AUSTRALIAN PRODUCT INFORMATION – PAMISOL™ (PAMIDRONATE DISODIUM)

1. NAME OF THE MEDICINE

Pamidronate disodium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Pamisol 15 mg/5 mL and 30 mg/10 mL concentrated injection contains 3 mg pamidronate disodium.

Each mL of Pamisol 60 mg/10 mL concentrated injection contains 6 mg pamidronate disodium.

Each mL of Pamisol 90 mg/10 mL concentrated injection contains 9 mg pamidronate disodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrated injection.

Pamisol is a clear, colourless, sterile solution. The pH of the solution is approximately 6.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of conditions associated with increased osteoclast activity:

- Predominantly lytic bone metastases from breast cancer and advanced multiple myeloma.
- Acute management of tumour induced hypercalcaemia (hypercalcaemia of malignancy).
- Treatment of symptomatic Paget's disease of bone.

4.2 Dose and method of administration

Dosage

Predominantly lytic bone metastases from breast cancer and advanced multiple myeloma

The recommended dose of pamidronate disodium for the treatment of predominantly lytic bone metastases from breast cancer and advanced 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 on a 3-weekly schedule.

The infusion rate should not exceed 60 mg/hour (1 mg/min) and the concentration of pamidronate disodium in the infusion solution should not exceed 90 mg/250 mL. In breast cancer patients, 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, it is recommended not to exceed a concentration of 90 mg in 500 mL administered over 4 hours.

Tumour induced hypercalcaemia

Rehydration with sodium chloride 0.9% before or during treatment is necessary.

Initial treatment: The total dose for a treatment course can be given as a single infusion. It can also be divided into 2 or 3 consecutive daily doses. The infusion rate should not exceed 60 mg/hour (1 milligram/min) and the concentration of pamidronate disodium in the infusion solution should not exceed 90 mg/250 mL. However, it is recommended not to exceed 90 mg in 500 mL over 4 hours.

The recommended total doses for each treatment course with pamidronate disodium are related to initial plasma calcium levels. A dosing guideline is shown in the table.

Table 1: Dosing Guidelines for Pamidronate Disodium

Initial Serum Calcium*		**Total Recommended Dose**
(millimoles/L)	**(mg%)**	**Pamidronate disodium (mg)**
Up to 3.0	Up to 12.0	30
3.0 to 3.5	12.0 to 14.0	30 to 60
3.5 to 4.0	14.0 to 16.0	60 to 90
>4.0	>16.0	90

* measured values not corrected for albumin.

Repeated treatment: If hypercalcaemia recurs, or if plasma calcium does not decrease within 2 days, further infusions of pamidronate disodium may be given according to the guidelines for initial treatment.

Clinical experience to date has revealed a possibility of a weaker therapeutic response in patients with advanced malignant disease and/or with increased number of treatments. Serum calcium levels in patients who have hypercalcaemia of malignancy may not reflect the severity of hypercalcaemia, since hypoalbuminaemia is commonly present.

The **maximum dose per treatment course** of pamidronate disodium is 90 mg whether for initial or repeat treatment. Higher doses bring no greater clinical benefit.

Paget's disease of bone

The recommended dose of pamidronate disodium in patients with symptomatic Paget's disease is a single infusion of 60 mg. The infusion rate should not exceed 15 to 30 mg/2 hours and the concentration of pamidronate disodium should not exceed 90 mg/L.

Re-treatment: When clinically indicated, patients should be re-treated at the dose of initial therapy.

Dosage adjustment

Renal impairment

Pamidronate disodium is not recommended for patients with severe renal impairment (see Section 4.4 Special warnings and precautions for use, Use in renal impairment).

In mild to moderate renal impairment, the maximum recommended pamidronate disodium infusion rate is 90 mg over 4 hours (approximately 20 – 22 mg/h).

Hepatic impairment

Dose reduction does not appear necessary in patients with mild to moderate hepatic impairment, however the data are limited (see Section 5.2 Pharmacokinetic properties). There are no data in patients with severe hepatic impairment. Until further experience is gained, a maximum infusion rate of 20 mg/hour pamidronate disodium is recommended in patients with mild to moderate hepatic impairment. Pamidronate disodium has not been studied in patients with severe hepatic impairment. No specific recommendation can be given for patients with severe hepatic impairment.

Method of administration

For intravenous use as infusion only.

Pamisol must never be given as a bolus injection since severe local reactions and thrombophlebitis may occur as a result of high local concentrations. Pamisol should be administered by slow infusion in 0.9% sodium chloride or 5% glucose. Regardless of the volume of solution in which Pamisol is diluted, slow intravenous infusion is absolutely necessary for safety.

Pamidronate disodium should be administered under the supervision of a physician with the right equipment for the monitoring of clinical and biochemical parameters.

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.

Pamisol contains no antimicrobial agent. The product is for single use only and any residue should be discarded after use. When the product was diluted to the following concentrations in PVC infusion bags, it was found to be chemically stable with 0.9% NaCl and 5% glucose infusion solutions for the periods shown in the following table:

Table 2: Storage Conditions and Stability Periods for Pamisol Diluted with 0.9% Sodium Chloride and 5% Glucose Infusion Solutions

Infusion Solution	Concentration (mg/mL)	Storage Condition	Stability Period (hours)
0.9% NaCl	0.06 to 0.36	25°C in the presence of light	24
0.9% NaCl	0.06 to 0.36	2 to 8°C in dark	24
5% Glucose	0.06 to 0.36	25°C in the presence of light	24
5% Glucose	0.06 to 0.36	2 to 8°C in dark	24

To reduce microbiological hazard, the diluted solution should be used immediately and any residue remaining discarded. If the diluted product cannot be used immediately or as soon as practicable after preparation, store between 2° to 8°C for not more than 24 hours.

In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

Monitoring recommendation

Serum creatinine should be measured **prior to each dose** of pamidronate disodium.

Patients receiving pamidronate disodium for bone metastases, multiple myeloma or for tumour-induced hypercalcaemia who show evidence of deterioration in renal function, treatment should be withheld until serum creatinine returns to within 10% of the baseline value unless treatment is required immediately for life-threatening hypercalcaemia. Deterioration of renal function is defined as follows:

- For patients with normal baseline serum creatinine, an increase of >45 micromol/L.
- For patients with abnormal baseline serum creatinine, an increase of >90 micromol/L.

Patients receiving frequent infusions of pamidronate disodium 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 evaluations of standard clinical and laboratory parameters of renal function prior to each dose. Fluid balance (urine output, daily weights) should also be followed carefully. The infusion must be stopped if there is deterioration of renal function during pamidronate disodium therapy.

In the initial treatment of tumour induced hypercalcaemia, it is essential that intravenous rehydration be instituted to restore urine output. Patients should be hydrated adequately throughout treatment, but overhydration must be avoided.

Standard hypercalcemia-related metabolic parameters, including serum electrolytes, calcium and phosphate should be monitored after commencing pamidronate disodium. Patients who have undergone thyroid surgery may be particularly susceptible to develop 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). Therefore, overhydration should be avoided especially in patients at risk of cardiac failure. Fever (influenza-like symptoms) may also contribute to this deterioration. Patients with anaemia, leukopenia or thrombocytopenia should have regular haematology assessments. Individual data revealed significant decreases in white cell and platelet counts in several patients. Haematological testing should be carried out if clinically indicated.

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.

4.3 Contraindications

Pamisol is contraindicated in:

- patients with known hypersensitivity to pamidronate disodium or other bisphosphonates, or to any of the other ingredients listed in Section 6.1 List of excipients.
- pregnancy.
- lactation.

4.4 Special warnings and precautions for use

The safety and efficacy of pamidronate disodium in the treatment of hyperparathyroidism has not been established.

The onset of action of pamidronate disodium is not immediate. Therefore, pamidronate disodium should be considered as only one component of the acute clinical management of tumour induced hypercalcaemia.

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

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with bisphosphonates including pamidronate disodium. Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis. Presentation may include jaw pain, toothache, exposed bone, altered sensation and local infection, including osteomyelitis. The condition may result in chronic pain, may be resistant to treatment, and in serious cases may result in disfigurement.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma, and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates. Patients and their dentists should be advised of the reports of osteonecrosis of the jaw so that dental symptoms developing during treatment can be fully assessed before commencing dental procedures.

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 not 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 patients based on individual benefit/risk assessment.

Osteonecrosis of external auditory canal

Cases of osteonecrosis of the external auditory canal have been reported predominantly in adult cancer patients treated with bisphosphonates including pamidronate disodium.

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.

Osteonecrosis of other anatomical sites

Cases of osteonecrosis of other anatomical sites including the hip and femur. have been reported predominantly in adult cancer patients treated with bisphosphonates including pamidronate disodium.

Atypical femur fracture

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Musculoskeletal pain

In post-marketing experience, severe and occasionally in capacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports have been infrequent. 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. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Use in renal impairment

Bisphosphonates including pamidronate disodium have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Pamidronate disodium is excreted intact primarily vial the kidney and therefore, the risk of renal adverse reactions may be greater in patients with impaired renal function. Renal deterioration, progression to renal failure and dialysis has 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. However, underlying disease progression and/or concomitant complications were also present and therefore a causal relationship with pamidronate disodium is unproven

Pamidronate disodium should not be administered to patients with severe renal impairment (creatinine clearance <30 mL/min) except in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. Although pamidronate disodium is excreted unchanged by the kidneys (see section 5.2 Pharmacokinetic properties, Special population, renal impairment), 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 haemodialysis and peritoneal dialysis). However, experience with pamidronate disodium in patients with severe renal impairment (serum creatinine: >440 micromoles/L, or 5 mg/dL in TIH patients; >180 micromoles/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.

Although a pharmacokinetic study conducted in patients with cancer and normal or impaired renal function (see Section 5.2 Pharmacokinetic properties) indicates that a dose reduction may not be necessary in patients with mild (creatinine clearance 61 – 90 mL/min) to moderate (creatinine clearance 30-60 mL/min) renal impairment, there are insufficient clinical data on the use of pamidronate disodium in such patients to support this recommendation (see Section 4.2 Dose and method of administration).

Use in hepatic impairment

As there are no clinical data available in patients with severe hepatic impairment, no specific recommendations can be given for this patient population but caution should be exercised when pamidronate disodium is given to these patients (see Section 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Use in the elderly

No data available. For elderly patients with cardiac disease, refer to Section 4.2 Dosage and method of administration, Monitoring recommendations.

Pediatric use

There is limited clinical experience to date in children. Pamidronate disodium should not be given to children unless other measures have either failed to control life-threatening hypercalcaemia or are deemed inappropriate. Until further experience is gained, pamidronate disodium is only recommended for use in adult patients.

Effects on laboratory tests

Since pamidronate disodium binds to bone it can interfere with bone scintigraphy examinations.

4.5 Interactions with other medicines and other forms of interactions

Pamidronate disodium has been used concomitantly with commonly used antitumour drugs (including aminoglutethimide, cisplatin, corticosteroids, cyclophosphamide, cytarabine, doxorubicin, etoposide, fluorouracil, megoestrol, melphalan, methotrexate, mitoxantrone, paclitaxel, tamoxifen, vinblastine and vincristine) without significant interactions.

Pamidronate disodium should not be used concomitantly with other bisphosphonates. Significant hypocalcaemia may result if other calcium lowering agents are used in conjunction with pamidronate disodium.

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

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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility and general reproductive performance were not affected by oral pamidronate disodium doses (to 150 mg/kg/day) although prolonged and abnormal parturition was seen, there were no such studies with intravenous administration.

Use in pregnancy – Category B3

Pamisol should not be used during pregnancy (see Section 4.3 Contraindications).

Pamidronate disodium has been shown to cross the placenta and has produced marked maternal and non-teratogenic embryo/fetal effects in rats and rabbits. It accumulates in fetal bone in a manner similar to that observed in adult animals. Pamidronate disodium has been shown to increase the length of gestation and parturition in rats resulting in increasing pup mortality when given orally at daily doses of 60 mg/kg and above (0.7 times the highest recommended human dose for a single intravenous infusion). In pregnant rats, high doses of intravenous pamidronate disodium (12 and 15 mg/kg/day) were associated with maternal toxicity and fetal developmental abnormalities (fetal oedema and shortened bones) and doses of 6 mg/kg and above with reduced ossification. Lower intravenous pamidronate disodium doses (1 to 6 mg/kg/day) interfered (prepartum distress and fetotoxicity) with normal parturition in the rat, and this may be associated with maternal hypocalcaemia.

Only low intravenous doses have been investigated in pregnant rabbits, because of maternal toxicity, and the highest dose used (1.5 mg/kg/day) was associated with an increased resorption rate and reduced ossification.

It is not known if pamidronate disodium crosses the human placenta. 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 disodium should not be used during pregnancy (see Section 4.3 Contraindications).

Women of child-bearing potential must use highly effective contraception during treatment.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are very limited data on

fetal risk in humans, bisphosphonates do cause fetal harm in animals. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

Use in lactation

Pamisol should not be used in lactating women (see Section 4.3 Contraindications).

There is no clinical experience with pamidronate disodium in lactating women. It is not known if pamidronate disodium and/or its metabolites pass into human milk. A study in lactating rats has shown that pamidronate disodium will pass into the milk. Therefore, mothers taking pamidronate disodium should not breastfeed (see Section 4.3 Contraindications)

4.7 Effects on ability to drive and use machines

Patients should be warned that somnolence and/or dizziness may occur following pamidronate disodium infusion, in which case the patient should not drive, operate potentially dangerous machinery or engage in other activities that may be hazardous. This effect rarely lasts more than 24 hours. Outpatients who have received a pamidronate disodium infusion should not drive themselves home.

4.8 Adverse effects (undesirable effects)

Adverse reactions with pamidronate disodium are usually mild and transient. The most common adverse reactions are asymptomatic hypocalcaemia, influenza like symptoms, joint swelling and mild fever (an increase in body temperature of >1^{o}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. Symptomatic hypocalcaemia is uncommon. Local soft tissue inflammation at the infusion site also occurs, especially at the highest dose (90 mg).

The frequency estimate for the adverse reactions below is as follows:

Very common: (>1/10), common: (>1/100 and <1/10), uncommon: (>1/1000, <1/100), rare: (>1/10,000, <1/1000) and very rare: (<1/10,000), including isolated reports.

Metabolism and nutrition disorders

Very common: Hypocalcaemia, hypophosphataemia.

Common: Hypomagnesaemia, hypokalaemia, tetany, anorexia.

*Very rare***:** Hperkalaemia, hypernatraemia.

Investigations

Common: Increase in serum creatinine.

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

Blood and lymphatic system disorders

Common: Anaemia, lymphocytopenia, thrombocytopenia, leucopenia.

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

Cardiac disorders

Common: Atrial fibrillation.

Very rare: Left ventricular failure (manifestation includes dyspnoea, pulmonary oedema), congestive heart failure (includes oedema) due to fluid overload.

Vascular disorders

Common: Hypertension.

Uncommon: Hypotension.

Nervous system disorders

Common: Headache, symptomatic paraesthesia, somnolence.

Uncommon: Lethargy, seizures, dizziness.

Psychiatric disorders

Very rare: Confusion, visual hallucinations, agitation, insomnia.

Gastrointestinal disorders

Common: Nausea, vomiting, abdominal pain, diarrhoea, constipation, gastritis.

Uncommon: Dyspepsia.

General disorders and administration site conditions

Very common: Fever and influenza like symptoms sometimes accompanied by malaise, chills, fatigue and flushes.

Common: Reactions at the infusion site includes pain, redness, swelling, induration, phlebitis, thrombophlebitis.

Immune system disorders

Uncommon: Hypersensitivity, anaphylactic reactions, bronchospasm, dyspnoea.

Very rare: Anaphylactic shock.

Infection and infestations

Very rare: Reactivation of herpes simplex and herpes zoster.

Musculoskeletal and connective tissue disorders

Common: Transient bone pain, arthralgia, myalgia, generalised pain, skeletal pain.

Uncommon: Muscle cramps.

Renal and urinary disorders

Uncommon: Acute renal failure.

Rare: Focal segmental glomerulosclerosis including the collapsing variant nephrotic syndrome.

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

Skin and subcutaneous disorders

Common: Rash.

Uncommon: Pruritus, Quincke´s (angioneurotic) oedema.

Eye disorders

Common: Conjunctivitis.

Uncommon: Uveitis (includes iritis, iridocyclitis).

Very rare: Scleritis, episcleritis, xanthopsia, orbital inflammation.

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

Post marketing experience

The following adverse reactions have been reported during post-approval use of pamidronate disodium. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, thoracic and mediastinal disorders

Acute respiratory distress syndrome (ARDS), interstitial lung disease (ILD).

Musculoskeletal and connective tissue disorders

Osteonecrosis, severe and occasionally incapacitating bone, joint and/or muscle pain (infrequent cases reported).

Renal and urinary disorders

Renal tubular disorders (RTD), tubulointerstitial nephritis, and glomerulonephropathies.

Eye disorders

Optic neuritis.

Nervous system disorders

Pseudotumor cerebri.

Ear and labyrinth disorders

Osteonecrosis of external auditory canal (bisphosphonate class adverse reaction).

Injury, Poisoning and Procedural Complications

Atypical femur fracture (atypical subtrochanteric and diaphyseal femoral fractures) are bisphosphonate class adverse reactions.

Description of selected adverse effects

Atrial fibrillation

Isolated instances of higher incidence of atrial fibrillation have been reported in a few studies with some bisphosphonates. The mechanism of this increased incidence of atrial fibrillation in isolated studies within these bisphosphonates is unknown.

Osteonecrosis of the jaw

Cases of osteonecrosis (primarily of the jaws) but also of other anatomical sites including the hip, femur and external auditory canal, have been reported predominantly in cancer patients treated with bisphosphonates, including pamidronate disodium (uncommon). Many of these patients had signs of local infection including osteomyelitis and 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, anti-angiogenic drugs, corticosteroids) and co-morbid conditions (e.g., anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4 Special warnings and precautions for use). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

Tumour induced hypercalcaemia and Paget's disease

Deterioration of renal function has been noted in patients treated with bisphosphonates. Since many patients with tumour induced hypercalcaemia have compromised renal function prior to receiving antihypercalcaemia therapy (see Section 4.4 Special warnings and precautions for use), it is difficult to estimate the role of individual in 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. The role of pamidronate disodium in these changes in renal function is unclear, but merits cautious observation.

Bone metastases and multiple myeloma

Deterioration of renal function (including renal failure) has been reported following long term treatment with pamidronate disodium in patients with multiple myeloma. However, underlying disease progression and/or concomitant complications were also present and therefore a causal relationship with pamidronate disodium is unproven.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and symptoms

Overdosage with pamidronate disodium would be likely to result in symptoms of hypocalcaemia, such as paraesthesia, tetany and hypotension.

Treatment

Patients who have received doses of pamidronate disodium 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. Acute hypocalcaemia is not expected to occur with pamidronate disodium since plasma calcium levels fall progressively for several days after treatment.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Pamidronate disodium is a potent inhibitor of osteoclastic bone resorption. This antiresorptive activity is responsible for its therapeutic effect.

Pamidronate disodium inhibits the formation and dissolution of calcium apatite crystals *in vitro*. The physicochemical interaction of pamidronate disodium with apatite crystals accounts for its avid binding to bone, but the mechanism for the anti-osteoclastic activity at the cellular level is unknown at present.

Pamidronate disodium 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*.

Changes in biochemical parameters which reflect a decrease in bone resorption and improvements secondary to normalisation of plasma calcium include decreased urinary hydroxyproline, urinary calcium and serum phosphate.

Hypercalcaemia can lead to haemoconcentration by inhibition of tubular reabsorption of water, and to decreased GFR, both of which lead to increased plasma creatinine concentration. A direct consequence of treatment with pamidronate disodium is improvement in GFR and decreased creatinine levels in most patients.

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 disodium. 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.

Clinical trials

Three randomised, double blind, placebo controlled trials investigated the effects of pamidronate disodium on the occurrence of skeletal related events (SREs: pathological fractures, radiation therapy or surgery to bone, spinal cord compression) and pain score in patients with multiple myeloma and in breast cancer patients with predominantly lytic bone metastases.

In the first trial, patients with advanced multiple myeloma received 90 mg of pamidronate disodium or placebo as a monthly 4 hour intravenous infusion for 9 months in addition to antimyeloma therapy. Patients had received appropriate chemotherapy for a minimum 2 months prior to entry into the trial. A total of 196 pamidronate disodium patients and 181 placebo patients were evaluable for efficacy. Compared with placebo, significantly fewer patients in the pamidronate disodium group had any SRE (24% vs 41%, $p<0.001$) and the mean skeletal morbidity rate was lower (1.1 vs 2.1 SREs/year, $p<0.02$). The times to first SRE, pathological fracture and radiation therapy to bone were significantly longer in the pamidronate disodium group ($p=0.001$, 0.006, and 0.046, respectively). Fewer pamidronate disodium patients suffered any pathological fracture (17% vs 30%, $p=0.004$) or needed radiation therapy to bone (14% vs 22%, $p=0.049$). In patients with pain at baseline, pain scores at the last assessment were significantly reduced with pamidronate disodium treatment ($p<0.05$) but not with placebo.

Patients completing the first part of the trial continued to receive 4-weekly infusions of pamidronate disodium or placebo for a further 11 infusions during the maintenance phase of the trial (observation period). After 21 months, the proportion of patients with any SRE was significantly less in the pamidronate disodium group than in the placebo group ($p=0.015$), the mean skeletal morbidity rate was lower ($p=0.008$) and the time to first SRE was longer ($p=0.016$). There was an increased incidence of renal toxicity observed in patients receiving pamidronate disodium during the observation period of the trial, although this was not statistically significantly different from the placebo group (see Section 4.4 Special warnings and precautions for use).

In the second and third trials, breast cancer patients with at least one predominantly osteolytic bone metastasis received 90 mg of pamidronate disodium or placebo as a 2 hour intravenous infusion every 3 or 4 weeks for 12 months.

Breast cancer patients in the second trial were treated with cytotoxic chemotherapy. A total of 185 pamidronate disodium patients and 195 placebo patients were evaluable for efficacy. Compared with placebo, significantly fewer patients in the pamidronate disodium group had any SRE (43% vs 56%, $p<0.01$), the mean skeletal morbidity rate was lower (2.5 vs 3.3 SREs/year, $p<0.01$) and the time to first SRE was longer (median 13.1 vs 7.0 months, $p<0.01$). Fewer patients in the pamidronate disodium group than the placebo group needed radiation therapy to bone, the mean skeletal morbidity rate for radiation therapy to bone was lower and the time to first radiation therapy was longer ($p<0.01$ for each). The complete plus partial response rate for bone lesions was 33% in pamidronate disodium patients and 18% in placebo patients ($p=0.001$).

Breast cancer patients in the third trial were treated with hormonal therapy at trial entry. A total of 182 pamidronate disodium patients and 189 placebo patients were evaluable for efficacy. The mean skeletal morbidity rate for radiation therapy to bone was lower with pamidronate disodium treatment than with placebo (0.6 vs 1.1 SREs/year, $p<0.01$) and the time to first

radiation therapy was longer ($p<0.01$; median time not reached during the trial). The proportion of patients having any radiation to bone was lower with pamidronate disodium treatment than with placebo (21% vs 33% at 12 months, $p<0.01$). There was no statistically significant difference in the proportion of patients with any SRE, in the skeletal morbidity rate for any SRE, in the time to first SRE and in the bone lesion response rate.

In both trials, pain scores (mean change from baseline at last measurement) showed that breast cancer patients treated with pamidronate disodium had significantly less pain than patients treated with placebo ($p<0.05$ for chemotherapy patients, $p<0.01$ for hormonal therapy patients).

5.2 Pharmacokinetic properties

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 intravenous 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 hours. Apparent steady state concentrations are therefore achieved with infusions of more than about 2 to 3 hours duration. Peak plasma concentrations of about 10 nanomoles/mL pamidronate disodium 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 disodium in bone is not capacity limited, and is dependent solely on the cumulative dose administered. Clinicians should be aware that some 50% of the infused material will remain in the patient's skeleton for years.

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

Excretion

Pamidronate disodium does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20 to 55% of the dose is recovered in the urine within 72 hours as unchanged pamidronate disodium. 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 to 180 mg) and the infusion rate (range 1.25 to 60 mg/hour). The elimination of pamidronate disodium in the urine is biexponential, with apparent half lives of about 1.6 and 27 hours. The apparent renal clearance is about 54 mL/min, and there is a tendency for the renal clearance to correlate with creatinine clearance.

Special Population

Hepatic impairment

Hepatic and metabolic clearance of pamidronate disodium are insignificant. Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate disodium. Pamidronate disodium, thus, displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see Section 4.5 Interactions with other medicines and other forms of interactions).

Renal impairment

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 disodium , therefore, is similar in patients with and without impaired renal function. Although this suggests that a dose reduction may not be necessary in patients with impaired renal function, there is insufficient clinical data on the use of pamidronate disodium in such patients to support this recommendation (see section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

The toxicity of pamidronate disodium is characterised by direct (cytotoxic) effects on organs with a copious blood supply, such as the stomach, lungs and kidneys. In animal studies with intravenous administration, renal tubular lesions were the prominent and consistent untoward effects of treatment.

Studies conducted in young rats have reported the disruption of dental dentine formation following single and multiple dose administration of bisphosphonates. The clinical significance of these findings is unknown.

Genotoxicity

Pamidronate disodium showed no genotoxic activity in a standard battery of assays for gene mutations and chromosomal damage.

Carcinogenicity

There is a lack of long term toxicology data from animal studies with intravenous administration. In a 104 week carcinogenicity study of daily oral administration to rats, there was a positive dose response relationship for benign phaeochromocytoma in male animals.

Although this condition was also observed in female animals, the incidence was not statistically significant. When the dosage calculations were adjusted to account for the limited oral bioavailability of pamidronate disodium in rats, the lowest daily dose associated with adrenal phaeochromocytoma was similar to the intended clinical dose in humans. In a second rat carcinogenicity study, adrenal phaeochromocytomas were not reported at doses similar to the intended clinical dose in humans. Pamidronate disodium by daily oral administration was not carcinogenic in an 80 week or a 104 week study in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Phosphoric acid and/or sodium hydroxide (for pH adjustment)

Water for Injections.

6.2 Incompatibilities

Pamisol should not be added to intravenous infusion fluids containing calcium, such as Ringer's solution and Hartmann's solution.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Undiluted

Store below 25°C.

After dilution

Following dilution in 0.9% sodium chloride and 5% glucose infusion solutions, chemical and physical in-use stability has been demonstrated for 24 hours, stored below 25°C.

From a microbiological viewpoint, the diluted solution should be used immediately and any residue remaining discarded. If the diluted product is not used immediately or as soon as practicable after preparation, store between 2° to 8°C for not more than 24 hours.

See Section 4.2 Dose and method of administration, Method of administration.

6.5 Nature and contents of container

Pamisol 15 mg/5 mL is supplied in clear glass vials in packs of 1 or 5 vials per pack.

Pamisol 30 mg/10 mL is supplied in clear glass vials in packs of 1 vial per pack.

Pamisol 60 mg/10 mL is supplied in clear glass vials in packs of 1 vial per pack.

Pamisol 90 mg/10 mL is supplied in clear glass vials in packs of 1 vial per pack.

* Not all presentations are supplied.

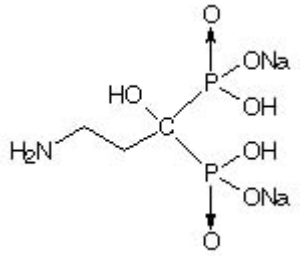
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Pamidronate disodium is a white crystalline powder that is soluble in water or 2N sodium hydroxide, poorly soluble in 0.1N hydrochloric acid and 0.1N acetic acid and virtually insoluble in organic solvents. The pH of a 1% solution in water is approximately 8.2.

Chemical structure



Chemical name: Disodium-3-amino-1-hydroxypropylidene-1,1-biphosphonate.

Molecular formula: $C_3H_9NO_7P_2Na_2$.

Molecular weight: 279.03 (anhydrous).

CAS number

57248-88-1.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000.

Toll Free Number: 1800 675 229.
www.pfizer.com.au.

9. DATE OF FIRST APPROVAL

01 August 2000.

10. DATE OF REVISION

09 September 2021.

Summary Table of Changes

Section changed	Summary of new information
4.4	Minor editorial change. Cross reference correctd to Section 5.2