

AFT-Pamidronate

Pamidronate disodium powder for Intravenous Infusion 30mg, 60mg and 90mg

Presentation

AFT-Pamidronate 30 mg is a white to practically white lyophilised powder which when reconstituted with 10mL water for injection results in a clear, colourless solution containing 3 mg/mL Pamidronate disodium.

AFT-Pamidronate 60 mg is a white to practically white lyophilised powder which when reconstituted with 10mL water for injection results in a clear, colourless solution containing 6 mg/mL Pamidronate disodium.

AFT-Pamidronate 90 mg is a white to practically white lyophilised powder which when reconstituted with 10mL water for injection results in a clear, colourless solution containing 9 mg/mL Pamidronate disodium.

Uses

Actions

Pamidronate disodium, the active substance of AFT-Pamidronate, 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 AFT-Pamidronate 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

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".

Pamidronate disodium is given by intravenous infusion. By definition, absorption is complete at the end of the infusion.

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.

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.

Hepatic and metabolic clearance of pamidronate is 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

AFT-Pamidronate must never be given as a bolus injection (see Warnings and Precautions). Each vial is for single use only. AFT-Pamidronate powder should be

completely dissolved in 10 ml water for injection before the reconstituted solution is withdrawn from the vial for dilution. AFT-Pamidronate 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 of 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 AFT-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 AFT-Pamidronate 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 AFT-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	> 16.0	90

The total dose of AFT-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 AFT-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 AFT-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, other bisphosphonates or mannitol.

Warnings and Precautions

AFT-Pamidronate should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see Dosage and Administration).

AFT-Pamidronate should not be given with other bisphosphonates because their combined effects have not been investigated.

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy with AFT-Pamidronate. 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 preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors. 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.

Use during Pregnancy and Lactation

Category B3

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. Pamidronate has been shown to increase the length of gestation and parturition in rats, resulting in an increasing pup mortality when given orally at doses of 60 mg/kg and above (0.7 times the highest recommended human dose for a single intravenous infusion). There was no unequivocal evidence for teratogenicity in studies with I.V. administration of pamidronate to pregnant rats although high doses (12 and 15 mg/kg/day) were associated with maternal toxicity and foetal developmental abnormalities (foetal oedema and shortened bones) and doses of 6 mg/kg and above with reduced ossification. Lower I.V. 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 I.V. doses have been investigated in rabbits, and the highest dose used (1.5 mg/kg/day) was associated with an increased resorption rate and reduced ossification. There was no evidence of teratogenicity.

It is not known if pamidronate crosses the human placenta. AFT-Pamidronate should not be given to pregnant women unless life-threatening hypercalcaemia cannot be controlled by other means.

There is no clinical experience in lactating women and it is unknown if pamidronate or its metabolites pass into human milk. However a study in lactating rats has shown that pamidronate will pass into the milk. Therefore for safety reasons mothers taking AFT-Pamidronate should not breast-feed their infants.

Use in Children

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

Effects on ability to drive and use machines

Patients should be warned that in rare cases somnolence and/or dizziness may occur following AFT-Pamidronate 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.

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.

Local soft-tissue inflammation at the infusion site also occurs especially at the highest dose (90 mg).

Frequency estimate for the reactions below is as follows:

Very common: > 10%,

Common: > 1 and < 10%,
Uncommon: > 0.1% and < 1%,
Rare: > 0.01% and < 0.1%
Very rare: < 0.01%.

Biochemical changes

Very common: hypocalcaemia, hypophosphataemia
Common: hypokalaemia, hypomagnesaemia, increase in serum creatinine
Uncommon: abnormal liver function tests, increase in serum urea
Very rare: hyperkalaemia, hypernatraemia

Blood

Common: anaemia, thrombocytopenia, lymphocytopenia
Very rare: leukopenia

Cardiovascular

Common: hypertension
Uncommon: hypotension
Very rare: left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload

Central nervous system

Common: symptomatic hypocalcaemia (paraesthesia, tetany), headache, insomnia, somnolence
Uncommon: seizures, agitation, dizziness, lethargy
Very rare: confusion, visual hallucinations

Gastrointestinal

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, fatigue and flushes
Common: reactions at the infusion site (pain, swelling, induration, phlebitis, thrombophlebitis)

Immune system

Uncommon: allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke's (angioneurotic) oedema
Very rare: anaphylactic shock

Infection

Very rare: reactivation of herpes simplex, reactivation of Herpes zoster

Musculoskeletal

Common: transient bone pain, arthralgia, myalgia, generalised pain
Uncommon: muscle cramps

Renal

Uncommon: acute renal failure
Rare: focal segmental glomerulosclerosis including the collapsing variant, nephrotic

syndrome

Very rare: deterioration of pre-existing renal disease, haematuria

Skin

Common: rash

Uncommon: pruritus

Special senses

Common: conjunctivitis

Uncommon: uveitis (iritis, iridocyclitis)

Very rare: scleritis, episcleritis, xanthopsia

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

Postmarketing very rare cases of osteonecrosis (primarily of the jaw) have been reported in patients treated with bisphosphonates. Many had signs of local infection including osteomyelitis. The majority of the reports related to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw 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 (see Warnings and Precautions)

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.

Pamidronate should not be used concomitantly with other bisphosphonates.

Care should be taken when pamidronate is used with other potentially nephrotoxic drugs.

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

Because 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.

Pharmaceutical Precautions

Store below 25°C.

AFT-Pamidronate should be used immediately after reconstitution and dilution and any unused material discarded. If the reconstituted or diluted product cannot be used immediately it can be stored under refrigeration (2-8°C) for up to 24 hours.

AFT-Pamidronate should not be added to I.V. infusion solutions containing calcium.

Medicines Classification

Prescription Medicine

Package Quantities

AFT-Pamidronate is available in single vial packs containing:

30 mg disodium pamidronate per vial

60 mg disodium pamidronate per vial

90 mg disodium pamidronate per vial

Further Information

AFT-Pamidronate powder for IV infusion also contains mannitol and phosphoric acid.

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