PRODUCT MONOGRAPH

[Pr]VAL-PAMIDRONATE DISODIUM

(Pamidronate Disodium for Injection)

9 mg/mL
For I.V. infusion only

Bone Metabolism Regulator

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Date of Preparation:
March 20, 2012

Submission Control No: 154009

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(Pamidronate Disodium for Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous	Solution / 9 mg/mL	Mannitol, water for injection, sodium hydroxide and phosphoric acid. Sodium hydroxide and phosphoric acid may have been added for pH adjustment. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

- **Tumor-induced hypercalcemia following adequate saline rehydration.**

  Prior to treatment with pamidronate disodium, renal excretion of excess calcium should be promoted by restoring and maintaining adequate fluid balance and urine output.
- **Conditions associated with increased osteoclast activity: predominantly lytic bone metastases and multiple myeloma.**
- **Symptomatic Paget's disease of bone.**

CONTRAINDICATIONS

Known or suspected hypersensitivity to pamidronate disodium, to any of its components (see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section), or to other bisphosphonates.

WARNINGS AND PRECAUTIONS

PAMIDRONATE DISODIUM MUST NEVER BE GIVEN AS A BOLUS INJECTION SINCE SEVERE LOCAL REACTIONS AND THROMBOPHLEBITIS MAY RESULT FROM HIGH LOCAL CONCENTRATIONS.

PAMIDRONATE DISODIUM SHOULD ALWAYS BE DILUTED AND ADMINISTERED AS A SLOW INTRAVENOUS INFUSION (see **DOSAGE AND ADMINISTRATION). REGARDLESS OF THE VOLUME OF SOLUTION IN WHICH PAMIDRONATE DISODIUM IS DILUTED, SLOW INTRAVENOUS INFUSION IS ABSOLUTELY NECESSARY FOR SAFETY.**

Bisphosphonates, including pamidronate disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of pamidronate disodium should not exceed 90 mg, and the recommended infusion time should be observed (see **DOSAGE AND ADMINISTRATION**).

As with other I.V. bisphosphonates renal monitoring is recommended for instance, measurement of serum creatinine prior to each dose of pamidronate disodium. Patients treated with pamidronate disodium for bone metastases should have the dose withheld if renal function has deteriorated (see **DOSAGE AND ADMINISTRATION**).

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

Pamidronate disodium should not be mixed with calcium-containing intravenous infusions.

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

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

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

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

recommendations can be given for this patient's population.

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

Osteonecrosis of the jaw

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

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

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

Patient Monitoring

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

Pamidronate disodium is excreted intact primarily via the kidney, thus the risk of renal adverse reactions may be greater in patients with impaired renal function.

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy with pamidronate disodium. Patients with anemia, leukopenia or thrombocytopenia should have regular hematology assessments. Occasional cases of mild, transient hypocalcemia, usually asymptomatic, have been reported. Symptomatic hypocalcemia occurs rarely and can be reversed with calcium gluconate. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcemia due to relative hypoparathyroidism.

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

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

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

Use in Pregnancy

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

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

Lactation

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

Pediatric Use

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

Effects on ability to drive or use machines

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

ADVERSE REACTIONS

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

Adverse experiences by body system:

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

Body as a whole

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

Local reactions

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

Musculoskeletal system

Common: transient bone pain, arthralgia, myalgia, generalized pain.

Uncommon: muscle cramps.

Gastrointestinal tract

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

Uncommon: dyspepsia.

Central nervous system

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

Uncommon: seizures, agitation, dizziness, lethargy.

Very rare: confusion, visual hallucinations.

Blood

Common: anemia, thrombocytopenia, lymphocytopenia.

Very rare: leukopenia.

One case of acute lymphoblastic leukemia has been reported in a patient with Paget's disease. The causal relationship to the treatment or the underlying disease is unknown.

Cardiovascular system

Common: hypertension.

Uncommon: hypotension

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

Respiratory system

Rare: adult respiratory distress syndrome, interstitial pneumonitis.

Renal system

Uncommon: acute renal failure.

Rare: focal segmental glomerulosclerosis including collapsing variant, nephrotic syndrome.

Very rare: hematuria, deterioration of pre-existing renal disease.

Skin

Common: rash.

Uncommon: pruritus.

Special senses

Common: conjunctivitis.

Uncommon: uveitis (iritis, iridocyclitis).

Very rare: scleritis, episcleritis, xanthopsia.

Infection

Very rare: reactivation of Herpes simplex and Herpes zoster.

Immune System

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

Very rare: anaphylactic shock.

Biochemical changes

Very common: hypocalcemia, hypophosphatemia.

Common: hypokalemia, hypomagnesemia, increase in serum creatinine.

Uncommon: abnormal liver function tests, increase in serum urea.

Very rare: hyperkalemia, hypernatremia.

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

Tumor-induced hypercalcemia and Paget's disease

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

Adverse experiences	**Tumor-induced hypercalcemia**	**Paget's Disease**
no. of patients	**n=910**	**n=395**
	(%)	(%)
Fever	6.9	8.9
Headache	0.0	4.8
Hypocalcemia	3.2	0.8
Influenza-like	0.0	11.9
Infusion site reaction	1.7	1.8
Malaise	0.0	5.8
Myalgia	0.0	2.0
Nausea	0.9	2.0
Pain (bone)	0.0	8.9
Pain (unspecified)	0.0	7.9
Rigors	0.0	2.8

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

Bone Metastases and Multiple Myeloma

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

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

Commonly reported Adverse Experiences in Three Controlled Trials
(regardless of causality)
Bone metastases and multiple myeloma patients

Adverse Event	**Pamidronate disodium 90 mg**	**Placebo**
no. of patients	**n=572**	**n=573**
	(%)	(%)
General		
Asthenia	16.4	15.4
Fatigue	30.4	35.5
Fever	35.5	30.5
Metastases	14.0	13.6
Digestive System		
Anorexia	20.8	18.0
Constipation	27.6	30.9
Diarrhea	24.3	26.2
Dyspepsia	13.6	12.4
Nausea	48.4	46.4
Pain Abdominal	17.3	14.0
Vomiting	30.9	28.1
Hemic and Lymphatic System		
Anemia	35.1	32.6
Granulocytopenia	16.8	17.3
Thrombocytopenia	11.0	13.1
Musculoskeletal System		
Myalgias	22.6	16.9
Skeletal Pain	59.4	69.1
CNS		
Headache	24.0	19.7
Insomnia	18.2	17.3
Respiratory System		
Coughing	21.2	18.8
Dyspnea	23.3	18.7

Upper Respiratory Infection	19.8	20.9
Urogenital System		
Urinary Tract Infection	14.5	10.8

Post-Market Adverse Drug Reactions

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

DRUG INTERACTIONS

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

Dilution of solution for I.V. Infusion

Pamidronate disodium for injection must be diluted prior to use with either 5% Dextrose Injection USP or 0.9% sodium Chloride Injection USP to concentrations of 0.06 - 0.36 mg/mL in PVC infusion bags. The admixture solutions are stable for 24 hours at 2 - 8°C, protected from light, followed by 24 hours at room temperature exposed to light, for a total of 48 hours. Discard the unused portion.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration, and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Incompatibilities

Pamidronate forms complexes with divalent cations. For this reason, Pamidronate disodium must not be mixed with calcium-containing intravenous solutions, such as Ringer's solution.

Renal Impairment

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

As with other bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of pamidronate disodium. In patients receiving pamidronate disodium for bone metastases who show evidence of deterioration in renal function, pamidronate disodium treatment should be withheld until renal function returns to within 10% of the baseline value. This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

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

For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.

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

Hepatic Impairment

A pharmacokinetic study indicates that no dose adjustment is necessary in patients with mild to moderate abnormal hepatic function (see **Pharmacokinetic - Hepatic impairment**).

Dosing Guidelines For Tumor-Induced Hypercalcemia

The recommended total dose of pamidronate disodium for a treatment course depends upon initial

plasma calcium levels. Doses should be adapted to the degree of severity of hypercalcemia to ensure normalization of plasma calcium and to optimize the duration of response. Rehydration with normal saline before treatment is recommended (see **WARNINGS AND PRECAUTIONS**). **A dose of 90 mg should be administered in 500 mL of infusion solution. The infusion rate should not exceed 22.5 mg/hour.**

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

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

Tumor-induced hypercalcemia				
Initial Serum Calcium		**Total Dose**	**Concentration of infusate**	**Maximum Infusion Rate**
(mmol/L)	**(mg %)**	**(mg)**	**(mg/mL)**	**(mg/h)**
Up to 3.0	Up to 12.0	30	30 mg/ 125 mL	22.5 mg/h
3.0 - 3.5	12.0 - 14.0	30 or 60	30 mg/ 125 mL 60 mg/ 250 mL	22.5 mg/h 22.5 mg/h
3.5 - 4.0	14.0 - 16.0	60 or 90	60 mg/ 250 mL 90 mg/ 500 mL	22.5 mg/h 22.5 mg/h
> 4.0	> 16.0	90	90 mg/ 500 mL	22.5 mg/h

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

Dosing Guidelines For Bone Metastases And Multiple Myeloma

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

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

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

* for patients receiving chemotherapy every 3 weeks

Dosing Guidelines For Paget's Disease of Bone

The recommended total dose of pamidronate disodium for a treatment course is 180-210 mg. This may be administered either as 6 doses of 30 mg once a week (total dose 180 mg). Alternatively, 3 doses of 60 mg may be administered every second week, but treatment should be initiated with a 30 mg dose (total dose 210 mg) as influenza-like reactions are common only with the first infusion. Each dose of 30 mg or 60 mg should be diluted at least 250 mL or 500 mL, respectively, of normal saline or D5W. An infusion rate of 15 mg per hour is recommended. This regimen, omitting the initial dose, can be repeated after 6 months until remission of disease is achieved, and when relapse occurs (see table below).

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

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

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

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

Tumor-induced hypercalcemia

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

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

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

Before pamidronate disodium therapy is initiated, patients should be adequately rehydrated with isotonic saline (0.9%) (see **PRECAUTIONS**). Normalization of plasma calcium levels by pamidronate disodium in adequately hydrated patients also normalize plasma parathyroid hormone (PTH) which is suppressed by hypercalcemia.

The duration of normocalcemia following pamidronate disodium treatment varies in patients with tumor-induced hypercalcemia because of early mortality, and the heterogeneity of diseases and cancer therapies. In general, recurrences tend to occur preferentially after treatment with lower doses: at doses of 30 mg or less, plasma calcium levels tend to increase after approximately 1

week, while at high doses (total treatment doses of 45-90 mg) plasma calcium levels remained normal for at least 2 weeks and up to several months. One study has shown a clear relationship between recurrence rates and pamidronate disodium dose: in patients treated with single I.V. infusions of 30, 45, 60 and 90 mg pamidronate disodium, recurrence rates were lower for the higher dose group 9 months after initial treatment. In patients in whom the underlying disease is well controlled by cancer therapy, the duration of response tends to be more prolonged.

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

In severe forms of hypercalcemia the dose of pamidronate disodium may be increased, or eventually, a combination drug therapy should be considered (see **WARNINGS AND PRECAUTIONS**).

Bone metastases and multiple myeloma

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

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

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

Paget's disease

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

Clinical and biochemical remission of Paget's disease has been demonstrated by bone scintigraphy, by decreases in urinary hydroxyproline and serum alkaline phosphatase, and by

symptomatic improvement. Bone scans show that pamidronate disodium reduces the number of bones and the percent of the skeleton affected and that bone scintigraphy significantly improves. Bone biopsies consistently show histological and histomorphometric improvement indicating the reversal of the disease process. Symptoms improve even in those with severe disease.

Pharmacokinetics

Plasma concentrations of pamidronate rise rapidly after infusion is started and fall rapidly when the infusion is stopped. The apparent plasma half-life is about 0.8 hours. Apparent steady state is therefore achieved with infusions of > 2-3 hours' duration. When infused I.V. at 60 mg over 1 hour, the peak plasma concentration is about 10 nmol/mL and the apparent total plasma clearance is about 180 mL/min.

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

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

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

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

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

Hepatic Impairment

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n = 6) and mild to moderate hepatic dysfunction (n = 9). Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (39.7%) and Cmax (28.6%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 - 36 hours after drug infusion. Because pamidronate disodium is administered on a monthly basis, drug accumulation is not expected. No change in pamidronate disodium dosing regimen are recommended for patients with mild to moderate abnormal hepatic function (see **DOSAGE AND ADMINISTRATION**).

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

Renal Impairment

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

STORAGE AND STABILITY

Store between 15 - 25°C. Do not freeze. The products are for single use only and unused portions should be discarded.

DOSAGE FORM, COMPOSITION AND PACKAGING

VAL-PAMIDRONATE DISODIUM, 90 mg/10 mL:

Each mL contains 9,0 mg pamidronate disodium (formed from 7.58 mg pamidronic acid and 2.58 mg sodium hydroxide), 37.5 mg mannitol and water for injection to volume. Sodium hydroxide and phosphoric acid are added to adjust the pH to 6.3 - 6.7.Available in single dose vials of 90 mg /10 mL. Available in cartons of 1 vial.

These preparations contain **NO** preservatives.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

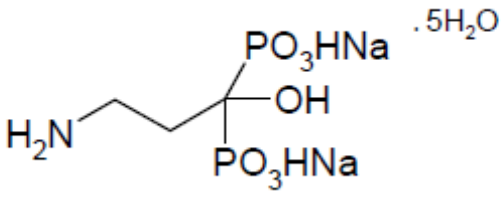
Drug Substance

Proper name: Pamidronate disodium

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

Molecular formula and molecular mass: $C_3H_9NO_7P_2Na_2$, M.M. 279.04

Structural formula:



Physicochemical properties:

Description**:** Colorless, crystalline powder

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

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

CLINICAL TRIALS

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

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

Normalization of plasma calcium levels was accompanied by a decrease in urinary calcium levels to normal, and in some cases, to below normal levels. Since it has been reported that calcium absorption from the kidney and gut are not increased by pamidronate disodium administration, the decreases in urinary calcium observed can be regarded as solely reflecting inhibition of bone resorption rather than effects on the kidney and gut.

Normalization of plasma calcium, including transient hypocalcemia, is dependent on the initial levels of plasma calcium and the dose of pamidronate disodium selected. Severe hypercalcemia (plasma calcium > 4.0 mmol/L) required higher doses of pamidronate disodium for normalization than moderate hypercalcemia. However, treatment of moderate hypercalcemia with high doses of pamidronate disodium (60 to 90 mg) can lead to transient hypocalcemia. A single infusion of 90 mg is indicated only for cases of severe hypercalcemia.

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

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

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

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

Bone metastases and multiple myeloma: Three large Phase III trials, one in multiple myeloma and two in breast cancer (one *versus* standard chemotherapy and one *versus* hormonal therapy) showed that 90 mg pamidronate disodium infused every 3-4 weeks significantly decreased the

skeletal morbidity rate (number of SREs/year) in all patients groups. Skeletal-related events (SREs) were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Radiation to bone was also significantly lower in all pamidronate disodium groups. The proportion of patients experiencing an SRE was significantly smaller, and the time to first SRE was significantly longer in pamidronate disodium-treated multiple myeloma and breast cancer + chemotherapy patients. The same trend was seen in the hormonally-treated breast cancer patients. Fewer pamidronate disodium-treated multiple myeloma patients suffered vertebral pathologic fractures.

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

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

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

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

Breast Cancer Patients Receiving Hormonal Therapy: 372 patients receiving hormonal therapy were randomized to receive either 90 mg of pamidronate disodium (182) or placebo (190)

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

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

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

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

Paget's disease: A clear dose response was demonstrated in a randomized, double-blind clinical trial in which patients received a single dose of pamidronate disodium (N = 64). A single infusion of pamidronate disodium 15 mg was not effective; 90 mg was most effective. A 50% fall from baseline was achieved in both ALP (alkaline phosphatase) and OHP:Cr (hydroxyproline:creatinine ratio) in > 20% of patients with both 45 and 90 mg pamidronate disodium ($p < 0.05$).

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

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

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

DETAILED PHARMACOLOGY

Animal Pharmacology

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

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

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

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

The intermittent administration of pamidronate disodium to animals was also effective in inhibiting bone resorption. In 10-week old pigs, administration of 1.6 μg/kg/day pamidronate disodium for 5 out of 21 days produced a significant inhibition of bone resorption that was equivalent to that produced with a continuous 60-day dosing regimen. In mice, once weekly

treatment for 1 year augmented diaphyseal wall thickness and the number of persisting trabeculae. This effect was mainly achieved by a suppression of endosteal bone resorption, which occurs during the retrogressive phase of C57BL/Silberberg mice aged more than 4 months. Bones of treated mice also demonstrated a higher femoral calcium content and ash weight, and increased resistance to fracture stress in comparison to untreated controls.

As a result of hormonal regulation, pamidronate disodium does not significantly affect serum calcium in normal, healthy animals. Under various experimental conditions however, changes in serum calcium values will reflect the effects of pamidronate disodium on bone metabolism. In thyroid-parathyroidectomized rats, the 1.25 $(OH)_2$ vitamin D3-stimulated mobilization of calcium from bone was inhibited by pamidronate disodium at daily doses of 0.02-0.6 mg/kg S.C. Similarity, pamidronate disodium reduced hypercalcemia of malignancy in rats bearing Walker 256 carcinosarcoma tumors. Mice bearing 5T2 myelomas had fewer skeletal lesions if treated with pamidronate disodium, although the myeloma itself was unaffected by pamidronate disodium treatment.

Twenty-four hours after single intravenous administration of 10 mg/kg to growing rats, approximately 50% of the dose is retained in bone, 0.1% in blood, 1.1% in spleen and 30% in liver. Pamidronate disodium is also stored in tracheal cartilage of rats. The percent uptake into the liver increases with dose, ranging from 3.0% at 0.01 mg/kg, to 30% at 10 mg/kg doses. Levels accumulated in liver at 10 mg/kg gradually decline during the 2 weeks after administration, with redistribution and uptake into bone, or elimination by the kidneys over 24-48 hours.

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

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

Human Pharmacology

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

TOXICOLOGY

Acute Toxicity

In acute toxicity studies, pamidronate disodium was better tolerated when administered as a short-

term I.V. infusion or I.P. than a bolus I.V. dose, presumably because of lower plasma concentrations. In mice, the I.V. bolus and I.P. LD_{50} of pamidronate disodium were 20.3 mg/kg and 40 mg/kg respectively; in rats 80 mg/kg and 65 mg/kg, and in rabbits, 18.5 mg/kg and 190 mg/kg. In dogs, the LD_{50} was > 10 mg/kg for a bolus I.V. dose and > 40 mg/kg when administered as an I.V. infusion.

Subacute And Chronic Toxicity

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

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

Carcinogenesis And Mutagenesis

Mutagenic potential was assessed by three different methods both *in vitro* (Ames test, point mutation test, and a cytogenetic test) and *in vivo* (nucleus anomaly test, sister chromatid exchange study and a micronucleus test). There was no evidence of mutagenic potential *in vivo*. *In vitro* tests were also negative apart from a slight increase in the number of chromosome aberrations in Chinese hamster ovary cells at the highest concentration only (2500 μg/mL).

Carcinogenic potential was assessed in both mice and rats treated with pamidronate disodium ≤40 mg/kg/day and ≤75 mg/kg/day, respectively, by gavage for 2 years. These studies repeated earlier studies completed in the 1970's, in which pamidronate disodium ≤1000 mg/kg was added to the food supply. From these studies, pamidronate disodium does not appear to have carcinogenic potential.

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

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

hepatomas was increased relative to control animals.

In both rat carcinogenicity studies, the incidence of neoplastic lesions was within the range observed with historical controls, apart from a slight increase in intestinal leiomyomas observed in females in one study only. Intestinal leiomyomas occur spontaneously in 0.44% Wistar rats (range 0-2%) used as controls in carcinogenicity studies. The mean incidence of these tumors in female Wistar rats administered 1000 mg/kg/day in the diet was 1.2% (range 0-3.7%). As no intestinal leiomyomas were observed in female rats in the other rat study, it is unlikely that these benign, non-fatal tumors are of biological or clinical significance.

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PART III: CONSUMER INFORMATION

PrVAL-PAMIDRONATE DISODIUM
(Pamidronate Disodium for Injection)

This leaflet is part III of a three-part "Product Monograph" published when PrVAL-PAMIDRONATE DISODIUM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PrVAL-PAMIDRONATE DISODIUM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Pamidronate Disodium is used to treat:
- the increased amount of calcium in the blood (hypercalcemia) in certain conditions
- bone tumors resulting from the spread of tumors at other sites and multiple myeloma (cancer of the cells of the immune system).
- Paget's disease of bone in patients with symptoms.

What it does:

Pamidronate disodium belongs to a group of medicines called bisphosphonates which strongly bind to the bone and slow down the rate of bone change.

When it should not be used:

You should not be given pamidronate disodium if you have previously had an allergic reaction to pamidronate disodium, to any of its components, or to other bisphosphonates.

What the medicinal ingredient is:

Pamidronate disodium

What the important non-medicinal ingredients are:

Mannitol, Sodium hydroxide, phosphoric acid and water for injection. Sodium hydroxide and phosphoric acid may have been added for pH adjustment.

What dosage forms it comes in:

One vial contains 90 mg of pamidronate disodium in solution. Available in single dose vials of 10 mL.

WARNING AND PRECAUTIONS

PAMIDRONATE DISODIUM MUST NEVER BE GIVEN AS A BOLUS INJECTION SINCE SEVERE LOCAL REACTIONS AND THROMBOPHLEBITIS MAY RESULT FROM HIGH LOCAL CONCENTRATIONS.

PAMIDRONATE DISODIUM SHOULD ALWAYS BE DILUTED AND ADMINISTERED AS A SLOW INTRAVENOUS INFUSION (see DOSAGE AND ADMINISTRATION). REGARDLESS OF THE VOLUME OF SOLUTION IN WHICH PAMIDRONATE DISODIUM IS DILUTED, SLOW INTRAVENOUS INFUSION IS ABSOLUTELY NECESSARY FOR SAFETY.BEFORE you use PAMIDRONATE DISODIUM talk to your doctor or pharmacist if:

- you have a heart or kidney problem

- you suffer from calcium or vitamin D deficiency (for example owing to your diet or as a result of digestive problems).

- you have any dental problems or any dental treatment/procedure planned in the future (see side effects).

Further Safety Measures

Please consult your doctor if a dental procedure (excluding dental cleaning) is required while you are receiving treatment with pamidronate disodium. If you experience any non healing of dental extraction or infection while taking pamidronate disodium, talk to your doctor. Let your dentist know you are taking pamidronate disodium.

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

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

If you drive a vehicle or use machinery
Pamidronate disodium may cause some patients to become sleepy or dizzy, especially immediately after infusion. If this happens you should not drive or use machinery or perform other tasks that need full attention.

INTERACTIONS WITH THIS MEDICATION

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

PROPER USE OF THIS MEDICATION

Usual dose:

Pamidronate disodium can be given only by slow infusion into a vein. This is usually 30-90 mg for patients with decreased blood calcium and 90 mg every 3-4 weeks for patients with tumors which have spread to the bone or multiple myeloma. Patients with Paget's disease of bone usually receive between 30-60 mg in one infusion.

An infusion may last one or more hours, depending on the dose given. Your doctor will decide how many infusions you need and how often you should receive them.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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

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

Some patients have reported problems with their jaw bones while receiving cancer treatments that include pamidronate disodium. Dental hygiene is an important element of your overall cancer care and is important in possibly decreasing the chances of this type of problem occurring. Removable dentures should fit properly and should be removed at night. Please consult with your doctor if you experience pain in your mouth, teeth or jaw, or if your gums or mouth heal poorly. Any non-healing of a dental extraction site or chronic dental infection should be assessed. If you notice any other effects, tell your doctor immediately. In addition, if possible you should not undergo tooth extraction or other dental procedures (excluding regular dental cleaning) while on therapy with pamidronate disodium**.** Please consult your doctor if a dental procedure (excluding regular dental cleaning) is required while you are receiving treatment with pamidronate disodium.

This is not a complete list of side effects. For any unexpected effects while taking* VAL-PAMIDRONATE DISODIUM*, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 - 25°C. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345
Toll-free fax: 1-866-678-6789
Email: cadrmp@hc-sc.gc.ca

Regular mail:

National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Valeo Pharma Inc., at:

Toll-free telephone: 1-886-694-0150

This leaflet was prepared by Valeo Pharma Inc., Ltd.

Last revised: March 20, 2012