SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pamidronate Disodium 3 mg/ml Sterile Concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 3 mg pamidronate disodium.
1 vial of 5 ml of sterile concentrate contains 15 mg of pamidronate disodium.
1 vial of 10 ml of sterile concentrate contains 30 mg of pamidronate disodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of tumour-induced hypercalcaemia

The prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, hypercalcaemia and bone pain) in patients with breast cancer with bone metastases, or multiple myeloma with bone lesions, in addition to specific treatment of the tumour

Paget’s disease of bone

4.2 Posology and method of administration

Patients treated with pamidronate disodium should be given the package leaflet and the patient reminder card.

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

Paediatric population
There is no clinical experience in the paediatric and adolescent (<18 years old) population.

Tumour-induced hypercalcaemia:
It is recommended that patients be rehydrated with 0.9% w/v sodium chloride solution before and during treatment.

The total dose of pamidronate disodium 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**
(mmol/litre)	**(mg %)**	**(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 pamidronate disodium 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 repeat courses.

A significant decrease in serum calcium is generally observed 24-48 hours after administration of pamidronate disodium, 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 disodium may become less effective as the number of treatments increases.

Osteolytic lesions and bone pain in multiple myeloma:
The recommended dose is 90 mg administered as a single infusion every 4 weeks.

Osteolytic lesions and bone pain in bone metastases associated with breast cancer:
The recommended dose is 90 mg administered as a single infusion every 4 weeks. This dose may also be administered at 3 weekly intervals to coincide with chemotherapy if desired.

Paget's disease of bone:
The recommended total dose of pamidronate disodium for a treatment course is 180 to 210 mg. This can be administered either in 6 unit doses of 30 mg once a week

(total dose 180 mg) or in 3 doses of 60 mg every other week. Experience to date suggests that any mild and transient unwanted effects (see "Undesirable Effects") tend to occur after the first dose. For this reason if unit doses of 60 mg are used it is recommended that treatment be started with an initial additional dose of 30 mg followed by 60 mg every other week (i.e. total dose 210 mg). Each dose of 30 or 60 mg should be diluted in 125 or 250 ml 0.9 % w/v Sodium Chloride Intravenous Infusion BP respectively, and the infusion rate should not exceed 60 mg/hour (1 mg/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 6 months until remission of disease is achieved, and if relapse occurs.

Renal impairment:
Pharmacokinetic studies indicate that no dose adjustment is necessary in patients with mild (creatinine clearance 61 to 90 mL/min) to moderate (creatinine clearance 30 to 60 mL/min) renal impairment (see section 5.2). In such patients, the infusion rate should not exceed 90 mg/4 h (approximately 22 mg/h).

Pamidronate disodium should not be administered to patients with severe renal impairment (creatinine clearance < 30 ml/min) unless in case of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. Because there is only limited clinical experience in patients with severe renal impairment no dose recommendations for this patient population can be made (see section 4.4).

As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of pamidronate disodium. In patients receiving pamidronate disodium for bone metastases or multiple myeloma who show evidence of deterioration in renal function, pamidronate disodium 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.

Hepatic impairment:
Although patients with hepatic impairment exhibited higher mean AUC and Cmax 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 it 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. Pamidronate disodium has not been studied in patients with severe hepatic impairment, and therefore it should be administered to this patient population with caution (see section 4.4).

<u>Method of administration</u>
For intravenous use as infusion only.

Pamidronate disodium must never be given as a bolus injection (see section 4.4). The solution must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, see section 6.2.

The infusion rate should never 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 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 22 mg/hour (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. A single dose of 90 mg should normally be administered as a 2 hour infusion in 250 ml of infusion solution. However in patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that no more than 90 mg in 500 ml is administered over a 4 hour period.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General

Pamidronate should never be given as a bolus injection since severe local reactions and thrombophlebitis may occur. It should always be diluted and then given as a slow intravenous infusion (see section 4.2).

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

Pamidronate disodium for injection should not be mixed with calcium-containing intravenous infusions (see section 6.2).

Pamidronate is not recommended during pregnancy.

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

Standard hypercalcaemia-related metabolic parameters including serum calcium and phosphate should be monitored following initiation of therapy with pamidronate. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

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

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 assessments.

The safety and efficacy of pamidronate in children has not been established. Until further experience is gained, pamidronate is only recommended for use in adult patients.

Patients with tumor-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.

It is essential in the initial treatment of tumour induced hypercalcaemia that intravenous rehydration be instituted to maintain urine output. Patients should be hydrated adequately throughout treatment but overhydration must be avoided.

Renal impairment

Bisphosphonates, including pamidronate disodium 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 pamidronate disodium. 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. If there is deterioration of renal function during pamidronate therapy, the infusion must be stopped.

Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of pamidronate should not exceed 90 mg, and the recommended infusion time should be observed (see section 4.2).

Pamidronate disodium is excreted intact primarily via the kidney (see section 5.2), thus the risk of renal adverse reactions may be greater in patients with impaired renal function.

Patients should have standard laboratory (serum creatinine and BUN) and clinical renal function parameters evaluated, prior to each dose of pamidronate, especially those receiving frequent pamidronate infusions over a prolonged period of time, and those with pre-existing renal disease or a predisposition to renal impairment (e.g. patients with multiple myeloma and/or tumour-induced hypercalcaemia). Fluid balance (urine output, daily weights) should also be followed carefully.

Experience with pamidronate in patients with severe renal impairment (serum creatinine: >440 micromol/litre, or 5 mg/dl in TIH patients; 180 micromol/litre, or 2 mg/dl in multiple myeloma patients) is limited. If clinical judgement determines that the potential benefits outweigh the risk in such cases, pamidronate should be used cautiously and renal function carefully monitored.

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

Patients treated with pamidronate for bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see section 4.2).

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

Hepatic impairment
Pamidronate disodium has not been studied in patients with severe hepatic impairment, therefore no specific recommendations can be given for this patient population (see section 4.2).

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 (e.g. through malabsorption or lack of exposure to sunlight), and patients with Paget's disease of the bone, should be given oral calcium and vitamin D supplementation, in order to minimise the potential risk of hypocalcaemia.

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

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 disodium. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to pamidronate administration.

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.

The management plan for the 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.

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.

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 varies 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 bisphosphate.

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.

Excipient information

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Pamidronate should not be used concomitantly with other bisphosphonates.

In patients with severe hypercalcaemia, pamidronate has been successfully combined with both calcitonin and mithramycin to accelerate and potentiate the calcium lowering effect.

Since pamidronate binds to bone, it could in theory interfere with bone scintigraphy examinations.

Caution is warranted when pamidronate is used with other potentially nephrotoxic drugs.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
In animal experiments, pamidronate showed no teratogenic potential and did not affect general reproductive performance or fertility. Pamidronate may pose a risk to the fetus/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.
The potential risk for humans is unknown, and there is insufficient clinical experience to support the use of pamidronate in pregnant women. It is not known if pamidronate crosses the human placenta. The drug should not be given to pregnant women at any stage unless life-threatening hypercalcaemia cannot be controlled by any other means.

Breast-feeding
It is not known whether pamidronate is excreted into human milk. Very limited experience indicates maternal milk levels of pamidronate under the limit of detection. A study in lactating rats has shown that pamidronate will pass into the milk. Moreover the oral bioavalibility 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

The effect of pamidronate disodium on the ability to drive or use machines has not been systematically evaluated.

Patients should be warned that in rare cases somnolence and/or dizziness may occur following pamidronate disodium 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. This effect rarely lasts more than 24 hours. Outpatients who have received a pamidronate infusion should not drive themselves home.

4.8 Undesirable effects

Adverse reactions to pamidronate disodium are usually mild and transient. The most common adverse reactions are asymptomatic hypocalcaemia, with influenza-like symptoms and mild fever (an increase in body temperature of >1°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 infusion. Symptomatic hypocalcaemia is uncommon. Local soft tissue inflammation at the infusion site also occurs, especially at the highest dose.

When the effects of zoledronate (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 zoledronate group (3/563, 0.5%).

Previously, it has been observed in a clinical trial, investigating patients with postmenopausal osteoporosis, that zoledronate treated patients (4 mg) had an increased rate of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism behind the increased incidence of atrial fibrillation in association with zoledronate and pamidronate treatment is unknown.

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 including isolated reports); not known (cannot be estimated from the available data).

The following adverse drug reactions were reported from clinical studies and from post-marketing experience with pamidronate.

Adverse Reactions Table

Infections and Infestations:	
Common	Conjunctivitis
Very rare	Herpes simplex, herpes zoster
Blood and Lymphatic System Disorders:	
Common	Anaemia, thrombocytopenia, lymphocytopenia
Very rare	Leukopenia
Immune System Disorders:	
Uncommon	Hypersensitivity, anaphylactic reaction, angioedema
Very rare	Anaphylactic shock
Metabolism and Nutrition Disorders:	
Very common	Hypocalcaemia, hypophosphataemia
Common	Hypokalaemia, hypomagnesaemia, anorexia, tetany
Very rare	Hyperkalaemia, hypernatraemia
Psychiatric disorders	
Common	Insomnia
Uncommon	Agitation
Very rare	Confusional state, hallucinations visual
Nervous System Disorders:	
Common	Paraesthesia, headache, somnolence
Uncommon	Seizures, dizziness, lethargy
Eye Disorders:	
Uncommon	Uveitis[a]
Very rare	Scleritis, episcleritis, xanthopsia
Not known	Parophthalmia inflammation
Ear and labyrinth disorders	
Very rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)

Cardiac Disorders:	
Very rare	Left ventricular failure[b], congestive heart failure[c]
Not known	Atrial fibrillation
Vascular Disorders:	
Common	Hypertension
Uncommon	Hypotension
Respiratory, Thoracic and Mediastinal Disorders:	
Uncommon	Bronchospasm, dyspnoea
Very rare	Acute respiratory distress syndrome, interstitial lung disease
Gastrointestinal Disorders:	
Common	Nausea, vomiting, abdominal pain, diarrhoea, constipation, gastritis
Uncommon	Dyspepsia
Skin and Subcutaneous Tissue Disorders:	
Common	Rash
Uncommon	Pruritus
Musculoskeletal, Connective Tissue and Bone Disorders:	
Common	Transient bone pain, arthralgia, myalgia
Uncommon	Muscle cramps, osteonecrosis
Not known	Osteonecrosis of the jaw
Renal and Urinary Disorders:	
Uncommon	Acute renal failure
Rare	Deterioration of renal function[d], focal segmental glomerulosclerosis[d], nephrotic syndrome[d]
Very rare	Haematuria, deterioration of pre-existing renal disease, renal tubular disorder, tubulointerstitial nephritis, glomerulonephropathy
General Disorders and Administration Site Conditions:	
Very common	Fever, influenza-like symptoms[e]
Common	Pain, infusion site reaction[f]
Investigations:	
Common	Blood creatinine increased
Uncommon	Abnormal liver function tests, blood urea increased
Injury, Poisoning and Procedural Complications	
Very rare	Atypical femur fracture[g]

a Includes uveitis iritis and iridocyclitis
b Manifestations include dyspnoea and pulmonary oedema
c Includes oedema due to fluid overload
d Reports of these events are generally associated with high dosage (exceeding the recommended dosage or reduced dosing intervals) and/or long-term use.
e Manifestations include malaise, chills, fatigue and flushing
f Includes pain, redness, swelling, induration, phlebitis, thrombophlebitis
g bisphosphonate class adverse reaction

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 disodium (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 refer to cancer patients following tooth extractions or other dental surgeries.

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

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. Acute hypocalcaemia is not expected to occur with pamidronate since plasma calcium levels fall progressively for several days after treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Inhibitor of bone resorption, ATC code: MO5B A03

Pamidronate disodium 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 biphosphonate 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 pamidronate disodium 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 disodium 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 pamidronate disodium 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 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.

5.2 Pharmacokinetic properties

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. 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.

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”.

Hepatic impairment:
Hepatic and metabolic clearance of pamidronate 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 above). As pamidronic acid is administered on a monthly basis, drug accumulation is not expected.

5.3 Preclinical safety data

Juvenile animal studies:
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 daily 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 intravenous 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 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, but there was no evidence for teratogenicity.

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 and Mutagenesis:
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 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 an 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Phosphoric acid

Sodium hydroxide

Water for Injections.

6.2 Incompatibilities

Pamidronate will form complexes with divalent cations and should not be added to calcium-containing intravenous solutions such as Ringer's solution.

6.3 Shelf life

As packaged for sale: 36 months.

In use: Following dilution in 0.9% sodium chloride and 5% glucose infusion solutions, chemical and physical in-use stability has been demonstrated for 24 hours at temperatures not exceeding 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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Prior to first use: Do not store above 25°C. Keep the container in the outer carton.

For storage conditions after dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

15 mg/5 ml clear glass vials in pack of 5 vials.

30 mg/10 ml clear glass vial in packs of 1 vial.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Must be diluted prior to administration.

The concentration of pamidronate disodium in the infusion solution should not exceed 90 mg/250 ml.

Do not use solution if particles are present.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Walton Oaks
Walton-On-The-Hill
Dorking Road
Tadworth
Surrey
KT20 7NS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04515/0118

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14 June 2001

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