SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pamidronatdinatrium Pfizer 3 mg/mL Concentrate for solution for infusion
Pamidronatdinatrium Pfizer 6 mg/mL Concentrate for solution for infusion
Pamidronatdinatrium Pfizer 9 mg/mL Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pamidronatdinatrium Pfizer 3 mg/mL concentrate for solution for infusion 5 mL and 10 mL contains 15 mg and 30 mg pamidronate disodium respectively.

Pamidronatdinatrium Pfizer 6 mg/mL concentrate for solution for infusion 10 mL contains 60 mg pamidronate disodium.

Pamidronatdinatrium Pfizer 9 mg/mL concentrate for solution for infusion 10 mL contains 90 mg pamidronate disodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

A clear colourless solution free from visible particulates.

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) in patients with breast cancer with bone metastases or multiple myeloma with bone lesions, in addition to specific treatment of the tumour.

4.2 Posology and method of administration

Patients treated with Pamidronatdinatrium Pfizer should be given the package leaflet and the patient reminder card.

Posology

For intravenous use as infusion only.

Method of administration

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.

For information concerning compatibility with infusion solutions, see 6.4 Special precautions for storage.

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 multiple myeloma and in patients with hypercalcaemia caused by malignant tumours it is recommended that no more than 90 mg in 500 mL is administered over a 4 hour period.

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 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.

Multiple myeloma stage III
The recommended dose is 90 mg every 4 weeks.

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

Renal impairment
Pharmacokinetic studies indicate that no dose adjustment is necessary in patients with mild (creatinine clearance 61 to 90 mL/min) to moderate renal impairment (creatinine clearance 30 to 60 mL/min) (see 5.2 Pharmacokinetic properties). 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 (see 4.4 Special warnings and precautions for use).

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
A pharmacokinetic study indicates that 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, therefore no specific recommendations can be given for this patient population (see 4.4 Special warnings and precautions for use).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General

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

Pamidronate can induce irritation of the eyes.
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 4.2 Posology and method of administration).

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; this is especially important for patients receiving diuretic therapy. 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.

Standard hypercalcaemia-related metabolic parameters including serum 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 with anaemia, leukopenia or thrombocytopenia should have regular haematology assessments.

Renal insufficiency

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

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. If there is deterioration of renal function during pamidronate therapy, the infusion must be stopped. 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. Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of pamidronate disodium should not exceed 90 mg, and the recommended infusion time should be observed (see 4.2, Posology and method of administration).

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

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. In such cases, pamidronate should be used cautiously and renal function carefully monitored.

Patients should have standard laboratory (serum creatinine and blood urea nitrogen; BUN) and clinical renal function parameters evaluated prior to each dose of pamidronate disodium, 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.

Hepatic insufficiency

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

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, should be given oral calcium and vitamin D supplementation, in order to minimise the risk of hypocalcaemia.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported uncommonly 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 Pamidronatdinatrium Pfizer. 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.

Pamidronate is not recommended during pregnancy.

Paediatric population

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

Excipient information

This medicinal product contains less than 1 mmol sodium (23 mg) per maximum dose (90 mg), i.e. essentially ‘sodium-free’.

However, if a solution of common salt (0.9% w/v sodium chloride solution) is used for the dilution of Pamidronatdinatrium Pfizer prior to administration then the dose of sodium received would be higher.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of other bisphosphonates, other antihypercalcaemic agents and calcitonin may lead to hypocalcaemia with associated clinical symptoms (paraesthesia, tetany, hypotension).

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.

Pamidronate disodium has been administered concomitantly with commonly used antitumor drugs without significant interactions.

Caution is warranted when pamidronate disodium 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 disodium is used in combination with thalidomide.

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.
The potential risk for humans is unknown. Therefore, pamidronate should not be administered to pregnant women except in cases of life-threatening hypercalcaemia.

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 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, influenza-like symptoms and fever (an increase in body temperature of 1 °C - 2 °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 common. Local soft tissue inflammation at the infusion site also occurs, especially at the highest dose. Osteonecrosis primarily involving the jaws has been reported uncommonly (see Section 4.4 ”Precautions”).

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 post-marketing experience with pamidronate.

Infections and infestations:
Very rare: Reactivation of Herpes simplex and Herpes zoster

Blood and lymphatic system disorders:
Common: Anaemia, thrombocytopenia, lymphocytopenia
Very rare: Leukopenia

Immune system disorders:
Uncommon: Allergic reactions, anaphylactic 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
Not known: Pseudotumor cerebri

Eye disorders:
Common: Conjunctivitis
Uncommon: Uveitis (iritis, iridocyclitis)
Very rare: Scleritis, episcleritis, xanthopsia.
Not known: Orbital inflammation

Ear and labyrinth disorders:
Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)

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: Adult respiratory distress syndrome, interstitial lung disease

Gastrointestinal disorders:
Common: Nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, gastritis
Uncommon: Dyspepsia

Skin and subcutaneous tissue disorders:
Common: Rash
Uncommon: Pruritus

Musculoskeletal and connective tissue disorders:
Common: Transient bone pain, arthralgia, myalgia, generalised pain
Uncommon: Muscle cramps, osteonecrosis
Not known: Osteonecrosis of the jaw

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 Pamidronatdinatrium Pfizer (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.

Renal and urinary disorders:
Uncommon: Acute renal failure
Rare: Focal segmental glomerulosclerosis including collapsing variant, nephrotic syndrome
Very rare: Haematuria, deterioration of pre-existing renal disease, renal tubular disorder, tubulointerstitial nephritis, glomerulonephropathy

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

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

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%). Previously, it has been observed in a clinical trial, investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 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 zoledronic acid and pamidronate treatment is unknown.

During post-marketing experience the following reactions have been reported (frequency uncommon): Cases of osteonecrosis (primarily of the jaw) predominantly in cancer patients treated with bisphosphonates. Many had signs of local infection including osteomyelitis. The majority of the reports refer 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 section 4.4). Data suggest a greater frequency of reports of osteonecrosis of the jaw 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 the national reporting system listed in Appendix V.

4.9 Overdose

There is no available information for overdose of pamidronate.

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: 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 be at least partly due to binding of the medicinal product 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 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 treated by chemotherapy and predominantly lytic bone metastases or with multiple myeloma stage III with associated osteolytic lesions showed that pamidronate disodium prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain.

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 timeframe 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
In patients with impaired renal function (those severely included), no plasmatic accumulation of pamidronate leading to any clinical side effect, was reported. Therefore, no dosage reduction is deemed necessary in patients with any degree of renal impairment (however, experience in patients with severe impairment is limited (see 4.4 Special warnings and precautions for use and 4.2 Posology and method of administration)).

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).

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 22 mg/hour is recommended in renally impaired patients.

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).

5.3 Preclinical safety data

In pregnant rats, pamidronate has been shown to cross the placenta and accumulate in fetal bone in a manner similar to that observed in adult animals. Pamidronate disodium has been shown to increase the length of gestation and parturition in rats resulting in increased pup mortality. High intravenous doses to pregnant rats were associated with maternal toxicity and fetal developmental abnormalities (fetal oedema and shortened bones) and reduced ossification. These effects were probably caused by a decrease in maternal serum calcium levels. In pregnant rabbits, increased resorption rate and reduced ossification, but no teratogenicity was observed at intravenous doses causing maternal toxicity.

In animal studies with intravenous administration, renal tubular lesions were prominent and consistent untoward effects of treatment.

Pamidronate showed no carcinogenic effects from long-term studies in rat and mice.

Pamidronate showed no genotoxic activity in mutagenesis studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Phosphoric acid
Sodium hydroxide solution
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

3 years

In-use: 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 – 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 – 8 °C.

6.4 Special precautions for storage

Do not store above 25 °C.

After dilution – See 6.3

6.5 Nature and content of container

Pamidronatdinatrium Pfizer 3 mg/mL:
5 mL clear glass vials in packs of 5 vials.
5 mL clear glass vials in packs of 4 × (5 × 5 mL) vials.

10 mL clear glass vials in packs of 1 vial.
10 mL clear glass vials in packs of 4 × (1 × 10 mL) vials.

Pamidronatdinatrium Pfizer 6 mg/mL and 9 mg/mL:
10 mL clear glass vials in packs of 1 vial.
10 mL clear glass vials in packs of 4 × (1 × 10 mL) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Must be diluted prior to administration. For information concerning compatibility with infusion solutions, see 6.4 Special precautions for storage.

The concentration of pamidronate disodium in the infusion solution should not exceed 90 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

<to be completed nationally>

8 MARKETING AUTHORISATION NUMBER(S)

Pamidronatdinatrium Pfizer 3 mg/mL: 17959
Pamidronatdinatrium Pfizer 6 mg/mL: 17960
Pamidronatdinatrium Pfizer 9 mg/mL: 17961

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2002-07-01/2006-06-14

10 DATE OF REVISION OF THE TEXT

27-Jun-2024