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706

PAMIDRONATE MYLAN

PAMIDRONATE DISODIUM INJECTION

3 mg/mL

PRODUCT DESCRIPTION:

Clear colorless solution free from visible particles.

COMPOSITION:

Each mL contains Pamidronate Disodium 3 mg/mL.

PHARMACOLOGY:

Pamidronate Disodium is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals *in vitro*. Inhibition of osteoclastic bone resorption *in vivo* may be at least partly due to binding of the drug to be bone mineral.

Pamidronate Disodium suppresses the accession of osteoclastic precursors on to the bone and their subsequent transformation into the mature, resorbing osteoclasts. However, the local and direct antiresorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*.

Experimental studies have demonstrated that Pamidronate Disodium inhibits tumour induced osteolysis when given prior to or at the time of inoculation or transplantation with tumour cells. Biochemical changes reflecting the inhibitory effect of Pamidronate Disodium on tumour-induced hypercalcaemia, are characterized by a decrease in serum calcium and phosphate and secondarily by decrease in urinary excretion of calcium, phosphate and hydroxyproline.

PHARMACOKINETICS

General Characteristics

Pamidronate Disodium has a strong affinity for calcified tissues and total elimination of Pamidronate Disodium from the body is not observed within the time frame of experimental studies. Calcified tissues are, therefore, regarded as site of apparent elimination.

Absorption

Pamidronate Disodium is given by IV infusion. By definition, absorption is complete at the end of the infusion.

Distribution

Plasma concentrations of Pamidronate Disodium rise rapidly after the start of an infusion and fall rapidly when the infusion is stopped. The apparent half-life in plasma is about 0.8 hr. Apparent steady-state concentrations are therefore achieved with infusions of more than about 2-3 hrs duration. Peak plasma Pamidronate Disodium concentrations of about 10nmol/mL are achieved after an IV infusion of 60 mg given over 1 hr.

In animals and in man, a similar percentage of the dose is retained in the body after each dose of Pamidronate Disodium. Thus, the accumulation of Pamidronate Disodium in bone is not capacity-limited and is dependent solely on the total cumulative dose administered.

The percentage of circulating Pamidronate Disodium bound to plasma proteins is relatively low (about 54 %) and increases when calcium concentrations are pathologically elevated.

Metabolism

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

Excretion

Pamidronate Disodium does not appear to be eliminated by biotransformation and it is almost exclusively eliminated by renal excretion. After an IV infusion, about 20-55% of the dose is recovered in the urine within 72 hours as unchanged Pamidronate Disodium.

Renal Insufficiency

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

Hepatic Insufficiency

The pharmacokinetics of Pamidronate Disodium were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90 mg dose of Pamidronate Disodium infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (39.7%) and C_{max} (28.6%) values. Nevertheless, Pamidronate Disodium was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 to 36 hours after drug infusion. Because Pamidronate Disodium is administered on a monthly basis, drug accumulation is not expected. No changes in Pamidronate Disodium dosing regimen are recommended for patients with mild to moderate abnormal hepatic function.

INDICATIONS:

Pamidronate Disodium is used in the treatment of conditions associated with increased osteoclast activity: Predominantly lytic bone metastases and multiple myeloma; tumour-induced hypercalcaemia; Paget's disease of bone.

RECOMMENDED DOSAGE:

Pamidronate Disodium must never be given as a bolus injection. Pamidronate Disodium must be infused slowly. The infusion rate should not exceed 60 mg/hr (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 hr infusion solution. However, in patients with multiple myeloma and in patients with tumour induced hypercalcaemia, it is recommended not to exceed 90 mg in 500 mL over 4 hrs. In order to minimize local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

Adults and Elderly

Predominantly Lytic Bone Metastases and Multiple Myeloma:

The recommended dose 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 on a 3-weekly schedule.

Tumour-Induced Hypercalcaemia

Patients must be adequately rehydrated prior to and during administration of Pamidronate Disodium. The total dose of Pamidronate Disodium to be used for a treatment course depends on the patient's initial serum calcium levels. The following guidelines are derived from clinical data on uncorrected calcium values. However, doses within the ranges given are also applicable for calcium values corrected for serum protein or albumin in rehydrated patients.

Initial serum calcium		Recommended total dose
Mmol/L	mg%	mg
Up to 3	Upto 12	15-30
3-3.5	12-14	30-60
3.5-4	14-16	60-90
>4	-	90

The total dose of Pamidronate Disodium may be administered either in a single infusion or in multiple infusions over 2-4 consecutive days. The maximum dose per treatment course is 90 mg for both initial and repeated courses.

A significant decrease in serum calcium is generally observed 24-48 hrs after administration of Pamidronate Disodium, and normalization is usually achieved within 3-7 days. If normocalcaemia is not achieved within this time, a further dose may be given. The duration of the response may vary from patient- to-patient and treatment can be repeated whenever hypercalcaemia recurs. Clinical experience to date suggests that Pamidronate Disodium may become less effective as the number of treatments increases.

Paget's Disease of Bone

The recommended total dose of Pamidronate Disodium for a treatment course is 180-210 mg. This can be administered either in 6-unit doses of 30 mg once a week (total dose 180 mg), or in 3-unit doses of 60 mg every week. If unit doses of 60 mg are used, it is recommended to start the treatment with an initial dose of 30 mg (total 210 mg).

This regimen, omitting the initial dose, can be repeated after 6 months until remission of disease is achieved, and when relapse occurs.

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 hypercalcaemia where the benefit outweighs the potential risk.

As with other IV bisphosphonates, renal monitoring is recommended ie., 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 and normal or impaired renal function indicates that the dose adjustment is not necessary in mild (creatinine clearance 61-90 mL/min) to moderate renal impairment (creatinine clearance 30-60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4 hr (approximately 20-22 mg/hr).

Hepatic impairment

A pharmacokinetic study indicates that no dose adjustment is necessary in patients with mild to moderate abnormal hepatic function.

Children

There is no clinical experience with Pamidronate Disodium in children.

MODE OF ADMINISTRATION:

Intravenous administration.

CONTRAINDICATIONS:

Known hypersensitivity to Pamidronate Disodium or other bisphosphonates or any of the excipients of Pamidronate Disodium.

WARNINGS AND PRECAUTIONS:

General

Pamidronate Disodium must never be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion.

Patients must be assessed prior to administration of Pamidronate Disodium to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

Standard hypercalcaemia-related metabolic parameters including serum, calcium and phosphate should be monitored following initiation of therapy with Pamidronate Disodium. Patients who have undergone thyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.

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.

Convulsions have been precipitated in some patients with tumour-induced hypercalcaemia due to the electrolyte changes associated with this condition and its effective treatment.

Renal Insufficiency

Bisphosphonates, including Pamidronate Disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Pamidronate Disodium. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate Disodium in patients with multiple myeloma.

FRONT SIDE

Product	**PAMIDRONATE MYLAN – Pamidronate Disodium Injection 3 mg/mL**				
Buyer/Country	Mylan / Malaysia	Component	Pack Insert		
Dimension	**280 x 210 mm**			Pack	--
New Item Code	**50106816 (1200013518)**	Old Item Code	1033286 (1200005590)		
Colour Shades	Black			No. of Colours	1

Change Control No.	PR# 3955812
Design/Style	Front & Back Printing. To be supplied in the folded size 35 x 55 mm - Brand name facing front side.
Substrate	40/45 GSM Paper.
Special Instructions	Printing clarity to be clear & sharp.
Autocartonator Requirements	NA

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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.

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.

As with other IV 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 or multiple myeloma should have the dose withheld if renal function has deteriorated.

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 hypercalcaemia where the benefit outweighs the potential risk. Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made. Pamidronate Disodium should not be given with other bisphosphonates because their combined effects have not been investigated. There is very little experience of the use of Pamidronate Disodium in patients receiving haemodialysis.

Hepatic Insufficiency
As there are no clinical data available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Calcium and Vitamin D Supplementation
In the absence of hypercalcaemia, patients with predominantly lytic bone metastases or multiple myeloma, who are at risk of calcium or Vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) and patients with Paget's disease of the bone should take oral calcium and vitamin D supplementation in order to minimize the potential risk of hypocalcaemia.

Osteonecrosis of the jaw
Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate Disodium. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

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

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

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes Pamidronate Disodium for infusion. The time to onset of symptoms varied from one day to several months after starting the drug with the majority occurring within a few days. Most patients had relief or improvement of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Effects on the ability to drive or operate machinery
Patients should be warned that somnolence and/or dizziness may occur following Pamidronate Disodium infusion, in which case they should not drive, operate potentially dangerous machinery or engage in other activities that may be hazardous because of decreased alertness.

DRUG INTERACTIONS:

Pamidronate Disodium has been administered concomitantly with commonly used anticancer agents eg. commonly used antitumour drugs (including aminogluthethimide, cisplatin, corticosteroids, cyclophosphamide, cytarabine, doxorubicin, etoposide, flurouracil, megoestrol, melphalan, methotrexate, mitoxantrone, paclitaxel, tamoxifen, vinblastine and vincristine) without interactions occurring.

Pamidronate Disodium has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.

Caution is indicated when Pamidronate Disodium is used with other potentially nephrotoxic drugs. In multiple myeloma patients, the risk of renal dysfunction may be increased when Pamidronate Disodium is used in combination with thalidomide.

Pamidronate Disodium should not be used concomitantly with other bisphosphonates.

Incompatibilities
Infusion bags made from polyvinylchloride and polyethylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with Pamidronate Disodium.

To avoid potential incompatibilities, Pamidronate Disodium Injection is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

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

USE IN PREGNANCY AND LACTATION:

There are no adequate and well-controlled studies in pregnant women and no clinical experience to support the use of Pamidronate Disodium in pregnant women. Therefore, Pamidronate should not be used during pregnancy.

Mothers treated with Pamidronate Disodium should also not breastfeed their infants.

SIDE EFFECTS:

Usually mild to transient. The most common adverse reactions are asymptomatic hypocalcaemia and fever (an increase in body temperature 1-2°C) typically occurring within 1st 48 hrs of infusion. Fever usually resolves spontaneously and does not require treatment.

Infection
Very rare: Reactivation of Herpes simplex and Herpes zoster.

Blood
Common: Anaemia, thrombocytopenia, lymphocytopenia.
Very rare: Leukopenia.

Immune system
Uncommon: Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke's (angioneutotic) edema.
Very Rare: Anaphylactic shock.

Central Nervous System
Common: Symptomatic hypocalcaemia, headache, insomnia, somnolence.
Uncommon: Siezures, agitation, dizziness, lethargy.
Very Rare: Confusion, visual hallucinations.

Special Senses
Common: Conjunctivitis.
Very rare: Scleritis, episcleritis, xanthopsia.

Cardiovascular system
Common: Hypertension.
Uncommon: Hypotension.
Very Rare: Left ventricular failure (dyspnoea, pulmonary edema), congestive heart failure (edema) due to fluid overload.

Gastrointestinal tract
Common: Nausea, vomiting, anorexia, abdominal pain, diarrohoea, constipation, gastritis.
Uncommon: Dyspnoea.

Skin
Common: Rash.
Uncommon: Pruritis

Musculoskeletal system
Common: Transient bone pain, arthralgia, myalgia and generalized pain.
Uncommon: Muscle cramps.
Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Renal system
Uncommon: Acute renal failure.
Rare: Focal segmental glomerulosclerosis including the collapsing variant, nephritic syndrome.
Very Rare: Deterioration of preexisting renal disease, haematuria.

General disorders and administration site conditions
Very common: Fever and influenza like symptoms sometimes accompanied by malaise, rigor, fatigue and flushes.
Common: Reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis).

Biochemical changes
Very common: Hypocalcaemia, hypophosphataemia.
Common: Hypokalemia, hypomagnesaemia, increase in serum creatinine.
Uncommon: Abnormal liver function tests, increase in serum urea.
Very Rare: Hyperkalemia, hypernatremia.

Many of these undesirable effects may have been related to the underlying disease.

OVERDOSE AND TREATMENT:

Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically significant hypocalcaemia with paraesthesia, tetany and hypotension, reversal may be achieved with an infusion of calcium gluconate.

STORAGE:

Store below 30°C. Protect from light. Discard any unused portion after opening.

AVAILABILITY:

Pack of 1 x 10mL vial

For further information, please consult your physician or pharmacist.

Date of revision: November, 2025

Mylan

Product Owner:
Mylan Laboratories Limited
Plot No. 564/A/22, Road No.92, Jubilee Hills,
Hyderabad – 500096, Telangana, India.

Importer and Product Registration Holder in Malaysia:
Unimed Sdn. Bhd. (69359V),
No 53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara,
52200, Kuala Lumpur, Malaysia.

Manufactured by:
M/S OneSource Specialty Pharma Limited
Sterile Product Division,
Opp. IIM, Bilekahalli, Bannerghatta Road,
Bangalore – 560076, India.

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BACK SIDE

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