

PAMISOL™

Name of medicine

Disodium Pamidronate

Presentation

Pamisol™ is a clear, colourless, sterile solution of disodium pamidronate, mannitol, phosphoric acid and sodium hydroxide in water for injections. Phosphoric acid and sodium hydroxide are added to adjust pH. The pH of the solution is approximately 6.5. Pamisol™ is available in 3 mg/mL, 6 mg/mL and 9 mg/mL strengths.

Uses

Actions

Pamidronate disodium, the active substance of Pamisol™, 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 the bone mineral.

Pamidronate suppresses the accession of osteoclast precursors onto 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 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 Pamisol™ on tumour-induced hypercalcaemia, are characterised by a decrease in serum calcium and phosphate and secondarily by decreases in urinary excretion of calcium, phosphate, and hydroxyproline.

Hypercalcaemia can lead to a depletion in the volume of extracellular fluid and a reduction in the glomerular filtration rate (GFR). By controlling hypercalcaemia, pamidronate improves GFR and lowers elevated serum creatinine levels in most patients.

Clinical trials in patients with predominantly lytic bone metastases or multiple myeloma showed that pamidronate prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain. When used in combination with standard anticancer treatment, pamidronate 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 stabilisation or sclerosis.

Paget's disease of bone, which is characterised by local areas of increased bone resorption and formation with qualitative changes in bone remodelling, responds well to treatment with pamidronate. Clinical and biochemical remission of the disease has been demonstrated by bone scintigraphy, decreases in urinary hydroxyproline and serum alkaline phosphatase, and by symptomatic improvement.

Pharmacokinetics

General characteristics

Pamidronate has a strong affinity for calcified tissues, and total elimination of pamidronate 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 intravenous infusion. By definition, absorption is complete at the end of the infusion.

Distribution

Plasma concentrations of pamidronate 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 hours. Apparent steady-state concentrations are therefore achieved with infusions of more than about 2-3 hours' duration. Peak plasma pamidronate concentrations of about 10 nmol/mL are achieved after an intravenous infusion of 60 mg given over 1 hour.

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 in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

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

Elimination

Pamidronate does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20-55 % of the dose is recovered in the urine within 72 hours as unchanged pamidronate. Within the time frame of experimental studies the remaining fraction of the dose is retained in the body. The percentage of the dose retained in the body is independent of both the dose (range 15-180 mg) and the infusion rate (range 1.25-60 mg/h). The elimination of pamidronate in the urine is biexponential, with apparent half-lives of about 1.6 and 27 hours. The apparent total plasma clearance is about 180 mL/min and the apparent renal clearance is about 54 mL/min. There is a tendency for the renal clearance of pamidronate to correlate with creatinine clearance.

Characteristics in patients

Hepatic and metabolic clearance of pamidronate are insignificant. Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate. Pamidronate thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).

The mean plasma AUC is approximately doubled in patients with severe renal impairment (creatinine clearance < 30 mL/min). Urinary excretion rate decreases with decreasing creatinine clearance, although the total amount excreted in the urine is not greatly influenced by renal function. Body retention of pamidronate is therefore similar in patients with and without impaired renal function, and dose adjustment is not necessary in these patients when using the recommended dose schedule.

Indications

Treatment of conditions associated with increased osteoclast activity:

Predominantly lytic bone metastases and multiple myeloma

Metastatic bone pain

Tumour-induced hypercalcaemia

Paget's disease of bone

Dosage and administration

Pamisol™ must never be given as a bolus injection (see "Special Warnings and Special Precautions"). Concentrated solution of Pamisol™ in vials should be diluted in a calcium-free infusion solution (e.g. 0.9 % sodium chloride or 5 % glucose) and infused slowly.

The infusion rate should not exceed 60 mg/h (1 mg/min), and the concentration of pamidronate in the infusion solution should not exceed 90 mg/250 mL. A dose of 90 mg should normally be administered as a 2-hour infusion in 250 mL infusion solution. However, in patients with multiple myeloma and in patients with tumour-induced hypercalcaemia, it is recommended not to exceed 90 mg in 500 mL over 4 hours. In order to minimise 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 of pamidronate 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 Pamisol™ 90 mg may also be given on a 3-weekly schedule.

Tumour-induced hypercalcaemia

It is recommended that patients be rehydrated with normal saline before or during treatment.

The total dose of pamidronate 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 (mg)
(mmol/L)	(mg %)	
up to 3.0	up to 12.0	15 - 30
3.0 - 3.5	12.0 - 14.0	30 - 60
3.5 - 4.0	14.0 - 16.0	60 - 90
> 4.0		90

The total dose of pamidronate 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 hours after administration of pamidronate, and normalisation is usually achieved within 3 to 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 may become less effective as the number of treatments increases.

Paget's disease of bone

The recommended total dose of pamidronate 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 other week. If unit doses of 60 mg are used, it is recommended to start the treatment with an initial dose of 30 mg (total dose 210 mg).

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

Renal impairment

Pharmacokinetic studies indicate that no dose adjustment is necessary in patients with any degree of renal impairment. However, until further experience is gained a maximum infusion rate of 20 mg/h is recommended in renally impaired patients.

Children

There is no clinical experience with pamidronate in children.

Contraindications

Known hypersensitivity to pamidronate or to other bisphosphonates.

Warnings and precautions

Warnings

Pamisol™ should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see "Dosage and method of administration").

Pamisol™ should not be given with other bisphosphonates because their combined effects have not been investigated.

Precautions

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy with Pamisol™. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

Patients receiving frequent infusions of pamidronate over a prolonged period of time, especially those with pre-existing renal disease or a predisposition to renal impairment (e.g. patients with multiple myeloma and/or tumour-induced hypercalcaemia), should have periodic evaluations of standard laboratory and clinical parameters of renal function as deterioration of renal function (including renal failure) has been reported following long-term treatment with pamidronate in patients with multiple myeloma. However, underlying disease progression and/or concomitant complications were also present and therefore a causal relationship with pamidronate is unproven.

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.

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 in order to minimise the risk of hypocalcaemia .

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

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, 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 judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Pregnancy and Lactation

In animal experiments, pamidronate showed no teratogenic potential and did not affect general reproductive performance or fertility. In rats, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels. In pregnant rats, pamidronate has been shown to cross the placental barrier and accumulate in foetal bone in a manner similar to that observed in adult animals.

There is no clinical experience to support the use of pamidronate in pregnant women. Therefore, Pamisol™ should not be administered during pregnancy except in cases of life-threatening hypercalcaemia.

A study in lactating rats has shown that pamidronate will pass into the milk. Mothers treated with Pamisol™ should therefore not breast-feed their infants.

Effects on ability to drive and use machines

Patients should be warned that in rare cases somnolence and/or dizziness may occur following Pamisol™ 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.

Other

Preclinical Safety Data

The toxicity of pamidronate is characterised by direct (cytotoxic) effects on organs with a copious blood supply, particularly the kidneys following i.v. exposure. The compound is not mutagenic and does not appear to have carcinogenic potential.

Adverse effects

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

Symptomatic hypocalcaemia is rare.

Frequency estimate: frequent > 10%, occasional > 1-10%, rare > 0.001-1%, isolated cases < 0.001%.

Body as a whole

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

Local reactions

Occasional: reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis

Musculoskeletal system

Occasional: transient bone pain, arthralgia, myalgia, generalised pain

Rare: muscle cramps

Gastrointestinal tract

Occasional: nausea, vomiting

Rare: anorexia, abdominal pain, diarrhoea, constipation, dyspepsia

Isolated cases: gastritis

Central nervous system

Occasional: headache

Rare: symptomatic hypocalcaemia (paraesthesia, tetany), agitation, confusion, dizziness, insomnia, somnolence, lethargy

Isolated cases: seizures, visual hallucinations

Blood

Occasional: lymphocytopenia

Rare: anaemia, leukopenia

Isolated cases: thrombocytopenia

Cardiovascular system

Rare: hypotension, hypertension

Isolated cases: left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload

Renal system

Isolated cases: haematuria, acute renal failure, deterioration of pre-existing renal disease

Skin

Rare: rash, pruritus

Special senses

Isolated cases: conjunctivitis, uveitis (iritis, iridocyclitis), scleritis, episcleritis, xanthopsia

Others

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

Very rare: anaphylactic shock

Isolated cases: reactivation of herpes simplex and herpes zoster

Biochemical changes

Frequent: hypocalcaemia, hypophosphataemia

Occasional: hypomagnesaemia

Rare: hyperkalaemia, hypokalaemia, hypernatraemia

Isolated cases: abnormal liver function tests, increase in serum creatinine and urea

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

Postmarketing:

Very rare cases of osteonecrosis (primarily of the jaws) have been reported in patients treated with biphosphonates. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged

Interactions

Pamidronate has been administered concomitantly with commonly used anticancer agents without interactions occurring.

Pamidronate 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.

Overdosage

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.

Incompatibilities

Pamidronate will form complexes with divalent cations and should not be added to calcium-containing intravenous solutions.

Special Precautions for Storage

Store below 25°C.

Medicine classification

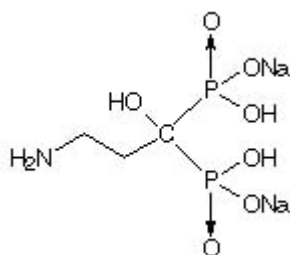
Prescription Medicine.

Package quantities

Pamisol™	Strength	Pack size
15 mg disodium pamidronate/5 mL	3 mg/mL	1 x 5 mL or 5 x 5 mL vial
30 mg disodium pamidronate/10 mL	3 mg/mL	1 x 10 mL vial
60 mg disodium pamidronate/10 mL	6 mg/mL	1 x 10 mL vial
90 mg disodium pamidronae/10 mL	9 mg/mL	1 x 10 mL vial

Further information

The chemical structure of disodium pamidronate:



The molecular formula of disodium pamidronate is C₃H₉NNa₂O₇P₂. The molecular weight of anhydrous disodium pamidronate is 279. The CAS Registry number of anhydrous disodium pamidronate is 57248-88-1. Disodium pamidronate is a white crystalline powder. It is soluble in water and in 2M sodium hydroxide; sparingly soluble in 0.1M hydrochloric acid and practically insoluble in organic solvents.

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