metastatic cells. The surface-to-volume ratio of trabecu... more floridly in trabecular bone than at sites of cortical tissue.
These bone changes can result in patients having evidence of osteolytic skeletal destruction ... both) for symptomatic relief. These changes also cause pathologic fractures of bone in both ... to spinal cord compression or vertebral body collapse with significant neurologic complica...

Clinical Trials

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced mu... underlying antimyeloma therapy to determine the effect of pamidronate on the occurre... fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Pa... 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for ... was significantly smaller in the pamidronate group (24% vs 41%, P<0.001), and the m... than for placebo patients (mean: 1.1 vs 2.1, P<.02). The times to the first SRE occurre... group (P=.001, .006, and .046, respectively). Moreover, fewer pamidronate patients su... 22%, P=.049).
In addition, decreases in pain scores from baseline occurred at the last measurement f... At the last measurement, a worsening from baseline was observed in the placebo grou... while there was no significant deterioration from baseline in these parameters observe... After 21 months, the proportion of patients experiencing any skeletal event remained s... addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for pamidronate ... pamidronate group compared to placebo (P=.016). Fewer pamidronate patients suffer... different between treatment groups.
Two double-blind, randomized, placebo-controlled trials compared the safety and effic... months to that of placebo in preventing SREs in breast cancer patients with osteolytic ... diameter: one in patients being treated with antineoplastic chemotherapy and the secon... 382 patients receiving chemotherapy were randomized, 185 to pamidronate and 197 to ... and 190 to placebo. All but three patients were evaluable for efficacy. Patients were fo... was 13 months in patients receiving chemotherapy and 17 months in patients receivir... 37% of the patients in the hormone therapy study received Pamidronate for 24 month...

	Breast Cancer Patients Receiving Chemotherapy				
	Any SRE		Radiation		Fr
N	PD 185	P 195	PD 185	P 195	PI 18
Skeletal Morbidity Rate (#SRE/Year)					
Mean	2.5	3.7	0.8	1.3	1
P-value	<.001		<.001*		
Proportion of Patients having an SRE	46%	65%	28%	45%	36
P-Value	<.001		<.001*		
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25
P-Value	<.001		<.001*		

*Fractures and radiation to bone were two of several secondary endpoints. The statis... performed.
**NR = Not Reached.

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 ... placebo patients treated with chemotherapy (P=.001). No difference was seen betwe...

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index ... the last measurement carried forward are shown in the table below:

Mean Change (Δ) from ...

	Breast Cancer Patients Receiving Chemotherapy				
	Pamidronate		Placebo		PD vs I
	N	Mean Δ	N	Mean Δ	P-value
Pain Score	175	+0.93	183	+1.69	.050
Analgesic Score	175	+0.74	183	+1.55	.009
ECOG PS	178	+0.81	186	+1.19	.002
Spitzer QOL	177	-1.76	185	-2.21	.103

Decreases in pain, analgesic scores and ECOG PS, and increases in Spitzer QOL inc...

*The statistical significance of analyses of these secondary endpoints of pain, qual... analyses were performed.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Pamidronate, in conjunction with adequate hydration, is indicated for the treatmen... metastases. Patients who have either epidermoid or non-epidermoid tumors respo...

Cancer patients (n=24) who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of pamidronate disodium over 4 hours and 90 mg of pamidronate disodium over 24 hours (Table 1).

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Special Populations

There are no data available on the effects of age, gender, or race on the pharmacokinetics of pamidronate.

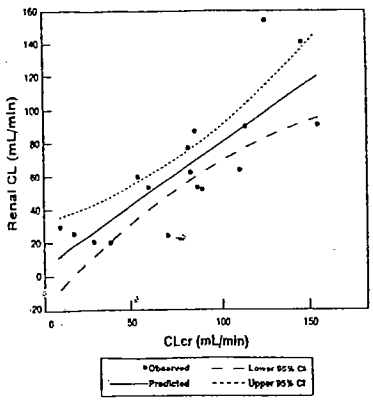
Pediatric

Pamidronate is not labelled for use in the pediatric population.

Renal Insufficiency

The pharmacokinetics of pamidronate were studied in cancer patients (n=19) with normal and varying degrees of renal impairment. Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. The renal clearance of pamidronate in patients was found to closely correlate with creatinine clearance (see Figure 1). A trend toward a lower percentage of drug excreted unchanged in urine was observed in renally impaired patients. Adverse experiences noted were not found to be related to changes in renal clearance of pamidronate. Given the recommended dose, 90 mg infused over 4 hours, excessive accumulation of pamidronate disodium in renally impaired patients is not anticipated if pamidronate is administered on a monthly basis.

Figure 1: Pamidronate renal clearance as a function of creatinine clearance in patients with normal and impaired renal function.
The lines are the mean prediction line and 95% confidence intervals.



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

Pharmacodynamics

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

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

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Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanism involved.

In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE and ADMINISTRATION).

Clinical Trials

In one double-blind clinical trial, 52 patients who had hypercalcemia of malignancy were enrolled to receive 30 mg, 60 mg, or 90 mg of pamidronate disodium as a single 24-hour intravenous infusion if their corrected serum calcium levels were ≥12.0 mg/dL after 48 hours of saline hydration.

The mean baseline-corrected serum calcium for the 30-mg, 60-mg, and 90-mg groups were 13.8 mg/dL, 13.8 mg/dL, and 13.3 mg/dL, respectively.

The majority of patients (64%) had decreases in albumin-corrected serum calcium levels by 24 hours after initiation of treatment. Mean-corrected serum calcium levels at days 2-7 after initiation of treatment with pamidronate were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with pamidronate, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of pamidronate disodium, respectively, had normal-corrected serum calcium levels. Many patients (33%-53%) in the 60-mg and 90-mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response (≥15% decrease of corrected serum calcium from baseline), at day 14.

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of ≥12.0 mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of pamidronate disodium as a single 24-hour intravenous infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive pamidronate and 35 to receive etidronate disodium.

The mean baseline-corrected serum calcium for the pamidronate disodium 60-mg and etidronate disodium groups were 14.6 mg/dL and 13.8 mg/dL, respectively.

By day 7, 70% of the patients in the pamidronate group and 41% of the patients in the etidronate disodium group had normal-corrected serum calcium levels (P<0.05). When partial responders (≥15% decrease of serum calcium from baseline) were also included, the response rates were 97% for the pamidronate group and 65% for the etidronate disodium group (P<0.01). Mean-corrected serum calcium for the pamidronate and etidronate disodium groups decreased from baseline values to 10.4 and 11.2 mg/dL, respectively, on day 7. At day 14, 43% of patients in the pamidronate group and 18% of patients in the etidronate disodium group still had normal-corrected serum calcium levels, or maintenance of a partial response. For responders in the pamidronate and etidronate disodium groups, the median duration of response was similar (7 and 5 days, respectively). The time course of effect on corrected serum calcium is summarized in the following table.

Change in Corrected Serum Calcium by Time from Initiation of Treatment

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)		
	Pamidronate	Etidronate Disodium	P-value[1]
Baseline	14.6	13.8	
24	-0.3	-0.5	
48	-1.5	-1.1	
72	-2.6	-2.0	
96	-3.5	-2.0	<0.01
168	-4.1	-2.5	<0.01

[1] Comparison between treatment groups.

The median maximum percent decreases from baseline in serum alkaline phosphatase and urine hyc 61% for the 15-mg, 45-mg, and 90-mg groups, respectively. The median time to response (≥50% d 90-mg group, and the response duration ranged from 1 to 372 days.

No statistically significant differences between treatment groups, or statistically significant changes global evaluation in the 45-mg and 90-mg groups. Improvement in radiologic lesions occurred in so Twenty-five patients who had Paget's disease were retreated with 90 mg of pamidronate disodium. baseline after treatment, and 39% had a ≥50% decrease in urine hydroxyproline/creatinine ratio fro

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

Osteolytic bone metastases commonly occur in patients with multiple myeloma or breast cancer. These possess an extraordinary affinity for bone. The distribution of osteolytic bone metastases in these cance rather than the appendicular skeleton, although lesions in the proximal femur and humerus are not uncor flow possibly assists attachment of metastatic cells. The surface-to-volume ratio of trabecular bone is m more floridly in trabecular bone than at sites of cortical tissue.

These bone changes can result in patients having evidence of osteolytic skeletal destruction leading to se both) for symptomatic relief. These changes also cause pathologic fractures of bone in both the axial an to spinal cord compression or vertebral body collapse with significant neurologic complications. Also, pa

Clinical Trials

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myelon underlying antimyeloma therapy to determine the effect of pamidronate on the occurrence of skelet fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Patients receive 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 was significantly smaller in the pamidronate group (24% vs 41%, P<0.001), and the mean skeletal r than for placebo patients (mean: 1.1 vs 2.1, P<.02). The times to the first SRE occurrence, patholog group (P=.001, .006, and .046, respectively). Moreover, fewer pamidronate patients suffered any pa 22%, P=.049).

In addition, decreases in pain scores from baseline occurred at the last measurement for those pam At the last measurement, a worsening from baseline was observed in the placebo group for the Spit while there was no significant deterioration from baseline in these parameters observed in pamidron After 21 months, the proportion of patients experiencing any skeletal event remained significantly sr addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for pamidronate patients vs pl pamidronate group compared to placebo (P=.016). Fewer pamidronate patients suffered vertebral p different between treatment groups.

Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastas diameter: one in patients being treated with antineoplastic chemotherapy and the second in patients 382 patients receiving chemotherapy were randomized, 185 to pamidronate and 197 to placebo. 372 and 190 to placebo. All but three patients were evaluable for efficacy. Patients were followed for 24 was 13 months in patients receiving chemotherapy and 17 months in patients receiving hormone th 37% of the patients in the hormone therapy study received Pamidronate for 24 months. The efficacy

	Breast Cancer Patients Receiving Chemotherapy					
	Any SRE		Radiation		Fractures	
N	PD 185	P 195	PD 185	P 195	PD 185	P 195
Skeletal Morbidity Rate (#SRE/Year) Mean	2.5	3.7	0.8	1.3	1.6	2.2
P-value	<.001		<.001*		.018*	
Proportion of Patients having an SRE	46%	65%	28%	45%	36%	49%
P-Value	<.001		<.001*		.014*	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3
P-Value	<.001		<.001*		.009*	

*Fractures and radiation to bone were two of several secondary endpoints. The statistical significan performed.

**NR = Not Reached.

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The co placebo patients treated with chemotherapy (P=.001). No difference was seen between pamidronate

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index were measure the last measurement carried forward are shown in the table below:

Mean Change (Δ) from Baseline at La

	Breast Cancer Patients Receiving Chemotherapy				
	Pamidronate		Placebo		PD vs P
	N	MeanΔ	N	MeanΔ	P-value*
Pain Score	175	+0.93	183	+1.69	.050
Analgesic Score	175	+0.74	183	+1.55	.009
ECOG PS	178	+0.81	186	+1.19	.002
Spitzer QOL	177	-1.76	185	-2.21	.103

Decreases in pain, analgesic scores and ECOG PS, and increases in Spitzer QOL indicate an improv

*The statistical significance of analyses of these secondary endpoints of pain, quality of life, and pe analyses were performed.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Pamidronate, in conjunction with adequate hydration, is indicated for the treatment of moderate or metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment v hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the hypercalcemia may be treated with conservative measures (i.e. saline hydration, with or without loo treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided hypovolemia. The safety and efficacy of pamidronate in the treatment of hypercalcemia associated been established.

Paget's Disease

Pamidronate is indicated for the treatment of patients with moderate to severe Paget's disease of b patients with serum alkaline phosphatase ≥3 times the upper limit of normal. Pamidronate therapy phosphatase and urinary hydroxyproline levels by ≥50% in at least 50% of patients, and by ≥30% reducing these biochemical markers in patients with Paget's disease who failed to respond, or no lc

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

Pamidronate is indicated, in conjunction with standard antineoplastic therapy, for the treatment of myeloma. The pamidronate treatment effect appeared to be smaller in the study of breast cancer pa chemotherapy, however, overall evidence of clinical benefit has been demonstrated (see CLINICAL Osteolytic Lesions of Multiple Myeloma, Clinical Trials section).

CONTRAINDICATIONS

Pamidronate is contraindicated in patients with clinically significant hypersensitivity to pamidronate

WARNINGS

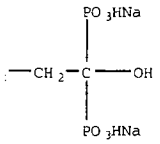
In both rats and dogs, nephropathy has been associated with intravenous (bolus and infusion) adm Two 7-day intravenous infusion studies were conducted in the dog wherein pamidronate first study, the compound was well tolerated at 3 mg/kg (1.7 x highest recommended human dose hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occ second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 h animals and renal tubular dilation and/or inflammation at ≥1 mg/kg after each infusion time.

Pamidronate disodium was given to rats at doses of 2, 6, and 20 mg/kg and to dogs at doses of 2, by a 1-month recovery period. In rats, nephrotoxicity was observed at ≥6 mg/kg and included incre findings were still present at 20 mg/kg at the end of the recovery period. In dogs, moribundity/deat BUN and creatinine levels at ≥6 mg/kg and renal tubular degeneration at ≥4 mg/kg. The kidney cha produced no adverse renal effects was considered to be 2 mg/kg (1.1 x HRHD for a single intravenc

Patients who receive an intravenous infusion of pamidronate should have periodic evaluations of st

Studies conducted in young rats have reported the disruption of dental dentine formation following significance of these findings is unknown.

), or 90-mg vials for intravenous administration. The pamidronate disodium obtained by combining on for injection.. Each mL of the 30 mg vial contains: 3 mg Pamidronate Disodium; 47 mg Mannitol, ıe 60 mg vial contains: 6 mg Pamidronate Disodium; 40 mg Mannitol, USP; Water for Injection, USP. nidronate Disodium; 37.5 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust nately 8.3. Pamidronate, a member of the group of chemical compounds known as bisphosphonates, ıs phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, and its structural formula is



gly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic 279.1 (calculated as the anhydrous form).
6.0 - 7.0) and water for injection.

ption. Although the mechanism of antiresorptive action is not completely understood, several m phosphate (hydroxyapatite) crystals in bone and may directly block dissolution of this mineral activity contributes to inhibition of bone resorption. In animal studies, at doses recommended for ıtly without inhibiting bone formation and mineralization. Of relevance to the treatment of erated bone resorption that results from osteoclast hyperactivity induced by various tumors in

n intravenous infusion of 30, 60, or 90 mg of pamidronate disodium over 4 hours and

of the dose over 120 hours.

ın.

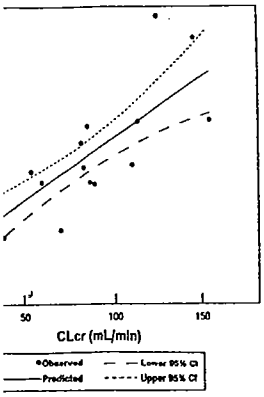
rs, and 90 mg of pamidronate disodium over 24 hours, an overall mean ± SD of 46 ± 16% of the ʏ excretion was linearly related to dose. The mean ±SD elimination half-life is 28 ± 7 hours. Mean ± 28 mL/min, respectively. The rate of elimination from bone has not been determined.

ıacokinetics of pamidronate.

with normal and varying degrees of renal impairment. Each patient received a single 90 mg dose of ste in patients was found to closely correlate with creatinine clearance (see Figure 1). A trend in renally impaired patients. Adverse experiences noted were not found to be related to changes in over 4 hours, excessive accumulation of pamidronate disodium in renally impaired patients is not

ın of creatinine clearance in patients with normal and impaired renal function.
ɜan prediction line and 95% confidence intervals.

Pamidronate Renal CL vs CLcr



ve hepatic insufficiency.

ıate.

Table 1

le Pharmacokinetic Parameters in Cancer Patients (n=6 for each group)

f dose excreted in urine	Total Clearance (mL/min)	Renal Clearance (mL/min)
3.9 (14.0, 31.9%)	136 (44, 32.4%)	58 (27, 46.5%)
7.4 (47.4, 54.4%)	88 (56, 63.6%)	42 (28, 66.7%)
5.3 (25.8, 56.9%)	103 (37, 35.9%)	44 (16, 36.4%)
7.5 (10.2, 21.5%)	101 (58, 57.4%)	52 (42, 80.8%)

nately 50%-60% of the compound was rapidly adsorbed by bone and slowly eliminated from the amidronate, approximately 30% of the compound was found in the liver shortly after administration ıurs. Studies in rats injected with radiolabeled pamidronate showed that the compound was rapidly and tracheal cartilage. Radioactivity was eliminated from most soft tissues within 1-4 days; was high in bones, trachea, and teeth for 6 months after dosing. Bone uptake occurred preferentially in e was estimated to be approximately 300 days.

ıamidronate, presumably because of decreased release of phosphate from bone and increased renal ercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered hosphate levels usually returned toward normal within 7-10 days.
ıse and usually return to within or below normal after treatment with pamidronate. These changes levels, and are consistent with an antiresorptive pharmacologic action.

ying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. ʼuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular ɜtting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and l to the management of hypercalcemia.
ıo have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; ʏpes of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-cemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally olved.
imulated by factors such as parathyroid-hormone-related protein, which are elaborated by the quamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-nal in these patients.
e to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly ltiple myeloma.
may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical ces in albumin levels is often used in place of measurement of ionized calcium; several nomograms

In a third multicenter, randomized, parallel double-blind trial, a group of 69 cancer patients who had with hypercalcemia was enrolled to receive 60 mg of pamidronate disodium as a 4- or 24-hour infusion, which was compared to a saline treatment group. Patients who had a corrected serum calcium level of ≥12.0 mg/dL after 24 hours of saline hydration were eligible for this trial.
The mean baseline-corrected serum calcium levels for pamidronate disodium 60-mg 4-hour infusion, pamidronate disodium 60-mg 24-hour infusion, and saline infusion were 14.2 mg/dL, 13.7 mg/dL, and 13.7 mg/dL, respectively.
By day 7 after initiation of treatment, 78%, 61%, and 22% of the patients had normal-corrected serum calcium levels for the 60-mg 4-hour infusion, 60-mg 24-hour infusion, and saline infusion, respectively. At day 14, 39% of the patients in the pamidronate disodium 60-mg 4-hour infusion group and 26% of the patients in the pamidronate disodium 60-mg 24-hour infusion group had normal-corrected serum calcium levels or maintenance of a partial response.
For responders, the median duration of complete responses was 4 days and 6.5 days for pamidronate disodium 60-mg 4-hour infusion and pamidronate disodium 60-mg 24-hour infusion, respectively.
In all three trials, patients treated with pamidronate had similar response rates in the presence or absence of bone metastases. Concomitant administration of furosemide did not affect response rates.
Thirty-two patients who had recurrent refractory hypercalcemia of malignancy were given a second course of 60 mg of pamidronate disodium over a 4- or 24-hour period. Of these, 41% showed a complete response and 16% showed a partial response to the retreatment, and these responders had about a 3-mg/dL fall in mean-corrected serum calcium levels 7 days after retreatment.
Unlike pamidronate disodium 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90-mg dose infused over a 4-hour period.

Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic disease characterized by chronic, focal areas of bone destruction complicated by concurrent excessive bone repair, affecting one or more bones. These changes result in thickened but weakened bones that may fracture or bend under stress. Signs and symptoms may be bone pain, deformity, fractures, neurological disorders resulting from cranial and spinal nerve entrapment and from spinal cord and brain stem compression, increased cardiac output to the involved bone, increased serum alkaline phosphatase levels (reflecting increased bone formation) and/or urine hydroxyproline excretion (reflecting increased bone resorption).

Clinical Trials

In one double-blind clinical trial, 64 patients with moderate to severe Paget's disease of bone were enrolled to receive 5 mg, 15 mg, or 30 mg of pamidronate disodium as a single 4-hour infusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 mg of pamidronate disodium.
The mean baseline serum alkaline phosphatase levels were 1409 U/L, 983 U/L, and 1085 U/L, and the mean baseline urine hydroxyproline/creatinine ratios were 0.25, 0.19, and 0.19 for the 15-mg, 45-mg, and 90-mg groups, respectively.
The effects of pamidronate on serum alkaline phosphatase (SAP) and urine hydroxy- proline/creatinine ratios (UOHP/C) are summarized in the following table:

Percent of Patients with Significant % Decreases in SAP and UOHP/C

	SAP			UOHP/C		
% Decrease	15 mg	45 mg	90 mg	15 mg	45 mg	90 mg
≥50	26	33	60	15	47	72
≥30	40	65	83	35	57	85

The median maximum percent decreases from baseline in serum alkaline phosphatase and urine hydroxyproline/creatinine ratios were 25%, 41%, and 57%, and 25%, 47% and 61% for the 15-mg, 45-mg, and 90-mg groups, respectively. The median time to response (≥50% decrease) for serum alkaline phosphatase was approximately 1 month for the 90-mg group, and the response duration ranged from 1 to 372 days.
No statistically significant differences between treatment groups, or statistically significant changes from baseline were observed for the bone pain response, mobility, and global evaluation in the 45-mg and 90-mg groups. Improvement in radiologic lesions occurred in some patients in the 90-mg group.
Twenty-five patients who had Paget's disease were retreated with 90 mg of pamidronate disodium. Of these, 44% had a ≥50% decrease in serum alkaline phosphatase from baseline after treatment, and 39% had a ≥50% decrease in urine hydroxyproline/creatinine ratio from baseline after treatment.

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

Osteolytic bone metastases commonly occur in patients with multiple myeloma or breast cancer. These cancers demonstrate a phenomenon known as osteotropism, meaning they possess an extraordinary affinity for bone. The distribution of osteolytic bone metastases in these cancers is predominantly in the axial skeleton, particularly the spine, pelvis and ribs, rather than the appendicular skeleton, although lesions in the proximal femur and humerus are not uncommon. This distribution is similar to the red bone marrow in which slow blood flow possibly assists attachment of metastatic cells. The surface-to-volume ratio of trabecular bone is much higher than cortical bone, and therefore disease processes tend to occur more floridly in trabecular bone than at sites of cortical tissue.
These bone changes can result in patients having evidence of osteolytic skeletal destruction leading to severe bone pain that requires either radiation therapy or narcotic analgesics (or both) for symptomatic relief. These changes also cause pathologic fractures of bone in both the axial and appendicular skeleton. Axial skeletal fractures of the vertebral bodies may lead to spinal cord compression or vertebral body collapse with significant neurologic complications. Also, patients may experience episode(s) of hypercalcemia.

Clinical Trials

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myeloma were enrolled to receive pamidronate or placebo in addition to their underlying antimyeloma therapy to determine the effect of pamidronate 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, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the pamidronate group (24% vs 41%, P<0.001), and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for pamidronate patients than for placebo patients (mean: 1.1 vs 2.1, P<.02). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the pamidronate group (P=.001, .006, and .046, respectively). Moreover, fewer pamidronate patients suffered any pathologic fracture (17% vs 30%, P=.004) or needed radiation to bone (14% vs 22%, P=.049).
In addition, decreases in pain scores from baseline occurred at the last measurement for those pamidronate patients with pain at baseline (P=.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<.001) and ECOG performance status (P<.011) while there was no significant deterioration from baseline in these parameters observed in pamidronate-treated patients.*
After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the pamidronate group than the placebo group (P=.015). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for pamidronate patients vs placebo patients (P=.008), and time to first SRE was significantly longer in the pamidronate group compared to placebo (P=.016). Fewer pamidronate patients suffered vertebral pathologic fractures (16% vs 27%, P=.005). Survival of all patients was not different between treatment groups.
Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of pamidronate disodium infused over 2 hours every 3 to 4 weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had one or more predominantly lytic metastases of a least 1 cm in diameter: one in patients being treated with antineoplastic chemotherapy and the second in patients being treated with hormonal antineoplastic therapy at trial entry.
382 patients receiving chemotherapy were randomized, 185 to pamidronate and 197 to placebo. 372 patients receiving hormonal therapy were randomized, 182 to pamidronate and 190 to placebo. All but three patients were evaluable for efficacy. Patients were followed for 24 months of therapy or until they went off study. Median duration of follow-up was 13 months in patients receiving chemotherapy and 17 months in patients receiving hormone therapy. Twenty five percent of the patients in the chemotherapy study and 37% of the patients in the hormone therapy study received Pamidronate for 24 months. The efficacy results are shown in the table below:

	Breast Cancer Patients Receiving Chemotherapy						Breast Cancer Patients Receiving Hormonal Therapy					
	Any SRE		Radiation		Fractures		Any SRE		Radiation		Fractures	
	PD	P	PD	P	PD	P	PD	P	PD	P	PD	P
N	185	195	185	195	185	195	182	189	182	189	182	189
Skeletal Morbidity Rate (#SRE/Year) Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-value	<.001		<.001*		.018*		.021		.013*		.040*	
Proportion of Patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001*		.014*		.094		.058*		.054*	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3	10.9	7.4	NR**	23.4	20.6	12.8
P-Value	<.001		<.001*		.009*		.118		.016*		.113*	

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

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The complete + partial response rate was 33% in pamidronate patients and 18% in placebo patients treated with chemotherapy (P=.001). No difference was seen between pamidronate and placebo in hormonally-treated patients.

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index were measured at baseline and periodically during the trials. The changes from baseline to the last measurement carried forward are shown in the table below:

Mean Change (Δ) from Baseline at Last Measurement

	Breast Cancer Patients Receiving Chemotherapy					Breast Cancer Patients Receiving Hormonal Therapy				
	Pamidronate		Placebo		PD vs P	Pamidronate		Placebo		PD vs P
	N	MeanΔ	N	MeanΔ	P-value*	N	MeanΔ	N	MeanΔ	P-value*
Pain Score	175	+0.93	183	+1.69	.050	173	+0.50	179	+1.60	.007
Analgesic Score	175	+0.74	183	+1.55	.009	173	+0.90	179	+2.28	<.001
ECOG PS	178	+0.81	186	+1.19	.002	175	+0.95	182	+0.90	.773
Spitzer QOL	177	-1.76	185	-2.21	.103	173	-1.86	181	-2.05	.409

Decreases in pain, analgesic scores and ECOG PS, and increases in Spitzer QOL indicate an improvement from baseline.

*The statistical significance of analyses of these secondary endpoints of pain, quality of life, and performance status in all three trials may be overestimated since numerous analyses were performed.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Pamidronate, in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment with pamidronate. Vigorous saline hydration, an integral part of

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and 90 mg of pamidronate disodium over 24 hours, an overall mean ± SD of 46 ± 16% of the xcretion was linearly related to dose. The mean ±SD elimination half-life is 28 ± 7 hours. Mean 9 mL/min, respectively. The rate of elimination from bone has not been determined.

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prediction line and 95% confidence intervals.

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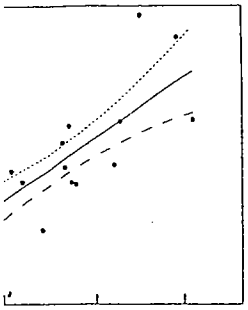

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were enrolled to receive 30 mg, 60 mg, or 90 mg of pamidronate disodium as a single 24-hour er 48 hours of saline hydration.
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n levels by 24 hours after initiation of treatment. Mean-corrected serum calcium levels at days baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with) mg of pamidronate disodium, respectively, had normal-corrected serum calcium levels. Many rmal-corrected serum calcium levels, or a partial response (≥15% decrease of corrected serum

ected serum calcium levels of ≥12.0 mg/dL after at least 24 hours of saline hydration were ntravenous infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous infusion daily ve etidronate disodium.
and etidronate disodium groups were 14.6 mg/dL and 13.8 mg/dL, respectively.
the etidronate disodium group had normal-corrected serum calcium levels (P<0.05). When luded, the response rates were 97% for the pamidronate group and 65% for the etidronate etidronate disodium groups decreased from baseline values to 10.4 and 11.2 mg/dL.
3% of patients in the etidronate disodium group still had normal-corrected serum calcium d etidronate disodium groups, the median duration of response was similar (7 and 5 days, d in the following table

alcium by Time from Initiation of Treatment

Baseline in Corrected Serum um (mg/dL)		
Etidronate Disodium		P-value†
13.8		
-0.5		
-1.1		
-2.0		
-2.0		<0.01
-2.5		<0.01

The median maximum percent decreases from baseline in serum alkaline phosphatase and urine hydroxyproline/creatinine ratios were 25%, 41%, and 57%, and 25%, 47% and 61% for the 15-mg, 45-mg, and 90-mg groups, respectively. The median time to response (≥50% decrease) for serum alkaline phosphatase was approximately 1 month for the 90-mg group, and the response duration ranged from 1 to 372 days.
No statistically significant differences between treatment groups, or statistically significant changes from baseline were observed for the bone pain response, mobility, and global evaluation in the 45-mg and 90-mg groups. Improvement in radiologic lesions occurred in some patients in the 90-mg group.
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In addition, decreases in pain scores from baseline occurred at the last measurement for those pamidronate patients with pain at baseline (P=.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<.001) and ECOG performance status (P<.011) while there was no significant deterioration from baseline in these parameters observed in pamidronate-treated patients.*
After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the pamidronate group than the placebo group (P=.015). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for pamidronate patients vs placebo patients (P=.008), and time to first SRE was significantly longer in the pamidronate group compared to placebo (P=.016). Fewer pamidronate patients suffered vertebral pathologic fractures (16% vs 27%, P=.005). Survival of all patients was not different between treatment groups.
Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of pamidronate disodium infused over 2 hours every 3 to 4 weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had one or more predominantly lytic metastases of a least 1 cm in diameter: one in patients being treated with antineoplastic chemotherapy and the second in patients being treated with hormonal antineoplastic therapy at trial entry.
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	Breast Cancer Patients Receiving Chemotherapy						Breast Cancer Patients Receiving Hormonal Therapy					
	Any SRE		Radiation		Fractures		Any SRE		Radiation		Fractures	
N	PD 185	P 195	PD 185	P 195	PD 185	P 195	PD 182	P 189	PD 182	P 189	PD 182	P 189
Skeletal Morbidity Rate (#SRE/Year) Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-value	<.001		<.001*		.018*		.021		.013*		.040*	
Proportion of Patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001*		.014*		.094		.058*		.054*	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3	10.9	7.4	NR**	23.4	20.6	12.8
P-Value	<.001		<.001*		.009*		.118		.016*		.113*	

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

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The complete + partial response rate was 33% in pamidronate patients and 18% in placebo patients treated with chemotherapy (P=.001). No difference was seen between pamidronate and placebo in hormonally-treated patients.

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index were measured at baseline and periodically during the trials. The changes from baseline to the last measurement carried forward are shown in the table below:

Mean Change (Δ) from Baseline at Last Measurement

	Breast Cancer Patients Receiving Chemotherapy					Breast Cancer Patients Receiving Hormonal Therapy				
	Pamidronate		Placebo		PD vs P	Pamidronate		Placebo		PD vs P
	N	MeanΔ	N	MeanΔ	P-value*	N	MeanΔ	N	MeanΔ	P-value*
Pain Score	175	+0.93	183	+1.69	.050	173	+0.50	179	+1.60	.007
Analgesic Score	175	+0.74	183	+1.55	.009	173	+0.90	179	+2.28	<.001
ECOG PS	178	+0.81	186	+1.19	.002	175	+0.95	182	+0.90	.773
Spitzer QOL	177	-1.76	185	-2.21	.103	173	-1.86	181	-2.05	.409

Decreases in pain, analgesic scores and ECOG PS, and increases in Spitzer QOL indicate an improvement from baseline.

*The statistical significance of analyses of these secondary endpoints of pain, quality of life, and performance status in all three trials may be overestimated since numerous analyses were performed.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Pamidronate, in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment with pamidronate. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e. saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of pamidronate in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

Paget's Disease

Pamidronate is indicated for the treatment of patients with moderate to severe Paget's disease of bone. The effectiveness of pamidronate was demonstrated primarily in patients with serum alkaline phosphatase ≥3 times the upper limit of normal. Pamidronate therapy in patients with Paget's disease has been effective in reducing serum alkaline phosphatase and urinary hydroxyproline levels by ≥50% in at least 50% of patients, and by ≥30% in at least 80% of patients. Pamidronate therapy has also been effective in reducing these biochemical markers in patients with Paget's disease who failed to respond, or no longer responded to other treatments.

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

Pamidronate is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The pamidronate treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated (see CLINICAL PHARMACOLOGY, Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma, Clinical Trials section).

CONTRAINDICATIONS

Pamidronate is contraindicated in patients with clinically significant hypersensitivity to pamidronate or other bisphosphonates.

WARNINGS

In both rats and dogs, nephropathy has been associated with intravenous (bolus and infusion) administration of pamidronate.
Two 7-day intravenous infusion studies were conducted in the dog wherein pamidronate disodium was given for 1, 4, or 24 hours at doses of 1-20 mg/kg for up to 7 days. In the first study, the compound was well tolerated at 3 mg/kg (1.7 x highest recommended human dose [HRHD] for a single intravenous infusion) when administered for 4 or 24 hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occurred when 3 mg/kg was infused for 1 hour and at doses of ≥10 mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 hours. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at ≥1 mg/kg after each infusion time.
Pamidronate disodium was given to rats at doses of 2, 6, and 20 mg/kg and to dogs at doses of 2, 4, 6, and 20 mg/kg as a 1-hour infusion, once a week, for 3 months followed by a 1-month recovery period. In rats, nephrotoxicity was observed at ≥6 mg/kg and included increased BUN and creatinine levels and tubular degeneration and necrosis. These findings were still present at 20 mg/kg at the end of the recovery period. In dogs, moribundity/death and renal toxicity occurred at 20 mg/kg as did kidney findings of elevated BUN and creatinine levels at ≥6 mg/kg and renal tubular degeneration at ≥4 mg/kg. The kidney changes were partially reversible at 6 mg/kg. In both studies, the dose level that produced no adverse renal effects was considered to be 2 mg/kg (1.1 x HRHD for a single intravenous infusion).
Patients who receive an intravenous infusion of pamidronate should have periodic evaluations of standard laboratory and clinical parameters of renal function.
Studies conducted in young rats have reported the disruption of dental dentine formation following single- and multi-dose administration of bisphosphonates. The clinical significance of these findings is unknown.

PRECAUTIONS

General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, and potassium, should be carefully monitored following initiation of therapy with pamidronate. Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5%-12%), were reported in pamidronate-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with pamidronate therapy. If hypocalcemia occurs, short-term calcium therapy may be necessary. In Paget's disease of bone, 17% of patients treated with 90 mg of pamidronate disodium showed serum calcium levels below 8 mg/dL.

Pamidronate has not been tested in patients who have class Dc renal impairment (creatinine >5.0 mg/dL), and in few multiple myeloma patients with serum creatinine ≥3.0 mg/dL. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics.) Clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

Laboratory Tests

Serum calcium, electrolytes, phosphate, magnesium and creatinine, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with pamidronate. Patients who have preexisting anemia, leukopenia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment.

Drug Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study (daily oral administration) in rats, there was a positive dose response relationship for benign adrenal pheochromocytoma in males ($P < 0.00001$). Although this condition was also observed in females, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited oral bioavailability of pamidronate in rats, the lowest daily dose associated with adrenal pheochromocytoma was similar to the intended clinical dose. Adrenal pheochromocytoma was also observed in low numbers in the control animals and is considered a relatively common spontaneous neoplasm in the rat. Pamidronate (daily oral administration) was not carcinogenic in an 80-week study in mice.

Pamidronate was nonmutagenic in six mutagenicity assays: Ames test, Salmonella and Escherichia/liver-microsome test, nucleus-anomaly test, sister-chromatid-exchange study, point-mutation test, and micronucleus test in the rat.

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

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

Bolus intravenous studies conducted in rats and rabbits determined that pamidronate produces maternal toxicity and embryo/fetal effects when given during organogenesis at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion. As it has been shown that pamidronate can cross the placenta in rats and has produced marked maternal and nonteratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

Clinical Studies

Hypercalcemia of Malignancy

Transient mild elevation of temperature by at least 1°C was noted 24 to 48 hours after administration of pamidronate in 34% of patients in clinical trials. In the saline trial, 18% of patients had a temperature elevation of at least 1°C 24 to 48 hours after treatment.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (18%) in patients treated with 90 mg of pamidronate disodium. When all on-therapy events are considered, that rate rises to 41%.

Symptomatic treatment resulted in rapid resolution in all patients.

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

Four of 128 patients (3%) who received pamidronate during the three U.S. controlled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure.

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

General: Fluid overload, generalized pain
Cardiovascular: Hypertension
Gastrointestinal: Abdominal pain, anorexia, constipation, nausea, vomiting
Genitourinary: Urinary tract infection
Musculoskeletal: Bone pain
Laboratory abnormality: Anemia, hypokalemia, hypomagnesemia, hypophosphatemia.

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

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

Treatment-Related Adverse Experiences Reported in Three U.S. Controlled Clinical Trials

	Percent of Patients				
	Pamidronate disodium			Etidronate Disodium	Saline
	60 mg over 4 hr n=23	60 mg over 24 hr n=73	90 mg over 24 hr n=17	7.5 mg/kg x 3 days n=35	n=23
General					
Edema	0	1	0	0	0
Fatigue	0	0	12	0	0
Fever	26	19	18	9	0
Fluid overload	0	0	0	6	0
Infusion-site reaction	0	4	18	0	0
Moniliasis	0	0	6	0	0
Rigors	0	0	0	0	4
Gastrointestinal					
Abdominal pain	0	1	0	0	0
Anorexia	4	1	12	0	0
Constipation	4	0	6	3	0
Diarrhea	0	1	0	0	0
Dyspepsia	4	0	0	0	0
Gastrointestinal hemorrhage	0	0	6	0	0
Nausea	4	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	0	0	0	0
Respiratory					
Dyspnea	0	0	0	3	0
Rales	0	0	6	0	0
Rhinitis	0	0	6	0	0
Upper respiratory infection	0	3	0	0	0
CNS					
Anxiety	0	0	0	0	4
Convulsions	0	0	0	3	0
Insomnia	0	1	0	0	0
Nervousness	0	0	0	0	4
Psychosis	4	0	0	0	0
Somnolence	0	1	6	0	0
Taste perversion	0	0	0	3	0
Cardiovascular					
Atrial fibrillation	0	0	6	0	4
Atrial flutter	0	1	0	0	0
Cardiac failure	0	1	0	0	0
Hypertension	0	0	6	0	4
Syncope	0	0	6	0	0
Tachycardia	0	0	6	0	4
Endocrine					
Hypothyroidism	0	0	6	0	0
Hemic and Lymphatic					
Anemia	0	0	6	0	0
Leukopenia	4	0	0	0	0
Neutropenia	0	1	0	0	0
Thrombocytopenia	0	1	0	0	0
Musculoskeletal					
Myalgia	0	1	0	0	0
Urogenital					
Uremia	4	0	0	0	0
Laboratory Abnormalities					
Hypocalcemia	0	1	12	0	0
Hypokalemia	4	4	18	0	0
Hypomagnesemia	4	10	12	3	4
Hypophosphatemia	0	9	18	3	0
Abnormal liver function	0	0	0	3	0

Paget's Disease

Transient mild elevation of temperature >1°C above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of pamidronate disodium in clinical trials.

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

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

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

Musculoskeletal System			
Arthralgias	10.7	7.0	15.3
Myalgia	25.4	15.0	26.4
Skeletal Pain	61.0	71.7	70.0
CNS			
Anxiety	7.8	9.1	18.0
Headache	24.4	19.8	27.2
Insomnia	17.1	17.2	25.1
Respiratory System			
Coughing	26.3	22.5	25.3
Dyspnea	22.0	21.4	35.1
Pleural Effusion	2.9	4.3	15.0
Sinusitis	14.6	16.6	16.1
Upper Resp Tract Infection	32.2	28.3	19.6
Urogenital System			
Urinary tract Infection	15.6	9.1	20.2

Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia stomatitis and alopecia occurred at a frequency similar to that in placebo patients. In the breas pamidronate patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, incl pamidronate-treated patients compared with those in the placebo group. The reported frequenc pamidronate-treated patients were 3.3%, 10.5%, 1.7%, and 4.4%, respectively, and for placebi hypercalcemia of malignancy trials, patients treated with pamidronate disodium (60 or 90 mg REACTIONS, Hypercalcemia of Malignancy).

Arthralgias and myalgias were reported slightly more frequently in the pamidronate group than In multiple myeloma patients, there were five pamidronate-related serious and unexpected adv the multiple myeloma trial. Three of the reports were of worsening renal function developing ir amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a pat pamidronate-treated patient experienced an allergic reaction characterized by swollen and itch In the breast cancer trials, there were four pamidronate-related adverse experiences, all mode due to interstitial pneumonitis, another to malaise and dyspnea. One pamidronate patient disc discontinued therapy due to severe bone pain after each infusion, which the investigator felt w

Post-Marketing Experience

Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, contraindicated in patients with clinically significant hypersensitivity to pamidronate or other t

OVERDOSAGE

There have been several cases of drug maladministration of intravenous pamidronate in hyper 4 days. All of these patients survived, but they experienced hypocalcemia that required intrave In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium to 90/60 mmHg), and transient taste perversion, noted about 6 hours after the first infusion. T If overdosage occurs, symptomatic hypocalcemia could also result; such patients should be t

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. V hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac fai glucocorticoid therapy may be helpful.

Moderate Hypercalcemia

The recommended dose of pamidronate disodium in moderate hypercalcemia (corrected s 60-mg dose is given as an initial, SINGLE-DOSE, intravenous infusion over at least 4 hour infusion over 24 hours.

Severe Hypercalcemia

The recommended dose of pamidronate disodium in severe hypercalcemia (corrected seri SINGLE-DOSE, intravenous infusion over 24 hours.

*Albumin-corrected serum calcium (CCa, mg/dL) = serum calcium, mg/dL + 0.8 (4.0-serum a

Retreatment

A limited number of patients have received more than one treatment with pamidronate for hy partial response initially, may be carried out if serum calcium does not return to normal or re **elapse before retreatment, to allow for full response to the initial dose.** The dose and mar

Paget's Disease

The recommended dose of pamidronate disodium in patients with moderate to severe Pag consecutive days for a total dose of 90 mg.

Retreatment

A limited number of patients with Paget's disease have received more than one treatment of at the dose of initial therapy.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of pamidronate disodium in patients with osteolytic bone lesions monthly basis.

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hyd Limited information is available on the use of pamidronate in multiple myeloma patients with The optimal duration of therapy is not yet known, however, in a study of patients with myelc TRIALS section).

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of pamidronate disodium in patients with osteolytic bone metas Pamidronate has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, m vincristine, megesterol, and tamoxifen. It has been given less frequently with etoposide, cis not known, however, in two breast cancer studies, final analyses performed after 24 month

Preparation of Infusion

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 4 hours for th be diluted in 1000 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Inje

Paget's Disease

The recommended daily dose of 30 mg should be diluted in 500 mL of sterile 0.45% or 0.9 hour period for 3 consecutive days.

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of 90 mg should be diluted in 250 mL of sterile 0.45% or 0.9% So period every 3-4 weeks.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% or 0.9% So period on a monthly basis.

Pamidronate must not be mixed with calcium-containing infusion solutions, such as Rir separate from all other drugs.

***Note:* Parenteral drug products should be inspected visually for particulate matter and d**

HOW SUPPLIED

Vials -3 mg/mL, 10 mL vial - each contains 30 mg of pamidronate disodium and 470 mg of Carton of 1 vial

Vials -6 mg/mL, 10 mL vial - each contains 60 mg of pamidronate disodium and 400 mg o Carton of 1 vial

Vials -9 mg/mL, 10 mL vial - each contains 90 mg of pamidronate disodium and 375 mg o Carton of 1 vial

Store below 25°C (77°F) Controlled Room Temperature.

Manufactured by:
F H Faulding & Co Limited
1-23 Lexia Place Mulgrave
Victoria 3170 Australia
for:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA

Revised: September 2001

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

ADVERSE REACTIONS

Clinical Studies

Hypercalcemia of Malignancy

Transient mild elevation of temperature by at least 1°C was noted 24 to 48 hours after administration of pamidronate in 34% of patients in clinical trials. In the saline trial, 18% of patients had a temperature elevation of at least 1°C 24 to 48 hours after treatment.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (18%) in patients treated with 90 mg of pamidronate disodium. When all on-therapy events are considered, that rate rises to 41%.

Symptomatic treatment resulted in rapid resolution in all patients.

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

Four of 128 patients (3%) who received pamidronate during the three U.S. controlled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure.

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

General: Fluid overload, generalized pain
Cardiovascular: Hypertension
Gastrointestinal: Abdominal pain, anorexia, constipation, nausea, vomiting
Genitourinary: Urinary tract infection
Musculoskeletal: Bone pain
Laboratory abnormality: Anemia, hypokalemia, hypomagnesemia, hypophosphatemia.

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

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

Treatment-Related Adverse Experiences Reported in Three U.S. Controlled Clinical Trials

	Percent of Patients				
	Pamidronate disodium			Etidronate Disodium	Saline
	60 mg over 4 hr	60 mg over 24 hr	90 mg over 24 hr	7.5 mg/kg x 3 days	
	n=23	n=73	n=17	n=35	n=23
General					
Edema	0	1	0	0	0
Fatigue	0	0	12	0	0
Fever	26	19	18	9	0
Fluid overload	0	0	0	6	0
Infusion-site reaction	0	4	18	0	0
Moniliasis	0	0	6	0	0
Rigors	0	0	0	0	4
Gastrointestinal					
Abdominal pain	0	1	0	0	0
Anorexia	4	1	12	0	0
Constipation	4	0	6	3	0
Diarrhea	0	1	0	0	0
Dyspepsia	4	0	0	0	0
Gastrointestinal hemorrhage	0	0	6	0	0
Nausea	4	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	0	0	0	0
Respiratory					
Dyspnea	0	0	0	3	0
Rales	0	0	6	0	0
Rhinitis	0	0	6	0	0
Upper respiratory infection	0	3	0	0	0
CNS					
Anxiety	0	0	0	0	4
Convulsions	0	0	0	3	0
Insomnia	0	1	0	0	0
Nervousness	0	0	0	0	4
Psychosis	4	0	0	0	0
Somnolence	0	1	6	0	0
Taste perversion	0	0	0	3	0
Cardiovascular					
Atrial fibrillation	0	0	6	0	4
Atrial flutter	0	1	0	0	0
Cardiac failure	0	1	0	0	0
Hypertension	0	0	6	0	4
Syncope	0	0	6	0	0
Tachycardia	0	0	6	0	4
Endocrine					
Hypothyroidism	0	0	6	0	0
Hemic and Lymphatic					
Anemia	0	0	6	0	0
Leukopenia	4	0	0	0	0
Neutropenia	0	1	0	0	0
Thrombocytopenia	0	1	0	0	0
Musculoskeletal					
Myalgia	0	1	0	0	0
Urogenital					
Uremia	4	0	0	0	0
Laboratory Abnormalities					
Hypocalcemia	0	1	12	0	0
Hypokalemia	4	4	18	0	0
Hypomagnesemia	4	10	12	3	4
Hypophosphatemia	0	9	18	3	0
Abnormal liver function	0	0	0	3	0

Paget's Disease

Transient mild elevation of temperature >1°C above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of pamidronate disodium in clinical trials.

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

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

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

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

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

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

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

Commonly Reported Adverse Experiences in Three U.S. Controlled Clinical Trials

	Pamidronate Disodium 90 mg over 4 hours N=205	Placebo N=187	Pamidronate Disodium 90 mg over 2 hours N=367	Placebo N=386	All Pamidronate Disodium 90 mg N=572	Placebo N=573
General	%	%	%	%	%	%
Asthenia	16.1	17.1	25.6	19.2	22.2	18.5
Fatigue	31.7	28.3	40.3	28.8	37.2	29.0
Fever	38.5	38.0	38.1	32.1	38.5	34.0
Metastases	1.0	3.0	31.3	24.4	20.5	17.5
Pain	13.2	11.8	15.0	18.1	14.3	16.1
Digestive System						
Anorexia	17.1	17.1	31.1	24.9	26.0	22.3
Constipation	28.3	31.7	36.0	38.6	33.2	35.1
Diarrhea	26.8	26.8	29.4	30.6	28.5	29.7
Dyspepsia	17.6	13.4	18.3	15.0	22.6	17.5
Nausea	35.6	37.4	63.5	59.1	53.5	51.8
Pain Abdominal	19.5	16.0	24.3	18.1	22.6	17.5
Vomiting	16.6	19.8	46.3	39.1	35.7	32.8
Hemic and Lymphatic						
Anemia	47.8	41.7	39.5	36.8	42.5	38.4
Granulocytopenia	20.5	15.5	19.3	20.5	19.8	18.8
Thrombocytopenia	16.6	17.1	12.5	14.0	14.0	15.0

Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or an
contraindicated in patients with clinically significant hypersensitivity to pamidronate or other bispho

OVERDOSAGE

There have been several cases of drug maladministration of intravenous pamidronate in hypercalce
4 days. All of these patients survived, but they experienced hypocalcemia that required intravenous
In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium/day f
to 90/60 mmHg), and transient taste perversion, noted about 6 hours after the first infusion. The fe
If overdosage occurs, symptomatic hypocalcemia could also result; such patients should be treated

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. Vigorou
hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. I
glucocorticoid therapy may be helpful.

Moderate Hypercalcemia

**The recommended dose of pamidronate disodium in moderate hypercalcemia (corrected serum c
60-mg dose is given as an initial, SINGLE-DOSE, intravenous infusion over at least 4 hours. The
infusion over 24 hours.**

Severe Hypercalcemia

**The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum cal
SINGLE-DOSE, intravenous infusion over 24 hours.**

*Albumin-corrected serum calcium (CCa, mg/dL) = serum calcium, mg/dL + 0.8 (4.0-serum albumi

Retreatment

A limited number of patients have received more than one treatment with pamidronate for hypercalc
partial response initially, may be carried out if serum calcium does not return to normal or remain r
elapse before retreatment, to allow for full response to the initial dose. The dose and manner of

Paget's Disease

**The recommended dose of pamidronate disodium in patients with moderate to severe Paget's di
consecutive days for a total dose of 90 mg.**

Retreatment

A limited number of patients with Paget's disease have received more than one treatment of pamidr
at the dose of initial therapy.

Osteolytic Bone Lesions of Multiple Myeloma

**The recommended dose of pamidronate disodium in patients with osteolytic bone lesions of mul
monthly basis.**

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration p
Limited information is available on the use of pamidronate in multiple myeloma patients with a seru
The optimal duration of therapy is not yet known, however, in a study of patients with myeloma, fin
TRIALS section).

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of pamidronate disodium in patients with osteolytic bone metastases is
Pamidronate has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotre
vincristine, megesterol, and tamoxifen. It has been given less frequently with etoposide, cisplatin, c
not known, however, in two breast cancer studies, final analyses performed after 24 months of ther

Preparation of Infusion

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 4 hours for the 60-mg
be diluted in 1000 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, U

Paget's Disease

The recommended daily dose of 30 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodiu
hour period for 3 consecutive days.

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of 90 mg should be diluted in 250 mL of sterile 0.45% or 0.9% Sodium Ch
period every 3-4 weeks.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Ch
period on a monthly basis.

**Pamidronate must not be mixed with calcium-containing infusion solutions, such as Ringer's so
separate from all other drugs.**
***Note:* Parenteral drug products should be inspected visually for particulate matter and discolora**

HOW SUPPLIED

Vials -3 mg/mL, 10 mL vial - each contains 30 mg of pamidronate disodium and 470 mg of mannitc
Carton of 1 vial
Vials –6 mg/mL, 10 mL vial - each contains 60 mg of pamidronate disodium and 400 mg of mannit
Carton of 1 vial
Vials –9 mg/mL, 10 mL vial - each contains 90 mg of pamidronate disodium and 375 mg of mannit
Carton of 1 vial

Store below 25°C (77°F) Controlled Room Temperature.

Manufactured by:
F H Faulding & Co Limited
1-23 Lexia Place Mulgrave
Victoria 3170 Australia
for:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA

Revised: September 2001

calcium, phosphate, magnesium, and potassium, should be carefully monitored following
nia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5%-12%), were
emia (including tetany) have been reported in association with pamidronate therapy. If
s disease of bone, 17% of patients treated with 90 mg of pamidronate disodium showed serum

creatinine >5.0 mg/dL), and in few multiple myeloma patients with serum creatinine
lgment should determine whether the potential benefit outweighs the potential risk in such patients.

differential, and hematocrit/hemoglobin must be closely monitored in patients treated with
topenia should be monitored carefully in the first 2 weeks following treatment.

ering action of pamidronate.

is a positive dose response relationship for benign adrenal pheochromocytoma in males
nce was not statistically significant. When the dose calculations were adjusted to account for the
ted with adrenal pheochromocytoma was similar to the intended clinical dose. Adrenal
ind is considered a relatively common spontaneous neoplasm in the rat. Pamidronate (daily oral

ella and Escherichia/liver-microsome test, nucleus-anomaly test, sister-chromatid-exchange

had received 150 mg/kg of pamidronate disodium orally; however, this occurred only when
ot been administered intravenously in such a study.

ronate produces maternal toxicity and embryo/fetal effects when given during organogenesis at
travenous infusion. As it has been shown that pamidronate can cross the placenta in rats and has
rabbits, it should not be given to women during pregnancy.

drugs are excreted in human milk, caution should be exercised when pamidronate is administered

ablished.

's after administration of pamidronate in 34% of patients in clinical trials. In the saline trial, 18%
tment.
ain on palpation) at the site of catheter insertion were most common (18%) in patients treated
ed, that rate rises to 41%.

ing one case of scleritis, and one case of uveitis upon separate rechallenges.
rolled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had
related by the investigators. However, a possible relationship between the drug and the
arm 1 patient (4%) had a seizure.
ncy also experienced the following adverse events during a clinical trial:

romiting

hypophosphatemia.
ease state.
lated during comparative, controlled U.S. trials.

nces Reported in Three U.S. Controlled Clinical Trials

Percent of Patients

Pamidronate disodium			Etidronate Disodium	Saline
60 mg	60 mg	90 mg	7.5 mg/kg	
ver 4 hr	over 24 hr	over 24 hr	x 3 days	
n=23	n=73	n=17	n=35	n=23
0	1	0	0	0
0	0	12	0	0
26	19	18	9	0
0	0	0	6	0
0	4	18	0	0
0	0	6	0	0
0	0	0	0	4
0	1	0	0	0
4	1	12	0	0
4	0	6	3	0
0	1	0	0	0
4	0	0	0	0
0	0	6	0	0
4	0	18	6	0
0	1	0	3	0
4	0	0	0	0
0	0	0	3	0
0	0	6	0	0
0	0	6	0	0
0	3	0	0	0
0	0	0	0	4
0	0	0	3	0
0	1	0	0	0
0	0	0	0	4
4	0	0	0	0
0	1	6	0	0
0	0	0	3	0
0	0	6	0	4
0	1	0	0	0
0	1	0	0	0
0	0	6	0	4
0	0	6	0	0
0	0	6	0	4
0	0	6	0	0
4	0	0	0	0
0	1	12	0	0
4	4	18	0	0
4	10	12	3	4
0	9	18	3	0
0	0	0	3	0

noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of

eadache, paresthesia, increased sweating) were more common in patients with Paget's disease
a of malignancy treated with the same dose.
least 5% of patients with Paget's disease treated with 90 mg of pamidronate disodium in two

ienced the following adverse experiences during clinical trials:

Musculoskeletal System					
Arthralgias	10.7	7.0	15.3	12.7	13.6	10.8
Myalgia	25.4	15.0	26.4	22.5	26.0	20.1
Skeletal Pain	61.0	71.7	70.0	75.4	66.8	74.0
CNS						
Anxiety	7.8	9.1	18.0	16.8	14.3	14.3
Headache	24.4	19.8	27.2	23.6	26.2	22.3
Insomnia	17.1	17.2	25.1	19.4	22.2	19.0
Respiratory System						
Coughing	26.3	22.5	25.3	19.7	25.7	20.6
Dyspnea	22.0	21.4	35.1	24.4	30.4	23.4
Pleural Effusion	2.9	4.3	15.0	9.1	10.7	7.5
Sinusitis	14.6	16.6	16.1	10.4	15.6	12.0
Upper Resp. Tract Infection	32.2	28.3	19.6	20.2	24.1	22.9
Urogenital System						
Urinary tract infection	15.6	9.1	20.2	17.6	18.5	15.6

Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia, and anemia were slightly more common in the pamidronate patients whereas stomatitis and alopecia occurred at a frequency similar to that in placebo patients. In the breast cancer trials, mild elevations of serum creatinine occurred in 18.5% of pamidronate patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of pamidronate-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for pamidronate-treated patients were 3.3%, 10.5%, 1.7%, and 4.4%, respectively, and for placebo-treated patients were 1.2%, 12%, 1.7%, and 4.5%, respectively. In previous hypercalcemia of malignancy trials, patients treated with pamidronate disodium (60 or 90 mg over 24 hours) developed electrolyte abnormalities more frequently (see ADVERSE REACTIONS, Hypercalcemia of Malignancy).
Arthralgias and myalgias were reported slightly more frequently in the pamidronate group than in the placebo group (13.6% and 26% vs 10.8% and 20.1%, respectively).
In multiple myeloma patients, there were five pamidronate-related serious and unexpected adverse experiences. Four of these were reported during the 12-month extension of the multiple myeloma trial. Three of the reports were of worsening renal function developing in patients with progressive multiple myeloma or multiple myeloma-associated amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a patient recovering from pneumonia and acute gangrenous cholecystitis. One pamidronate-treated patient experienced an allergic reaction characterized by swollen and itchy eyes, runny nose, and scratchy throat within 24 hours after the sixth infusion.
In the breast cancer trials, there were four pamidronate-related adverse experiences, all moderate severity, that caused a patient to discontinue participation in the trial. One was due to interstitial pneumonitis, another to malaise and dyspnea. One pamidronate patient discontinued the trial due to a symptomatic hypocalcemia. Another pamidronate patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

Post-Marketing Experience

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

OVERDOSAGE

There have been several cases of drug maladministration of intravenous pamidronate in hypercalcemia patients with total doses of 225 mg to 300 mg given over 2½ to 4 days. All of these patients survived, but they experienced hypocalcemia that required intravenous and/or oral administration of calcium.
In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium/day for 3 days experienced high fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), and transient taste perversion, noted about 6 hours after the first infusion. The fever and hypotension were rapidly corrected with steroids.
If overdosage occurs, symptomatic hypocalcemia could also result; such patients should be treated with short-term intravenous calcium.

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. Vigorous saline hydration alone may be sufficient for treating mild, asymptomatic hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. In hypercalcemia associated with hematologic malignancies, the use of glucocorticoid therapy may be helpful.

Moderate Hypercalcemia

The recommended dose of pamidronate disodium in moderate hypercalcemia (corrected serum calcium* of approximately 12-13.5 mg/dL) is 60 to 90 mg. The 60-mg dose is given as an initial, SINGLE-DOSE, intravenous infusion over at least 4 hours. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

Severe Hypercalcemia

The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum calcium* >13.5 mg/dL) is 90 mg. The 90-mg dose must be given by an initial SINGLE-DOSE, intravenous infusion over 24 hours.
*Albumin-corrected serum calcium (CCa, mg/dL) = serum calcium, mg/dL + 0.8 (4.0-serum albumin, g/dL).

Retreatment

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

Paget's Disease

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

Retreatment

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

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of pamidronate disodium in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4-hour infusion given on a monthly basis.
Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to pamidronate infusion.
Limited information is available on the use of pamidronate in multiple myeloma patients with a serum creatinine ≥3.0 mg/dL.
The optimal duration of therapy is not yet known, however, in a study of patients with myeloma, final analysis after 21 months demonstrated overall benefit (see CLINICAL TRIALS section).

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of pamidronate disodium in patients with osteolytic bone metastases is 90 mg administered over a 2-hour infusion given every 3-4 weeks.
Pamidronate has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotrexate, mitoxantrone, vinblastine, dexamethasone, prednisone, melphalan, vincristine, megesterol, and tamoxifen. It has been given less frequently with etoposide, cisplatin, cytarabine, paclitaxel, and aminoglutethimide. The optimal duration of therapy is not known, however, in two breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefit (see CLINICAL TRIALS section).

Preparation of Infusion

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 4 hours for the 60-mg dose, and over 24 hours for the 90-mg dose. The recommended dose should be diluted in 1000 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. This infusion solution is stable for up to 24 hours at room temperature.

Paget's Disease

The recommended daily dose of 30 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, and administered over a 4-hour period for 3 consecutive days.

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of 90 mg should be diluted in 250 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP and administered over a 2-hour period every 3-4 weeks.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP and administered over a 4-hour period on a monthly basis.

Pamidronate must not be mixed with calcium-containing infusion solutions, such as Ringer's solution, and should be given in a single intravenous solution and line separate from all other drugs.
Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

HOW SUPPLIED

Vials -3 mg/mL, 10 mL vial - each contains 30 mg of pamidronate disodium and 470 mg of mannitol, USP in 10 mL water for injection, USP.
Carton of 1 vial
Vials –6 mg/mL, 10 mL vial - each contains 60 mg of pamidronate disodium and 400 mg of mannitol, USP in 10 mL water for injection, USP.
Carton of 1 vial
Vials –9 mg/mL, 10 mL vial - each contains 90 mg of pamidronate disodium and 375 mg of mannitol, USP in 10 mL water for injection, USP.
Carton of 1 vial

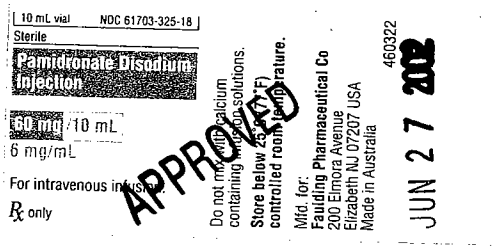
Store below 25°C (77°F) Controlled Room Temperature.

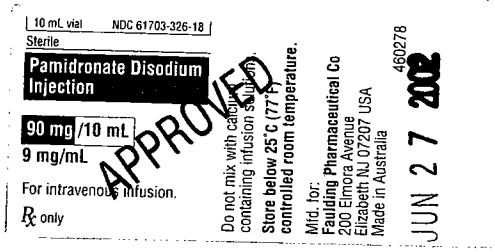
Manufactured by:
F H Faulding & Co Limited
1-23 Lexia Place Mulgrave
Victoria 3170 Australia
for:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA

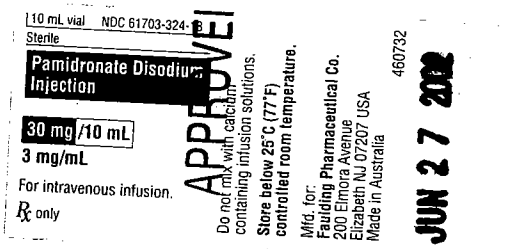
Revised: September 2001

75-841

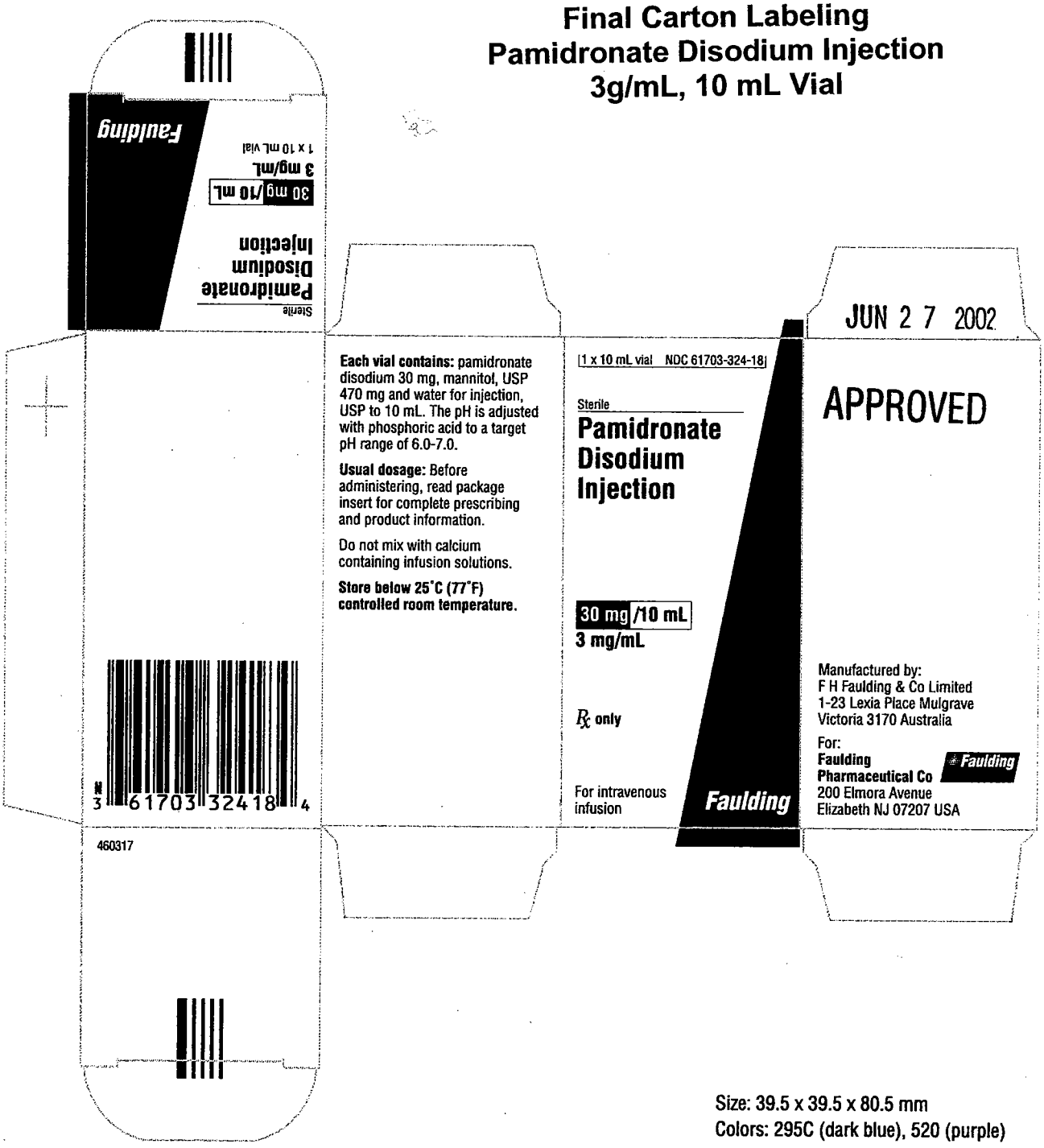
6/27/02


10 mL vial NDC 61703-325-18
Sterile
Pamidronate Disodium Injection
60 mg/10 mL
6 mg/mL
For intravenous infusion.
℞ only
APPROVED
Do not mix with calcium containing infusion solutions.
Store below 25°C (77°F) controlled room temperature.
Mfd. for:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA
Made in Australia
460322
JUN 27 2002


10 mL vial NDC 61703-326-18
Sterile
Pamidronate Disodium Injection
90 mg/10 mL
9 mg/mL
For intravenous infusion.
℞ only
APPROVED
Do not mix with calcium containing infusion solutions.
Store below 25°C (77°F) controlled room temperature.
Mfd. for:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA
Made in Australia
460278
JUN 27 2002

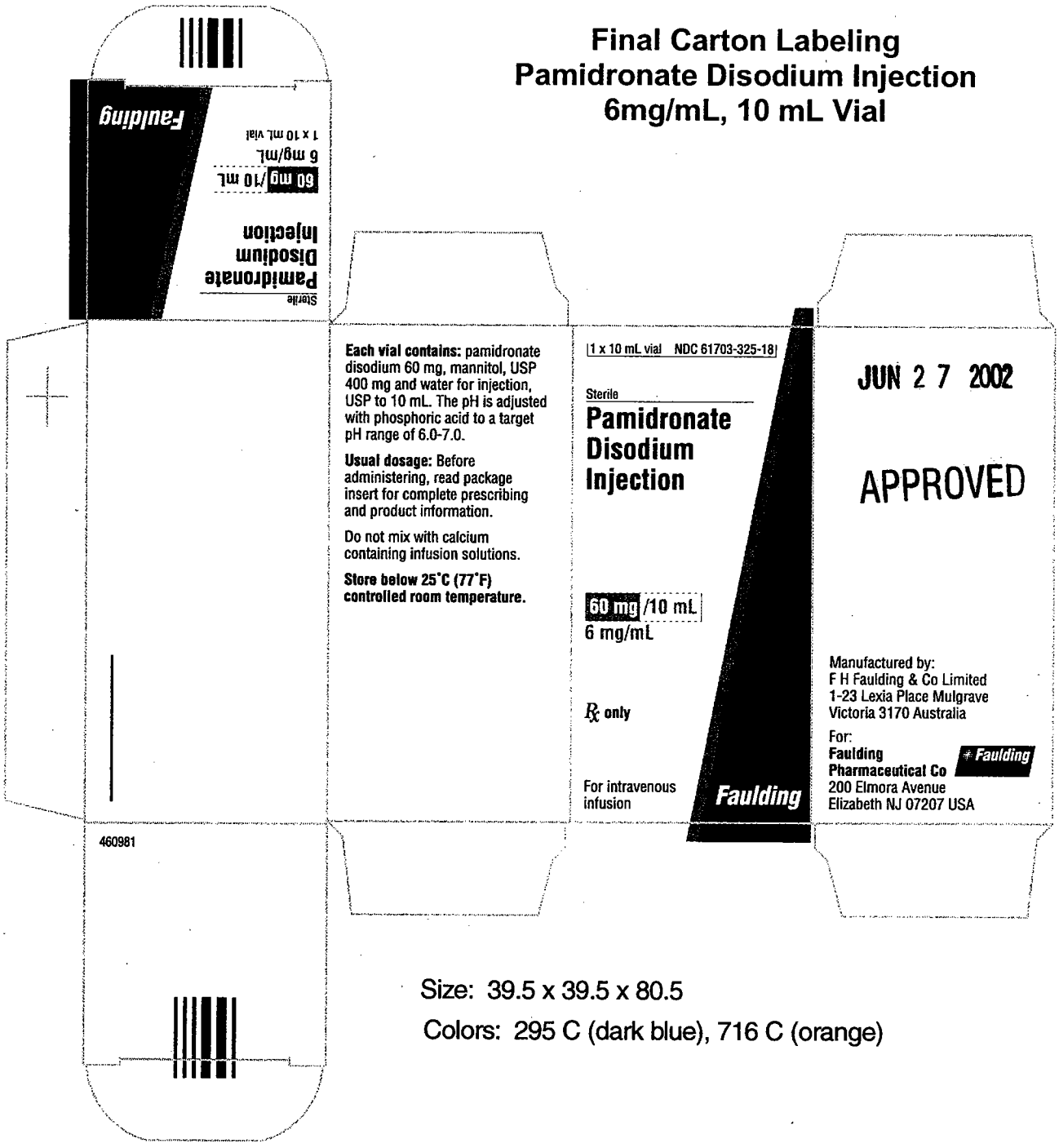

10 mL vial NDC 61703-324-18
Sterile
Pamidronate Disodium Injection
30 mg/10 mL
3 mg/mL
For intravenous infusion.
℞ only
APPROVED
Do not mix with calcium containing infusion solutions.
Store below 25°C (77°F) controlled room temperature.
Mfd. for:
Faulding Pharmaceutical Co.
200 Elmora Avenue
Elizabeth NJ 07207 USA
Made in Australia
460732
JUN 27 2002

Final Carton Labeling
Pamidronate Disodium Injection
3g/mL, 10 mL Vial



Size: 39.5 x 39.5 x 80.5 mm
Colors: 295C (dark blue), 520 (purple)

Final Carton Labeling
Pamidronate Disodium Injection
6mg/mL, 10 mL Vial



Size: 39.5 x 39.5 x 80.5

Colors: 295 C (dark blue), 716 C (orange)

75-841

AP 6/27/02

JUN 27 2002

APPROVED

Sterile
Pamidronate Disodium Injection
90 mg/10 mL
9 mg/mL
1 x 10 mL vial

Faulding

Each vial contains: pamidronate disodium 90 mg, mannitol, USP 375 mg and water for injection, USP to 10 mL. The pH is adjusted with phosphoric acid to a target pH range of 6.0-7.0.

Usual dosage: Before administering, read package insert for complete prescribing and product information.

Do not mix with calcium containing infusion solutions.

Store below 25°C (77°F) controlled room temperature.

[1 x 10 mL vial NDC 61703-326-18]

Sterile

Pamidronate Disodium Injection

90 mg/10 mL
9 mg/mL

℞ only

For intravenous infusion

Faulding

Manufactured by:
F H Faulding & Co Limited
1-23 Lexia Place Mulgrave
Victoria 3170 Australia

For:
Faulding Pharmaceutical Co
200 Elmora Avenue
Elizabeth NJ 07207 USA

N 3 61703 32618 8

460395

Size: 39.5 x 39.5 x 80.5 mm
Colors: 295C (dark blue), 225 (bright pink)