Pamidronate BNM

Disodium pamidronate 15 mg/5 mL, 30 mg/10 mL, 60 mg/10 mL and 90 mg/10 mL
Solution for infusion

Presentation(s)

Pamidronate BNM solution for infusion is a clear, colourless, sterile solution of disodium pamidronate, mannitol, phosphoric acid and sodium hydroxide in water for injection. Phosphoric acid is added to adjust the pH to 6.4-6.8.

The vials are uncoloured, type I glass vial with bromobutyl rubber stopper and flip-off cap.

Indications

Treatment of conditions associated with increased osteoclast activity:
- Predominantly lytic bone metastases from breast cancer and advanced multiple myeloma
- Tumour-induced hypercalcaemia. Acute management of tumour-induced hypercalcaemia (Hypercalcaemia of malignancy).


Dosage and administration

Pamidronate BNM must never be given as a bolus injection since severe local reactions and thrombophlebitis may occur as a result of high local concentrations.

Pamidronate BNM should always be diluted and administered by slow intravenous infusion in sodium chloride 0.9% or dextrose 5%.

Do not co-administer with other bisphosphonates. If other calcium lowering agents are used in conjunction with pamidronate, significant hypocalcaemia may result.

Pamidronate BNM should not be added to intravenous infusion fluids containing calcium.

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

**Dosage regimen**

Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of Pamidronate BNM should not exceed 90 mg and the recommended infusion time should be observed.

**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 Pamidronate BNM 90 mg may also be given on a 3-weekly schedule.

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. 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 normal saline 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/h (1 mg/min) and the concentration of Pamidronate BNM 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 are related to initial plasma calcium levels. A dosing guideline is shown in the table.

<table>
<thead>
<tr>
<th>Initial serum calcium (mmol/L)</th>
<th>Recommended total dose (mg)</th>
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<tbody>
<tr>
<td>up to 3.0</td>
<td>up to 12.0</td>
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<tr>
<td>3.0 - 3.5</td>
<td>12.0 - 14.0</td>
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<td>3.5 - 4.0</td>
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<td>&gt; 4.0</td>
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**Repeated treatment:**

If hypercalcaemia recurs, or if plasma calcium does not decrease within 2 days, further infusions of Pamidronate BNM 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.

The maximum dose per treatment course of Pamidronate BNM 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 BNM in patients with symptomatic Paget's disease is a single infusion of 60 mg. The infusion rate should not exceed 15 - 30 mg/2 hours and the concentration of Pamidronate BNM should not exceed 90 mg/L.

**Retreatment:**

When clinically indicated, patients should be retreated at the dose of initial therapy.

**Renal impairment**

Pamidronate BNM is not recommended for patients with severe renal impairment (see "Contraindications").

In mild to moderate renal impairment, the maximum recommended Pamidronate BNM 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 "Pharmacokinetics"). There are no data in patients with severe hepatic impairment. Until further experience is gained, a maximum infusion rate of 20 mg/h is recommended in patients with mild to moderate hepatic impairment. Pamidronate BNM has not been studied in patients with severe hepatic impairment. No specific recommendation can be given for patients with severe hepatic impairment.

**Patient monitoring**

Serum creatinine should be measured prior to each dose of Pamidronate BNM.

In patients receiving Pamidronate BNM for bone metastases, multiple myeloma or for tumour-induced hypercalcaemia who have a deterioration in renal function defined as:

- 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

Pamidronate BNM should be withheld until serum creatinine returns to within 10% of the baseline value, unless treatment is required immediately for life-threatening hypercalcaemia.

Serum electrolytes, calcium and phosphate should be monitored after commencing Pamidronate BNM.

Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

Patients receiving frequent infusions of Pamidronate BNM 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.

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.

Individual data revealed significant decreases in white cell and platelet counts in several patients. Haematological testing should be carried out if clinically indicated.

**Contraindications**

- Known hypersensitivity to pamidronate or to other bisphosphonates, or to any of the other ingredients in the formulation of Pamidronate BNM
- Renal impairment (refer to Warnings and precautions)
- Pre-existing hypocalcaemia (see Dosage and administration, patient monitoring)
- Pregnancy
- Breastfeeding

**Warnings and precautions**

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

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

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

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

**Use in patients with renal impairment:**

Bisphosphonates, including pamidronate, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Pamidronate is excreted intact primarily via 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 have been reported in patients after the initial dose or a single dose of pamidronate. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with pamidronate in patients with multiple myeloma.

Pamidronate BNM 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 a pharmacokinetic study conducted in patients with cancer and normal or impaired renal function (see "Pharmacokinetics – Renal impairment") 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 in such patients to support this recommendation (see "Dosage and administration").

Very little information has been gathered on the use of pamidronate in patients receiving haemodialysis.

**Osteonecrosis of the jaw:**

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with bisphosphonates, including pamidronate. 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 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.

**Musculoskeletal pain:**

In post-marketing experience, severe and occasionally incapacitating 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 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.

**Atypical fractures of the femur:**

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.

**Use in pregnancy (Category B3)**

Pamidronate 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 has been shown to increase the length of gestation and parturition in rats resulting in an 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 (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 doses (1-6 mg/kg/day) interfered (pre-partum 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 BNM 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 BNM in pregnant women. Therefore, Pamidronate BNM should not be used during pregnancy (see “Contraindications”).

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**

There is no clinical experience in lactating women and it is unknown if pamidronate and/or its metabolites pass into human milk. A study in lactating rats has shown that pamidronate will pass into the milk. Therefore, mothers taking Pamidronate BNM should not breastfeed (see “Contraindications”).

**Effects on ability to drive and use machinery:**

Patients should be warned that somnolence and/or dizziness may occur following pamidronate 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 infusion should not drive themselves home.

**Other**

*Use in children*

There is limited clinical experience to date in children. Pamidronate BNM 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 BNM is only recommended for use in adult patients.

**Preclinical safety data:**

The toxicity of pamidronate 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.

*Carcinogenesis, mutagenesis and impairment of fertility:*

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.

The compound is not mutagenic and does not appear to have carcinogenic potential.

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 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 by daily oral administration was not carcinogenic in either a 80-week or a 104-week study in mice.

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

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

**Adverse effects**

Adverse reactions to Pamidronate BNM are usually not sufficient to require intervention. The most common adverse reactions are asymptomatic hypocalcaemia and pyrexia (an increase in body temperature >1°C, which may last for 48 hours). Pyrexia usually resolves spontaneously and does not require treatment. 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 (≥ 10%), common (< 10% but ≥ 1%), uncommon (< 1% but ≥ 0.1%), rare (< 0.1% but ≥ 0.01%), very rare (< 0.01%), including isolated reports.

**Metabolism and nutrition disorders:**
Very common: hypocalcaemia, hypophosphataemia
Common: hypokalaemia, hypomagnesaemia,
Very rare: hyperkalaemia, hypernatraemia

**Investigations:**
Common: increase in serum creatinine
Uncommon: abnormal liver function tests, increase in serum urea

**Blood and lymphatic system disorders:**
Common: anaemia, thrombocytopenia, lymphocytopenia
Very rare: leukopenia

**Vascular disorders:**
Very rare: left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload

**Cardiac disorders:**
Common: hypertension
Uncommon: hypotension

**Nervous system disorders:**
Common: headache, symptomatic hypocalcemia (paraesthesia, tetany), insomnia, somnolence
Uncommon: seizures, agitation, dizziness, lethargy
Very rare: confusion, visual hallucinations

**Gastrointestinal disorders:**
Common: nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, gastritis
Uncommon: dyspepsia

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

**Immune system disorders:**
Uncommon: allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke's (angioneurotic) oedema
Very rare: anaphylactic shock
**Infections and infestations:**
Very rare: reactivation of Herpes simplex, reactivation of Herpes zoster

**Musculoskeletal and connective tissue disorders:**
Common: transient bone pain, arthralgia, myalgia, generalised pain
Uncommon: muscle cramps

**Renal and urinary disorders:**
Uncommon: acute renal failure
Rare: focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome
Very rare: deterioration of pre-existing renal disease, haematuria

**Skin and subcutaneous disorders:**
Common: rash
Uncommon: pruritus

**Eye disorders:**
Common: conjunctivitis
Uncommon: uveitis (iritis, iridocyclitis)
Very rare: scleritis, episcleritis, xanthopsia

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

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

**Post-marketing experience**

The following adverse reactions have been reported during post-approval use of pamidronate. 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.

Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with bisphosphonates, including pamidronate (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, 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 “Precautions”). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

Rare cases of atypical subtrochanteric and diaphyseal femoral fractures have been reported (bisphosphonate class adverse reaction).

Very rare cases of orbital inflammation events have been reported.
Interactions

Pamidronate has been used concomitantly with commonly used anti-tumour drugs without interactions.

Pamidronate should not be used concomitantly with other bisphosphonates.

Pamidronate 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 BNM is used with other potentially nephrotoxic drugs.

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

Interference with laboratory tests:
Since pamidronate binds to bone it can interfere with bone scintigraphy examinations.

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.

Further information

Actions

Pharmacotherapeutic category: Drugs affecting bone structure and mineralization (Bisphosphonates)  ATC code – M05BA03

Pamidronate is a potent inhibitor of osteoclastic bone resorption. This anti-resorptive activity is responsible for its therapeutic effect.

Pamidronate inhibits the formation and dissolution of calcium apatite crystals in vitro. The physico-chemical interaction of pamidronate 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 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. The onset of action of pamidronate is not immediate.
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 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. 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 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. 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 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).

**Renal impairment:**

A pharmacokinetic study conducted in 19 patients with cancer showed no differences in plasma AUC of pamidronate between patients with normal renal function and patients with mild (creatinine clearance 61-90 mL/min) to moderate (creatinine clearance 30-60 mL/min) renal impairment, following administration of a single 90 mg intravenous dose.

In patients with severe renal impairment (creatinine clearance < 30 mL/min), the AUC of pamidronate was approximately 3 times higher than in patients with normal renal function (creatinine clearance > 90 mL/min) [see "Precautions" and "Dosage and administration"].

**Hepatic impairment:**

A single 90 mg dose of pamidronate was infused intravenously over 4 hours in male cancer patients at risk of bone metastases (n = 14), some of whom (n= 8) had mild to moderate hepatic impairment (AST ≤ 86 u/L and/or ALT ≤ 60 u/L). There was an average 60% increase in AUC_{0-36h} and C_{max} and the drug was cleared more slowly from plasma (within 36 hours versus within 12 hours) in patients with hepatic impairment compared with other patients. The increase in AUC was statistically significant (p = 0.02). It was not determined if the percentage of the dose retained in the body is increased in hepatic impairment. Patients with hepatic impairment did not experience an increased incidence of adverse events over the limited observation period of the study (6 days). If pamidronate is administered monthly, the pharmacokinetic changes in mild to moderate hepatic impairment are unlikely to be clinically relevant (see "Dosage and administration").

**Other**

**Clinical trials**

Clinical trials in patients with advanced multiple myeloma or predominantly lytic bone metastases from breast cancer:

Three randomised, double-blind, placebo-controlled trials investigated the effects of pamidronate 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 or placebo as a monthly 4-hour intravenous infusion for 9 months, in addition to antmyeloma therapy. Patients had received appropriate chemotherapy for a minimum 2 months prior to entry into the trial. A total of 196 pamidronate patients and 181 placebo patients were evaluable for efficacy. Compared with placebo, significantly fewer patients in the pamidronate 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
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pamidronate group (P = 0.001, 0.006, and 0.046, respectively). Fewer pamidronate 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 treatment (P < 0.05) but not with placebo.

Patients completing the first part of the trial continued to receive 4-weekly infusions of pamidronate 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 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 during the observation period of the trial, although this was not statistically significantly different from the placebo group (see "Dosage and administration").

In the second and third trials, breast cancer patients with at least one predominantly osteolytic bone metastasis received 90 mg of pamidronate 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 patients and 195 placebo patients were evaluable for efficacy. Compared with placebo, significantly fewer patients in the pamidronate 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 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 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 patients and 189 placebo patients were evaluable for efficacy. The mean skeletal morbidity rate for radiation therapy to bone was lower with pamidronate 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 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 had significantly less pain than patients treated with placebo (P < 0.05 for chemotherapy patients, P < 0.01 for hormonal therapy patients).
Chemical structure

Molecular formula: C₇H₉NNa₂O₇P₂
Molecular weight of anhydrous disodium pamidronate: 279
CAS Registry number: 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.

Active ingredient
Disodium pamidronate

Inactive ingredients
Mannitol
Phosphoric acid
Sodium hydroxide
Water for injections

Pharmaceutical precautions

Instructions for handling
Concentrated solution of Pamidronate BNM in vials should be diluted in a calcium-free infusion solution (e.g. 0.9 % sodium chloride or 5 % dextrose) and infused slowly.

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

Shelf life
24 months

Once diluted, the injection solution must be used within 8 hours since physical and chemical stability has been demonstrated for this time frame at below 25°C. However from a microbiological point of view, it should be used immediately. If not, in use storage times and conditions are the responsibility of the user.
Pamidronate BNM

Special precautions for storage
Store below 25°C.

Package quantities

Pamidronate BNM 15 mg/5 mL solution for infusion
One 5 mL vial contains 15 mg disodium pamidronate 4 x 5 mL vials

Pamidronate BNM 30 mg/10 mL solution or infusion
One 10 mL vial contains 30 mg disodium pamidronate 1 x 10 mL vial

Pamidronate BNM 60 mg/10 mL solution for infusion
One 10 mL vial contains 60 mg disodium pamidronate 1 x 10 mL vial

Pamidronate BNM 90 mg/10 mL solution for infusion
One 10 mL vial contains 90 mg disodium pamidronate 1 x 10 mL vial

Medicine schedule

Prescription Only Medicine

Sponsor details

Boucher & Muir (New Zealand) Ltd, trading as BNM Group
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