Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Disodium Pamidronate 15mg/ml Concentrate for Solution for Infusion, 2ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml of concentrate contains 15mg disodium pamidronate. One ampoule of 2ml contains 30mg of disodium pamidronate.
Excipient with known effect
Each 2 ml ampoule contains 12 mg sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless solution, free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer or multiple myeloma
- Paget's disease of bone.

4.2 Posology and method of administration

Method of administration
Disodium pamidronate concentrate must never be given as a bolus injection (see Warnings). The concentrate of disodium pamidronate concentrate in ampoules should be diluted in a calcium-free infusion solution (0.9 % Sodium Chloride Intravenous Infusion B.P. is recommended) and infused slowly.

The infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of disodium pamidronate concentrate in the infusion solution should not exceed 90mg/250mL. A dose of 90mg should normally be administered as a 2-hour infusion in 250mL infusion solution. However, in patients with multiple myeloma and in patients with tumour-induced hypercalcaemia, it is recommended not to exceed 90mg in 500mL over 4 hours.

In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20mg/h (see also Renal Impairment). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

Until further experience is gained, disodium pamidronate concentrate is only recommended for use in adult patients.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Disodium Pamidronate on an individual patient basis, particularly after 5 or more years of use.
Posology
Tumour-induced hypercalcaemia

It is recommended that patients be rehydrated with 0.9% w/v sodium chloride solution before or during treatment.

The total dose of disodium pamidronate concentrate 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.

Table 1

Initial serum calcium		Recommended total
(mmol/l)	(mg %)	dose (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 disodium pamidronate concentrate 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 Disodium Pamidronate Injection, and normalisation is usually achieved within three to sevendays. 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 disodium pamidronate concentrate may become less effective as the number of treatments increases.

Adults and Elderly

Predominantly lytic bone metastases and multiple myeloma
The recommended dose of disodium pamidronate for the treatment of predominantly lytic bone metastases and multiple myeloma is 90mg administered as a single infusion every 4 weeks.
In patients with bone metastases who receive chemotherapy at 3-weekly intervals, disodium pamidroante 90mg may also be given on a 3-weekly schedule.

Osteolytic lesions and bone pain in bone metastases associated with breast cancer

The recommended dose is 90mg every four weeks. This dose may also be administered at threeweekly intervals to coincide with chemotherapy if desired.

Paget's disease of Bone

The recommended total dose of disodium pamidronate for a treatment course is 180 to 210mg. This can be administered either in 6 unit doses of 30mg once a week (total dose of 180mg), or in 3 unit doses of 60mg every other week. Experience to date suggests that any mild and transient unwanted effects (see Side-effects) tend to occur after the first dose. For this reason if unit doses of 60mg are used it is recommended that treatment be started with an initial additional dose of 30mg (i.e. total dose 210mg). Each dose of 30 or 60mg should be diluted in 125 or 250 ml 0.9% w/v Sodium Chloride Intravenous Infusion B.P. respectively, and the infusion rate should not exceed 60mg/hour (1mg/min). This regimen or increased dose levels according to disease severity, up to a maximum total dose of 360mg (in divided doses of 60mg) can be repeated every six months until remission of disease is achieved, and if relapse occurs.

Renal Impairment

Disodium pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia when the benefit outweighs the potential risk.
As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of disodium pamidronate. In patients receiving disodium pamidronate for bone metastases or multiple myeloma who show evidence of deterioration in renal function, disodium pamidronate treatment should be withheld until renal function returns to within 10% of the baseline value. This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL.
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.
-

A pharmacokinetic study conducted in patients with cancer and normal or impaired renal function indicates that the dose adjustment is not necessary in mild (creatinine clearance 61 to 90 mL/min) to moderate renal impairment (creatinine clearance 30 to 60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4h (approximately 20 to 22 mg/h).

Hepatic impairment

Although patients with hepatic impairment exhibited higher mean AUC and C_{max} values compared to patients with normal hepatic function, this is not perceived as being clinically relevant. As pamidronate is still rapidly cleared from the plasma almost entirely into the bone, and as is administered on a monthly basis for chronic treatment, drug accumulation is not expected.

Therefore no dose adjustment is necessary in patients with mild to moderate abnormal hepatic function (see Pharmacokinetic properties - Hepatic impairment). Clinical data in patients with severe hepatic impairment is not available. Pamidronate should be administered to this patient population with caution**.**

Children

There is no clinical experience of the use of disodium pamidronate in children.
Patients treated with disodium pamidronate should be given the package leaflet and the patient reminder card.

4.3 Contraindications

Hypersensitivity to the active substance or to other bisphosphonates, or to any of the excipients listed in section 6.1.

Disodium Pamidronate is contraindicated in pregnancy and in breast feeding women.

4.4 Special warnings and precautions for use

Warnings

Disodium pamidronate concentrate should be given under the supervision of a physician with the facilities to monitor clinical and biochemical effects.

Disodium pamidronate concentrate should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see Section 4.2Posology and Method of Administration).

Disodium pamidronate concentrate should not be given with other bisphosphonates because their combined effects have not been investigated.

Convulsions have been precipitated in some patients with tumour-induced hypercalcaemia due to the electrolyte changes associated with this condition and its effective treatment.
Standard hypercalcaemia-related metabolic parameters including serum calcium and phosphate should be monitored following initiation of therapy with disodium pamidronate. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (OJN) has been reported in clinical trials and in the post-marketing setting in patients receiving pamidronate.

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.
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).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth except in medical emergency situations.

A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors.

The following risk factors should be considered when evaluating an individual's risk of developing ONJ:

- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bisphosphonate
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking
- Concomitant therapies: chemotherapy, angiogenesis inhibitors (see section 4.5), radiotherapy to neck and head, corticosteroids
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with pamidronate. While on treatment, invasive dental procedures should be perfomed only after careful consideration and be avoided in close proximity of pamidronate administration. For patients who develop ONJ 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 ONJ.

The management plan for patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ.

Temporary interruption of pamidronate treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

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.

Osteonecrosis of the external auditory canal
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.

Precautions

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

Renal Insufficiency
Bisphosphonates, including disodium pamidronate, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of disodium pamidronate. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with disodium pamidronate in patients with multiple myeloma.
Disodium pamidronate is excreted intact primarily via the kidney (see section 5.2 Pharmacokinetic properties), thus the risk of renal adverse reactions may be greater in patients with impaired renal function.
Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of disodium pamidronate should not exceed 90 mg, and the recommended infusion time should be observed (see section 4.2 Posology and method of administration).
As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of disodium pamidronate.
Patients receiving frequent infusions of disodium pamidroante 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 laboratory and clinical parameters of renal function prior to each dose of disodium pamidronate.
Patients treated with disodium pamidronate for bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see section 4.2 Posology and method of administration).
Disodium pamidroante should not be given with other bisphosphonates because their combined effects have not been investigated.

Hepatic Insufficiency
Although there is no clinical data available in patients with severe hepatic impairment, disodium pamidronate should be used with caution in this patient population.

There is very little experience of the use of disodium pamidronate concentrate in patients receiving haemodialysis.

Patients should be adequately hydrated throughout treatment, this is especially important for patients receiving diuretic therapy, but overhydration should be avoided. 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 anaemia, leukopenia or thrombocytopenia should have regular haematology.

Calcium and Vitamin D Supplementation

In the absence of hypercalcaemia, patients with predominantly lytic bone metastases or multiple myeloma, who are at risk of calcium or vitamin D deficiency, and patients with Paget's disease of the bone, should be given oral calcium and vitamin D supplementation, in order to minimise the risk of hypocalcaemia

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 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule i.e. that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interactions

Disodium pamidronate concentrate has been administered concomitantly with commonly used anticancer agents without interactions occurring. Caution is advised when pamidronate is administered with anti-angiogenic medicinal products, as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these medicinal products.
Disodium pamidronate concentrate has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.
Caution is warranted when disodium pamidronate is used with other potentially nephrotoxic drugs.
In multiple myeloma patients, the risk of renal dysfunction may be increased when disodium pamidronate is used in combination with thalidomide.
Since pamidronate binds to bone, it could in theory interfere with bone scintigraphy examinations.

Antibacterials: There may be an increased risk of hypocalcaemia when biphosphonates and aminoglycosides are used concurrently or sequentially.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data for the use of pamidronate in pregnant women. There is no unequivocal evidence for teratogenicity in animal studies. Pamidronate may pose a risk to the foetus/newborn child through its pharmacological action on calcium homeostasis. When administered during the entire period of gestation in animals, pamidronate can cause bone mineralisation defects, especially in long bones, resulting in angular distortion.
There is insufficient clinical experience to support the use of disodium pamidronate concentrate in pregnant women. Therefore, disodium pamidronate concentrate should not be administered during pregnancy except in cases of life-threatening hypercalcaemia. Evidence is limited to a few cases but if used in the treatment of women with life threatening hypercalcemia, infants should be monitored for hypocalcemia during the first few days after birth.
Breastfeeding:
Very limited experience indicates maternal milk levels of pamidronate under the limit of detection. Moreover the oral bioavailability is poor so the total absorption of pamidronate by a breastfed infant is not likely. However due to extremely limited experience and the potential of pamidronate to have an important impact on bone mineralisation breastfeeding during the therapy is not recommended.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions to disodium pamidronate concentrate 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.
Adverse reactions (Table 1) are ranked under headings of frequency, the most frequent first,using the following convention:
Frequency estimate:
Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data.
The following adverse drug reactions were reported from clinical studies and from postmarketing experience with pamidronate.

Table 2

Infections and infestations	
Very rare:	Reactivation of Herpes simplex, reactivation of Herpes zoster.
Blood and lymphatic system disorders	
Common:	Anaemia, thrombocytopenia, lymphocytopenia.
Very rare:	Leukopenia.
Immune system disorders	
Uncommon:	Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke's (angioneurotic) oedema.
Very rare:	Anaphylactic shock.
Metabolism and nutrition disorders	
Very common:	Hypocalcaemia, hypophosphataemia.
Common:	Hypokalaemia, hypomagnesaemia.
Very rare:	Hyperkalaemia, hypernatraemia.
Nervous system disorders	
Common:	Symptomatic hypocalcaemia (paraesthesia, tetany), headache, insomnia, somnolence.
Uncommon:	Seizures, agitation, dizziness, lethargy.
Very rare:	Confusion, visual hallucinations.
Eye disorders	
Common:	Conjunctivitis.
Uncommon:	Uveitis (iritis, iridocyclitis).
Very rare:	Scleritis, episcleritis, xanthopsia.
Not known	Orbital inflammation.
Cardiac disorders	
Very rare:	Left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.
Not known	Atrial fibrillation.
Vascular disorders	
Common:	Hypertension.
Uncommon:	Hypotension.
Respiratory, thoracic and mediastinal disorders	
Very rare:	Acute respiratory distress syndrome, interstitial lung disease.
Gastrointestinal disorders	
Common:	Nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, gastritis.
Uncommon:	Dyspepsia.
Skin and subcutaneous disorders	
Common:	Rash.
Uncommon:	Pruritus.
Musculoskeletal and connective tissue disorders	
Common:	Transient bone pain, arthralgia, myalgia, generalised pain.

Uncommon:	Muscle cramps, Osteonecrosis.
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Unknown	Osteonecrosis of the jaw
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, renal tubular disorder, tubulointerstitial nephritis, glomeruloephropathy.
General disorders and administration site conditions	
Very Common:	Fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue, and flushes.
Common:	Reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis).
Investigations	
Common:	Increase in serum creatinine.
Uncommon:	Abnormal liver function tests, increase in serum urea.

Atrial fibrillation: When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Isolated instances of higher incidence of atrial fibrillation have also been reported in a few studies with other bisphosphonates. The mechanism of this increased incidence of atrial fibrillation in isolated studies with some bisphosphonates, including disodium pamidronate, is unknown.

Post-marketing experience:

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

Osteonecrosis of the jaw

Cases of osteonecrosis (of the jaw) have been reported predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as pamidronate (see section 4.4). Many of these patients were also receiving chemotherapy and corticosteroids and had signs of local infection including osteomyelitis. The majority of the reports refers 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. Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

During post-marketing experience the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Inhibitor of bone resorption, ATC code: MO5BA03.

Pamidronate disodium, the active substance of disodium pamidronate concentrate, 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. 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 disodium pamidronate concentrate 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, disodium pamidronate concentrate improves GFR and lowers elevated serum creatinine levels in most patients.

Clinical trials in patients with breast cancer and predominantly lytic bone metastases or with multiple myeloma showed that disodium pamidronate concentrate prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain.

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 disodium pamidronate concentrate. 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.

5.2 Pharmacokinetic properties

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 sites of apparent elimination.

Absorption

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

Distribution

Plasma concentrations of pamidronate rise rapidly after the start of an infusion and fall rapidly when the infusion is stopped. The apparent half-life in plasma is about 0.8 hours. Apparent steady-state concentrations are therefore achieved with infusions of more than about 2-3 hours' duration. Peak plasma pamidronate concentrations of about 10 nmol/ml are achieved after an intravenous infusion of 60 mg given over 1 hour, and the apparent plasma clearance is about 180 ml/min.

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

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

Elimination

Pamidronate does not appear to be eliminated by biotransformation and it is almost exclusively eliminated by renal excretion. 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). From the urinary elimination of pamidronate, two decay phases, with apparent half-lives of about 1.6 and 27 hours, can be observed. The apparent renal clearance is about 54 ml/min, and there is a tendency for the renal clearance to correlate with creatinine clearance.

Characteristics in patients

Hepatic and metabolic clearance of pamidronate are insignificant. Disodium pamidronate concentrate thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).

Hepatic impairment

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=9). Each patient received a single 90mg dose of disodium pamidronate concentrate infused over 4 hours. There was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function. Patients with hepatic impairment exhibited higher mean AUC (39.7%) and C_{max} (28.6%) values. The difference was not considered clinically relevant. The mean ratio based on log transformed parameters of impaired versus normal patients was 1.38 (90% C.I. 1.12 – 1.70, P=0.02) for AUC and 1.23 (90% C.I. 0.89 – 1.70, P=0.27) for C_{max}. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because disodium pamidronate concentrate is administered on a monthly basis, drug accumulation is not expected. No changes in disodium pamidronate concentrate dosing regimen are recommended for patients with mild to moderate abnormal hepatic function (see Posology and method of administration).

Renal impairment

The mean plasma AUC was approximately doubled in cancer patients at risk for bone metastases with severe renal impairment (creatinine clearance <30ml/min, n=4). Urinary excretion rate decreased with decreasing creatinine clearance, although the total amount excreted in the urine was not greatly influenced by renal function. Body retention of pamidronate was therefore similar in cancer patients with and without impaired renal function, and dose adjustment is not necessary in these patients when using the recommended dose schedule (see Posology and method of administration).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

Three years.
Reconstituted solutions that have been further diluted with one of the recommended diluents for intravenous infusion should be used immediately. Discard the unused portion.

6.4 Special precautions for storage

Do not store above 25C.

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Also refer to section 6.3.

6.5 Nature and contents of container

2ml polyethylene ampoules in packs of 1, 2 or 4 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The concentrate should be diluted with a calcium-free infusion solution (0.9% w/v Sodium Chloride Intravenous Infusion BP is recommended) before administration.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/227/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2005
Date of last renewal: 31 March 2010

10 DATE OF REVISION OF THE TEXT

December 2020