

vomiting.

Hematic and lymphatic system: anemia, granulocytopenia and thrombocytopenia.**Musculoskeletal system:** arthralgias, myalgia, bone pain.**CNS:** anxiety, headache, insomnia.**Respiratory system:** coughing, dyspnea, pleural effusion, sinusitis, upper respiratory tract infection.**Urogenital system:** urinary tract infection.

Of the toxicities commonly associated with chemotherapy, anorexia, vomiting and anemia were less frequent in patients treated with pamidronate disodium, while stomatitis and alopecia occurred with a similar frequency in patients treated with placebo.

In breast cancer studies, mild elevation of serum creatinine occurred in 18.5% of patients receiving pamidronate disodium and in 12.3% of patients receiving placebo.

Mineral and electrolyte disturbances including hypocalcemia were reported in some patients treated with pamidronate disodium; percentage was similar in placebo-treated patients.

The reported percentages of hypocalcemia, hypokalemia, hypophosphatemia and hypomagnesemia in patients treated with pamidronate disodium were 3.3, 10.5, 1.7, and 4.4%, respectively; and in placebo-treated patients were 1.2, 12, 1.7, and 4.5, respectively.

In patients treated with pamidronate disodium, arthralgias and mild myalgias were reported more frequently than in patients receiving placebo (13.6 and 26% compared to 10.8 and 20.1%, respectively).

In multiple myeloma patients, 5 cases of unexpected adverse reactions were reported, 4 of them were reported during the 12-month treatment, 3 of them involved worsening of renal function (patients with progressive multiple myeloma or multiple myeloma associated with amyloidosis).

OVERDOSAGE: an overdose of intravenous pamidronate disodium may cause acute symptomatic hypocalcemia or mild asymptomatic hypocalcemia, depending on the administered dose. In the first case, it is required to administer intravenous calcium (acetate, chloride or gluconate), which rapidly increases ionized serum calcium. In the second case, patients may be given oral calcium with or without vitamin D. Hypotension and high fever (> 39 °C) may be reversed with corticosteroids.

In case of overdose, go to the nearest Hospital.

PATIENT INFORMATION: pamidronate disodium is a medication used for the prevention of bone lysis caused by Paget's disease of bone or some bone tumors. It must not be used during pregnancy and in case of allergy to bisphosphonates. Most of this medicine, administered intravenously, binds to bones and prevents their lysis, thus preventing the fractures resulting from bone lysis.

Treatment duration: for Paget's disease, treatment should last about 6 months, and for the rest of diseases, it may last weeks or months depending on the severity of the illness.

Unwanted effects: in some cases you may experience general feeling of body discomfort, fever, tiredness or digestive problems such as heartburn, nausea or vomiting. In these cases, you should stop taking the medicine and consult your doctor, who will determine the origin of symptoms and whether they are caused by pamidronate disodium. Your doctor will explain that these symptoms are generally temporary and they may be reversed by medical means in order to resume treatment. If your blood test shows a decrease of red blood cells, WBC or platelets, check with your doctor.

Missed dose: If you miss a dose, consult your doctor who will tell you how to make it up.

Pregnancy: if you suspect you may be pregnant, stop taking your medicine and consult your doctor.

Note: tell your doctor if you have an illness other than bone disease, if you failed to have your clinical analyses as indicated or if you start taking another medicine to treat a different medical condition.

CONSERVATION: at room temperature below 30 °C.

PRESENTATION: Pamidronato Servycal 30 and 90 mg: carton with 1 vial containing lyophilized powder and 1 ampoule containing diluent.

KEEP OUT FROM THE REACH OF CHILDREN

Medicinal Specialty authorized by Argentine Ministry of Health (ANMAT).
Certificate No. 50.819

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Pamidronato Servycal Pamidronate Disodium 30 and 90 mg

LYOPHILIZED POWDER FOR INJECTION, FOR IV INFUSION

**Sale under prescription
Made in Argentina**

COMPOSITION: Presentation:	30 mg	90 mg
Each vial contains:		
Pamidronate disodium pentahydrate (Equivalent to 30 mg and 90 mg of Anhydrous pamidronate disodium)	39.68 mg	119.05 mg
Mannitol	470.00 mg	375.00 mg
Each ampoule of diluent contains:		
Sterile distilled water	10.0 ml	

THERAPEUTIC ACTION:

Bone resorption inhibitor. Antihypercalcaemic.

Excessive bone resorption due to osteoclast activity results in bone diseases such as Paget's disease, hypercalcaemia or malignant osteolysis. The intravenous administration of pamidronate disodium dose-dependently inhibits bone resorption.

INDICATIONS: Pamidronate disodium is indicated for the treatment of hypercalcaemia of malignancy, Paget's disease of bone, osteolytic bone metastases of breast cancer or osteolytic bone lesions of multiple myeloma.

CLINICAL PHARMACOLOGY:

Hypercalcaemia of malignancy: pamidronate disodium, together with an adequate hydration, is indicated for the treatment of moderate or severe hypercalcaemia associated with malignancies, with or without bone metastases. Patients who have epidermoid or non-epidermoid tumors respond to treatment with pamidronate disodium. Vigorous saline hydration, which is part of hypercalcaemia therapy, should be initiated promptly, restoring the urine output of 2L/day throughout treatment. Moderate or asymptomatic hypercalcaemia may be treated with conservative measures, like saline hydration, with or without diuretics. Patients should be hydrated during treatment, but overhydration should be avoided in patients who have cardiac failure. Diuretic therapy should not be undertaken before the correction of hypovolemia. The safety and efficacy of pamidronate disodium in the treatment of hypercalcaemia associated with hyperparathyroidism or with non-tumor-related hypercalcaemia has not been established.

Paget's disease: pamidronate disodium is indicated for the treatment of patients with moderate or severe Paget's disease. The effectiveness of this medication was first demonstrated in patients with serum alkaline phosphatase exceeding 3 times the upper limit of normal value. Therapy with pamidronate disodium reduces serum alkaline phosphatase and urinary hydroxyproline levels by 50% in at least 50% of patients and 30% in at least 80% of patients. This medication has also been effective in reducing these biochemical values in patients with Paget's disease refractory to other treatment.

Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma: pamidronate disodium, in conjunction with standard antineoplastic therapy, is indicated for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. Treatment with pamidronate disodium seems to be less effective in patients with breast cancer receiving hormonal therapy than in those patients receiving chemotherapy; however, the clinical benefit has not been demonstrated.

PHARMACOLOGIC ACTION: the main pharmacologic action of pamidronate disodium is the inhibition of bone resorption. Although this mechanism of antiresorptive action has not been completely studied, it is believed that several factors contribute to this action. Pamidronate disodium adsorbs to calcium phosphate crystals of hydroxyapatite in bone and may directly block dissolution of this mineral component of bone.

In vitro studies also suggest that the inhibition of the osteoclast activity contributes to inhibition of bone resorption. In animal studies at doses recommended for the treatment of hypercalcaemia, pamidronate disodium inhibits bone resorption, apparently without inhibiting bone formation and mineralization. Within the framework of the treatment of hypercalcaemia of malignancy, it is important the finding that pamidronate disodium inhibits the accelerated bone resorption that results from osteoclast hyperactivity induced by various tumors in studied animals.

Pharmacokinetics: after dose infusion, 30 to 54 % of pamidronate disodium binds to plasma proteins, while the remaining fraction is rapidly taken up by bone tissue. The fraction retained by bone is 30 to 40%, and it decreases as treatment proceeds. It is transiently distributed to soft tissues, to be finally eliminated by the kidneys.

Distribution: the mean \pm SD retention of pamidronate disodium is 54 \pm 16 % of the dose over 120 hours.

Metabolism: pamidronate disodium is not metabolized and is exclusively eliminated in the urine.

Excretion: after administering 30 – 60 and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate disodium over 24 hours, a mean \pm SD of 46 \pm 16 % of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly connected with the dose. The mean elimination half-life is 28 \pm 7 hours. The total mean \pm SD and renal clearance of pamidronate disodium were 107 \pm 50 ml/min and 49 \pm 28 ml/min, respectively. The rate of elimination from bones has not been determined.

After the intravenous administration of radiolabeled pamidronate disodium in rats, approximately 50 to 60% of compound was rapidly adsorbed by bone and slowly eliminated by the kidneys.

When 10mg/kg bolus injection of pamidronate disodium was administered in rats, 30% of compound was found in the liver shortly after administration, then redistributed to bone or eliminated by the kidneys over 24 to 48 hours. Studies in rats injected with radiolabeled pamidronate disodium showed that compound was rapidly eliminated from circulation and mainly

taken up by bones, liver, spleen, teeth and trachea. Radioactivity was eliminated from most soft tissues within 1 to 4 days; it was detected in liver and spleen during 1 to 3 months respectively; it remained in bones, trachea and teeth for 6 months after administration. Bone uptake occurs preferentially in bone areas of high turnover. The terminal phase of half-life elimination in bone is estimated to be about 300 days.

Pharmacodynamics:

Serum phosphate levels decrease after pamidronate disodium administration, presumably due to the decrease of phosphate release from bone and the increase in renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcaemia of malignancy, return to normal. Phosphate therapy was administered in 30% of patients in response to the decrease in serum phosphate levels, which return to normal within 7 to 10 days.

The ratios of urinary calcium/creatinine and urinary hydroxyproline/creatinine decrease and generally return within or below normal values after the administration of pamidronate disodium. These changes occur within the first week after treatment, and serum calcium levels decrease producing an antiresorptive pharmacologic action.

DO dosage AND ADMINISTRATION:

Pamidronate disodium should be administered as a slow IV infusion. It must not be given as a bolus injection since it may damage tissues at injection site or increase the risks of renal damage. Dosing is related to patient's condition.

In hypercalcaemia, the administration of pamidronate disodium should be accompanied by adequate saline hydration, trying that urine output be about 2l. Overhydration should be avoided in patients who have cardiac failure.

Mild – moderate hypercalcaemia: the recommended dose of pamidronate disodium (corrected serum calcium of approximately 12-13.5 mg/dl) is 30 to 60 mg as a single dose. Initial single dose of 60 mg, IV slow infusion over at least 4 hours. Initial single dose of 90 mg, IV slow infusion over at least 24 hours.

Severe hypercalcaemia: the recommended dose of pamidronate disodium (corrected serum calcium above 13.5 mg/dl) is 30 to 60 mg/day (maximum dose is 90 mg), which should be administered as IV slow infusion, until serum calcium returns to normal. Treatment should last between 5 and 10 days.

Retreatment: a limited number of patients have received more than one treatment with pamidronate disodium for hypercalcaemia. In order to retreat patients who initially show partial response, it is recommended that at least 7 days elapse before retreatment to allow for full response to the initial dose. The dose and form of retreatment is identical to that of the initial therapy.

Paget's disease: the recommended dose of pamidronate disodium in patients with severe to moderate Paget's disease is 30 mg /day infused over 4 hours for 3 consecutive days up to a total dose of 90 mg. It is also possible to give 30 mg/week for 6 weeks or 60 mg each 15 days without exceeding the total cumulated dose allowed that is 200 mg.

Retreatment: a limited number of patients with this disease have received more than one treatment with pamidronate disodium in clinical trials. When clinically indicated, patients should be retreated at a dose identical to that of the initial therapy.

Osteolytic lesions of multiple myeloma: the recommended dose is 90 mg infused over 4 hours on a monthly basis. Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to pamidronate disodium infusion. There is limited information on the use of pamidronate disodium in patients with multiple myeloma and a serum creatinine > 3.0 mg/dl. The optimal duration of therapy is still unknown; however, in studies of patients with multiple myeloma, final analysis after 2 months demonstrated overall benefits.

Osteolytic bone metastases of breast cancer: the recommended dose of pamidronate disodium is 90 mg infused over 2 hours every 2 or 3 weeks.

Pamidronate disodium has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotrexate, mitoxantrone, vinblastine, dexmethasone, prednisone, melphalan, vincristine, megestrol, and tamoxifen. It has been less frequently used with etoposide, cisplatin, cytarabine, paclitaxel, and aminoglutethimide. The optimal duration of therapy is still unknown, however, in two studies of breast cancer patients, final analysis after 24 months demonstrated overall benefits.

Hypercalcaemia of malignancy: the daily dose of 60 mg should be administered as IV infusion over at least 4 hours; the daily dose of 90 mg should be administered as IV infusion over 24 hours. It is recommended to dilute the reconstituted content in 1,000 mL of sterile 0.45% to 0.9% sodium chloride, or 5% dextrose injection. The prepared solution is stable for 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% to 0.9% sodium chloride, or 5% dextrose injection, and infused over 4 hours 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% to 0.9% sodium chloride, or 5% dextrose injection, infused over 2 hours every 3 or 4 weeks.

Osteolytic lesions of multiple myeloma: the recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% to 0.9% sodium chloride injection, infused over 4 hours on a monthly basis.

Reconstitution: pamidronate disodium is reconstituted with the solvent ampoule, shake until total dissolution. The reconstituted solution is stable for 24 hours, if stored under refrigeration between 2 °C and 8 °C. This medicine should not be diluted with infusion solutions containing calcium, such as Ringer's solution, and it should be administered in an infusion separated from other drugs.

NOTE: solutions should be visually inspected prior to administration. Whenever particles in suspension or discoloration are observed, solutions must be discarded.

CONTRAINDICATIONS: this medicine is contraindicated in patients with hypersensitivity to pamidronate disodium and other bisphosphonates.

Warnings: pamidronate disodium must be administered under medical supervision. According to studies in animals, it is recommended to assess renal function in patients receiving pamidronate disodium. Studies conducted in young rats have shown that after single- and multi-dose administration of bisphosphonates as infusion, the formation of dental dentine was interrupted. The clinical significance of this finding is still unknown.

Due to the fact that this medication may cause confusion or somnolence, it is recommended to avoid driving vehicles or operating dangerous machinery immediately after pamidronate disodium infusion.

PRECAUTIONS: serum levels of phosphate, calcium, magnesium and potassium should be monitored following commencement of therapy with pamidronate disodium. After administration, the following cases were reported: asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%) and hypocalcaemia (5 to 12%). Some cases of asymptomatic hypocalcaemia were reported in association with pamidronate disodium therapy. If hypocalcaemia

occurs, short-term calcium therapy should be provided. In Paget's disease, 17% of patients treated with 90 mg of pamidronate disodium have shown serum calcium levels below 8 mg/dl. This medicine was not tested in patients with renal impairment (creatinine over 5.0 mg/dl), or in multiple myeloma patients with creatinine over 3.0 mg/dl. Medical judgment should consider the risk-benefit relation in these cases.

Laboratory tests:

The following should be monitored in patients receiving pamidronate disodium treatment: serum calcium, electrolytes, phosphates, magnesium, creatinine, CBC, and hemocrit/hemoglobin.

Patients who have preexisting anemia, leukopenia or thrombocytopenia should be carefully monitored during the first two weeks of treatment.

Interactions: there are no human pharmacokinetic data of drug interactions with pamidronate disodium. Nevertheless, it should be used cautiously in those patients who are concomitantly receiving oral anticoagulants, oral hypoglycemics, and any other medication interacting in the transportation of ionized calcium. In hypercalcaemia patients, the concurrent administration of pamidronate disodium and medicines containing calcium, vitamin D, or calcitriol may antagonize the effects of pamidronate disodium.

Carcinogenesis, tumorigenesis:

In studies conducted in mice which were given pamidronate disodium, it was observed that this medication is not carcinogenic or tumorigenic. However, the administration of a dose greater than the recommended dose over to years cause the occurrence of dose-related benign pheochromocytoma.

Mutagenesis and teratogenesis: mutagenicity assays showed that pamidronate disodium is nonmutagenic. Other studies conducted in rats, where pamidronate disodium 30, 60, 90 mg/kg of body weight was administered orally, showed no teratogenic potential.

Reproduction: no alterations was observed in humans. Studies in male and female rats did not show any alteration in estrus and reproduction.

Pregnancy: there is no available information concerning pamidronate disodium use in pregnant women, therefore it should not be given during pregnancy.

Breast-feeding: it is not known whether pamidronate disodium is excreted in breast milk. Because many drugs are excreted in human milk, it is not advised to give pamidronate disodium to nursing women.

Pediatric use: safety and effectiveness of pamidronate disodium in children have not been established.

Geriatric use: it should be cautiously administered in patients with hypertension or ventricular failure due to fluid overload caused by infusion.

Renal insufficiency: the pharmacokinetics of pamidronate disodium was studied in 19 cancer patients with normal renal function and different degrees of renal insufficiency. Each patient received a single dose of 90 mg of pamidronate disodium infused over 4 hours. The renal clearance of pamidronate disodium in patients was found to be closely related to creatinine clearance. In patients with renal insufficiency it was observed that the percentage of unchanged excretion is low. When the recommended dose of pamidronate disodium is administered, 90 mg infused over 4 hours, excessive accumulation in renally impaired patients does not occur if this medication is given on a monthly basis.

Hepatic insufficiency: there are no pharmacokinetic data for the use of pamidronate disodium in this specific population.

ADVERSE REACTIONS:

Hypercalcaemia of malignancy: after 24 to 48 hours after pamidronate disodium administration, a transient mild elevation of body temperature (of at least 1 °C) occurred in 34% of treated patients. In some studies, 18% of patients had temperature elevation of at least 1 °C 24 to 48 hours after infusion.

Redness, swelling or induration and pain on palpation at the site of catheter insertion were observed in 18% of patients receiving 90 mg of pamidronate disodium. Uveitis, iritis, scleritis and episcleritis have been rarely reported.

At least 15% of patients treated with pamidronate disodium for hypercalcaemia of malignancy experienced the following adverse reactions:

General: edema, fatigue, fever, fluid overload, infusion-site reaction, moniliasis.

Gastrointestinal: abdominal pain, anorexia, constipation, diarrhea, dyspepsia, gastrointestinal hemorrhage, nausea, stomatitis, vomiting.

Respiratory: dyspnea, rhinitis, rales, upper respiratory infection.

CNS: anxiety, convulsions, insomnia, nervousness, psychosis, somnolence.

Cardiovascular system: atrial fibrillation, atrial flutter, cardiac failure, hypertension, syncope, tachycardia.

Endocrine: hypothyroidism.

Hematic and lymphatic: anemia, leukopenia, neutropenia and thrombocytopenia.

Urogenital: uremia.

Musculoskeletal: myalgia, osteonecrosis of the jaw.

Renal: some cases of hematuria, increase in serum creatinine and/or urea, and deterioration of preexisting disease.

Laboratory abnormalities: hypocalcaemia, hypokalemia, hypomagnesemia, hypophosphatemia and abnormal liver function.

Special sense: uveitis, conjunctivitis, scleritis, episcleritis or xanthopsia; may be reversed with treatment interruption.

Paget's disease: 21% of patients treated with 90 mg of pamidronate disodium had a mild elevation of body temperature above 1 °C within 48 hours. 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 hypercalcaemia of malignancy treated with the same dose. It has also been noted that after administration patients had fever, nausea, back pain and bone pain.

At least 10% of patients with Paget's disease treated with pamidronate disodium experienced the following adverse reactions:

Cardiovascular system: hypertension.

Musculoskeletal: arthrosis, bone pain.

Nervous system: headache.

Most of these reactions have been related to the disease state.

Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma: most of the adverse reactions (more than 15%) have occurred with similar frequency in patients treated with pamidronate disodium and placebo, and these reactions have been related to the disease state or cancer therapy.

Adverse reactions reported in clinical trials conducted in the U.S.:

General: asthenia, fatigue, fever, pain.

Digestive system: anorexia, constipation, diarrhea, dyspepsia, nausea, abdominal pain and

PRODUCTO: Pamidronato Servycal - Ingles - Prospecto		VERSION - 02	
COLORES	ALTERACIONES	Código Actual: 71063-02	
	Emisión inicial: Actualización de textos y nuevo DT.		
	Código anterior: N/A		
	Medida: 220 x 340 mm	Trazado	Desarrollo de Packaging
		Director Técnico	