Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pamidronate Disodium 3 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The concentrate for solution for infusion contains 3 mg pamidronate disodium per ml.

Each 10 ml vial contains 30 mg pamidronate disodium.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
A clear colourless solution free from visible particulates.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- For the treatment of tumour-induced osteolysis with or without tumour-induced hypercalcaemia.
- For the treatment of Paget's disease of bone.

4.2 Posology and method of administration

For intravenous use as infusion only.

Pamidronate disodium must never be given as a bolus injection (see 4.4 "Special Warnings and Special Precautions for Use"). The solution must be diluted before use (see below) and must be infused slowly.

Preparation of infusion:
The required dose should be withdrawn from the vial using aseptic technique and further diluted using the recommended diluents sodium chloride 0.9% or 5% glucose. The final concentration of pamidronate in the infusion solution should not exceed 30mg/250ml.

The infusion rate should not exceed 30 mg/2 hour. 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 20 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.

<u>Tumour induced Osteolysis:</u>
The recommended dose is 30mg once a week for four consecutive weeks and then once every two weeks for six months or until there is evidence of disease progression in the bone, when patient management should be reassessed.

If patients progress to clinically significant hypercalcaemia, the following regime should be adopted.

<u>Tumour-induced hypercalcaemia:</u>
It is recommended that patients be rehydrated with 0.9% w/v sodium chloride solution before or 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 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

A dose of 30 – 60mg has been found to be appropriate for the majority of patients. 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. Patients experience indicates that dose above 90 mg bring no increased clinical benefit.

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.

Paget's disease of the bone:
Treatment should be administered under the supervision of a hospital based specialist.
The recommended treatment course consists of 180mg administered in unit doses of either 30mg once a week for six consecutive weeks or 60mg every other week over three weeks.
Experience to date suggests that any mild or transient unwanted effects (See Undesirable 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 dose of 30mg (total dose of 210mg).
This regimen or increased dose levels according to the disease severity, up to a maximum total dose of 360mg (omitting the initial 30mg dose), can be repeated every 6 months until remission of disease is achieved or if relapse occurs.

Renal Impairment
Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30ml/min) unless in cases of life threatening tumour induced hypercalcaemia where the benefit outweighs the potential risk.

As with other i.v. biphosphonates, renal monitoring is recommended e.g. measurement of serum creatinine prior to each dose. In patients receiving Pamidronate for bone metastases who show evidence of deterioration in renal function, Pamidronate therapy should be withheld until the 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 an increase of 0.5mg/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 dose adjustment is not necessary in mild (creatinine clearance 61 – 90 mL/min) to moderate renal impairment (creatinine 30 - 60 mL/min). In such patients, the infusion rate should not exceed 90 ml/4 hours (approximately 20 – 22 mg/hour).

However, experience with pamidronate disodium 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 (See 4.4. Special Warnings and Special Precautions for Use).

Until further experience is gained a maximum infusion rate of 20 mg/hour is recommended in renally impaired patients.

Children:
There is no clinical experience in children.

4.3 Contraindications

Known hypersensitivity to pamidronate disodium or other bisphosphonates or to any of the excipients.

4.4 Special warnings and precautions for use

Pamidronate disodium must never be given as a bolus injection since local reactions and thrombophlebitis may occur. Pamidronate disodium should always be diluted and given as a slow intravenous infusion. (See Posology and Method of Administration). Pamidronate disodium should not be given with other bisphosphonates because their combined effects have not been investigated.

Rapid IV administration of pamidronate disodium may possibly lead to renal problems due to formation of insoluble calcium bisphosphonate complexes in the blood.

There is a possibility of precipitating convulsions in some patients due to the electrolyte changes associated with tumour-induced hypercalcaemia and its effective treatment.

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

Patients receiving frequent infusion of Pamidronate Disodium over a prolonged period of time, especially those with pre-existing renal disease or a disposition to renal impairment (eg tumour induced hypercalcaemia) should have periodic evaluations of standard laboratory and clinical parameters of renal function.

Due to a risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Pamidronate should not exceed 90 mg. The concentration of Pamidronate in the infusion solution should not exceed 30mg/250ml, and the infusion rate should not exceed 30mg/2 hours (see section 4.2).

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

Reduced intestinal absorption of both iron and calcium may occur with concurrent administration of Pamidronate disodium and it is advisable to periodically monitor serum levels of these minerals.

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

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.

Pagetic patients at risk of calcium or Vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) should take oral supplements of both during Pamidronate disodium therapy to minimise the potential risk of hypocalcaemia.

Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects.

Osteonecrosis of the jaw has been reported in patients with cancer receiving treatment regimens including biphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority were associated with dental procedures such as tooth extraction and many had signs of local infection including osteomyelitis.

Dental examination with appropriate preventative dentistry should be considered prior to treatment with

biphosphonates in patients with concomitant risk factors (for e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on biphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there is no data available to suggest whether discontinuation of biphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgment of the treating physician should guide the management plan of each patient assessed on an individual benefit/risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Pamidronate disodium has been administered concomitantly with commonly used anti-cancer agents without interaction occurring.

Pamidronate disodium should not be co-administered with other bisphosphonates because their combined effects have not been investigated.

Severe hypocalcaemia may develop if aminoglycosides are given together with bisphosphonates.

Pamidronate disodium 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.

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

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

4.6 Pregnancy and lactation

In animal experiments, pamidronate disodium showed no teratogenic potential and did not affect general reproductive performance or fertility. In rats, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels. In pregnant rats, pamidronate disodium has been shown to cross the placental barrier and accumulate in fetal bones in a manner similar to that observed in adult animals.

There is insufficient clinical experience to support the use of Pamidronate disodium in pregnant women. Therefore, Pamidronate disodium should not be administered during pregnancy except in cases of life-threatening hypercalcaemia.

A study in lactating rats has shown that pamidronate disodium will pass into the milk. Mothers treated with Pamidronate disodium should therefore not breast feed their infants.

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 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.

4.8 Undesirable effects

Adverse reactions to Pamidronate disodium are usually mild and transient. The most common adverse reactions are asymptomatic hypocalcaemia and fever (an increase in body temperature of 1-2^{o}C), typically occurring within the first 48 hours of infusion. Fever usually resolves spontaneously and does not require treatment. Symptomatic hypocalcaemia is rare.

Frequency estimate: frequent > 10%; occasionally 1 - 10%; rare > 0.001% - 1%; isolated cases < 0.001%.

Body as a whole
Frequent: fever and influenza like symptoms sometimes accompanied by malaise, rigor, fatigue and flushes.

Local reactions:
Occasional: reactions at the infusion site; pain; redness; swelling; induration; phlebitis; thrombophlebitis.

Musculoskeletal system:
Occasional: transient bone pain; arthralgia, myalgia, generalised pain.
Rare: muscle cramps.

Gastro-intestinal tract:
Occasional: nausea, vomiting.
Rare: anorexia, abdominal pain, constipation, diarrhoea and dyspepsia.
Isolated cases: gastritis.

Central Nervous System
Occasional: headache.
Rare: symptomatic hypocalcaemia (paraesthesia, tetany), agitation, confusion, dizziness, insomnia, somnolence and lethargy.
Isolated cases: seizures, visual hallucinations.

Blood;
Occasional: lymphocytopenia.
Rare: anaemia, leukopenia.
Isolated cases: thrombocytopenia.

Cardiovascular System:
Rare: hypotension, hypertension.
Isolated cases: left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.

Renal system:
Isolated cases: haematuria, acute renal failure, and deterioration of pre-existing renal disease.

Skin
Rare: rash, pruritis.

Special senses:
Isolated cases: conjunctivitis, uveitis (iritis, iridocyclitis) scleritis, episcleritis, xanthopsia.

Biochemical changes:
Frequent: hypocalcaemia, hypophosphataemia.
Occasional: hypomagnesaemia.
Rare: hyperkalaemia, hypokalaemia, hypernatraemia.
Isolated cases: abnormal liver function tests, increase in serum creatinine and urea.
Many of these undesirable effects have been related to underlying disease.

Others

Rare: allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quinche's (angioneurotic) oedema. Ototoxicity, aseptic peritonitis and central nervous system toxicity following 60mg pamidronate IV.

Very rare: anaphylactic shock.

Isolated cases: reactivation of herpes simplex and herpes zoster.

4.9 Overdose

There is no experience of overdosage with Pamidronate disodium.

Symptoms: Overdosage would be clinically manifested as the signs and symptoms of hypocalcaemia, i.e. paraesthesia and carpopedal spasm.

Treatment: In the event of clinically significant hypocalcaemia, reversal may be achieved with an infusion of calcium gluconate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug affecting mineralisation – Bisphosphonate.

ATC code: M05B 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 at least in part be due to binding of the drug to the bone mineral.

Pamidronate disodium suppresses the accession of the osteoclast precursors onto the bone and their subsequent transformation into 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 in animals have demonstrated that Pamidronate disodium 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 osteolysis, and specifically on tumour-induced hypercalcaemia, are characterised by a decrease in serum calcium and, secondarily by decrease 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.

Paget's disease of bone, which is characterised by local areas of increased bone resorption and formation with qualitative changes in bone remodelling.

5.2 Pharmacokinetic properties

General characteristics
Pamidronate disodium has a strong affinity for calcified tissues, and total elimination of pamidronate disodium from the body is not observed within the time frame of experimental studies. Calcified tissues are therefore regarded as site of "apparent elimination".

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

Distribution
Plasma concentrations of pamidronate disodium rise rapidly after the start of an infusion and fall rapidly when the infusion is stopped. The apparent half-life in plasma is about 0.8 hours. Apparent steady-state concentrations are therefore achieved with infusions of more than about 2-3 hours' duration. Peak plasma pamidronate disodium 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 disodium in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

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

Elimination
Pamidronate disodium 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 disodium.
Within the time frame of experimental studies the remaining fraction of the dose is retained in the body. The percentage of the dose retained in the body is independent of both the dose (range 15-180 mg) and the infusion rate (range 1.25-60 mg/hour).
The elimination of pamidronate disodium in the urine is biexponential, with apparent half-lives of about 1.6 and 27 hours.
The apparent total plasma clearance is about 180 ml/min and 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 clearances of pamidronate disodium are insignificant. Impairment of liver function is therefore not expected to influence the pharmacokinetics of Pamidronate disodium. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).

A pharmacokinetic study conducted in patients with cancer showed no differences in plasma AUC of Pamidronate between patients with normal renal function and patients with mild to moderate renal impairment. 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).

5.3 Preclinical safety data

The toxicity of pamidronate disodium 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

Mannitol
Phosphoric acid
Sodium hydroxide solution
Water for injections

6.2 Incompatibilities

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

6.3 Shelf Life

Prior to first use:	36 months.
In use:	24 hours.

6.4 Special precautions for storage

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

Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride and 5% glucose for 24 hours when stored at 2°C to 8°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°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

10 ml Type I glass vials with elastomeric stoppers. Each vial is supplied in an individual outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The concentrate for solution for infusion must be diluted prior to administration with 0.9% sodium chloride or 5% glucose.

The concentration of pamidronate disodium in the infusion solution should not exceed 30 mg/250 ml.
Only clear solutions practically free from particles should be used.

For single use only. Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1064/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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