SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medac Disodium Pamidronate 3 mg/ml, sterile concentrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml sterile concentrate contains 3 mg pamidronate disodium as pamidronic acid 2.527 mg.

1 vial with 5 ml sterile concentrate contains 15 mg pamidronate disodium.
1 vial with 10 ml sterile concentrate contains 30 mg pamidronate disodium.
1 vial with 20 ml sterile concentrate contains 60 mg pamidronate disodium.
1 vial with 30 ml sterile concentrate contains 90 mg pamidronate disodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile concentrate.
Clear and colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Medac Disodium Pamidronate 3 mg/ml is indicated for the treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia
- Osteolytic lesions in patients with bone metastases associated with breast cancer
- Multiple myeloma stage III

4.2 Posology and method of administration

Posology

Tumour-induced hypercalcaemia:
Patients must be adequately rehydrated with 0.9 % w/v sodium chloride solution before or/and during administration of pamidronate disodium (see section 4.4).
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.

Table 1

Initial plasma calcium level		Recommended total dose of pamidronate disodium	Concentration of solution for infusion	Maximum infusion rate
(mmol/l)	(mg %) (mg/100 ml)	(mg)	mg/ml	mg/h
< 3.0	< 12.0	15-30	30/125	22.5
3.0-3.5	12.0-14.0	30-60	30/125 60/250	22.5
3.5-4.0	14.0-16.0	60-90	60/250 90/500	22.5
> 4.0	>16.0	90	90/500	22.5

The total dose of pamidronate disodium may be administered either in a single infusion or in multiple infusions over 2 to 4 consecutive days. The maximum dose per treatment course is 90 mg for both initial and repeat courses.
Higher doses did not improve clinical response.

A significant decrease in serum calcium is generally observed 24 to 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 in multiple myeloma:
The recommended dose is 90 mg every 4 weeks.

Osteolytic lesions in 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.
Treatment should be continued until there is evidence of a substantial decrease in a patient's general performance status.

Indication	Treatment scheme	Solution for infusion (mg/ml)	Infusion rate (mg/h)
Bone metastases	90 mg/2 h every 4 weeks	90/250	45
Multiple Myeloma	90 mg/4 h every 4 weeks	90/500	22.5

Renal impairment
Medac Disodium Pamidronate 3 mg/ml 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 also section 4.4 and 5.2).

As with other intravenous bisphosphonates, monitoring of renal function is recommended, for instance, measurements 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, treatment with pamidronate disodium 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/4 h (approximately 20 to 22 mg/h).

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 pamidronate disodium in such patients (see section 4.4).

Paediatric population
The safety and efficacy of pamidronate disodium in children and adolescents aged < 18 years have not been established (see section 4.4).

Method of administration

Medac Disodium Pamidronate 3 mg/ml is a sterile concentrate and must therefore always be diluted in a calcium-free infusion solution (0.9 % sodium chloride or 5 % glucose) before use. The resulting solution must be infused slowly (see also section 4.4).

For information concerning compatibility with infusion solutions, see section 6.6.

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. A dose of 90 mg must usually be administered as a 2-hour infusion in a 250 ml solution for infusion. In patients with multiple myeloma and patients with tumour-induced hypercalcaemia, it is recommended that the infusion rate does not exceed 90 mg in 500 ml over 4 hours. In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects. Patients treated with Medac Disodium Pamidronate 3 mg/ml should be given the package leaflet and the patient reminder card.

Use only freshly prepared and clear dilutions!

4.3 Contraindications

Medac Disodium Pamidronate 3 mg/ml is contraindicated in the case of

- hypersensitivity to the active substance or to other bisphosphonates, or to any of the excipients listed in section 6.1.
- breast-feeding

4.4 Special warnings and precautions for use

General

Medac Disodium Pamidronate 3 mg/ml must never be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see section 4.2).

Patients must be assessed prior to administration of Medac Disodium Pamidronate 3 mg/ml to assure that they are appropriately hydrated. 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 Medac Disodium Pamidronate 3 mg/ml. Patients

who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

Convulsions have been occurred in some patients with tumour-induced hypercalcaemia due to electrolyte changes associated with this condition and its effective treatment.

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 disodium in children and adolescents (< 18 years) has not been established.

The medicinal product contains 0.65 mmol sodium per maximum dose (90 mg). To be taken into consideration by patients on a controlled sodium diet.

Renal insufficiency
Bisphosphonates, including Medac Disodium Pamidronate 3 mg/ml, 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 Medac Disodium Pamidronate 3 mg/ml. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Medac Disodium Pamidronate 3 mg/ml in patients with multiple myeloma.

Medac Disodium Pamidronate 3 mg/ml 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.

Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of Medac Disodium Pamidronate 3 mg/ml should not exceed 90 mg, and the recommended infusion time should be observed (see section 4.2).

As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Medac Disodium Pamidronate 3 mg/ml.

Patients receiving frequent infusions of Medac Disodium Pamidronate 3 mg/ml 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 Medac Disodium Pamidronate 3 mg/ml.

Patients treated with Medac Disodium Pamidronate 3 mg/ml for bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see section 4.2).
Medac Disodium Pamidronate 3 mg/ml should not be given with other bisphosphonates because their combined effects have not been investigated.

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

Hepatic insufficiency
As there are no clinical data available in patients with severe hepatic insufficiency, 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, 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.

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 Medac Disodium Pamidronate 3 mg/ml. 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.

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.

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 medicinal products includes Medac Disodium Pamidronate 3 mg/ml (pamidronate disodium for infusion).The time to onset of symptoms varied from one day to several months after starting treatment with the medicinal product. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Excipients with known effect
This medicinal product 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 anticancer agents without significant interactions.

Medac Disodium Pamidronate 3 mg/ml should not be used concomitantly with other bisphosphonates (see also section 4.4).

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

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.

Caution is warranted when pamidronate disodium is used with other potentially nephrotoxic medicinal products.

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

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.

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women of child-bearing potential must use highly effective contraception during treatment.

Pregnancy
There are no adequate data from 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. Evidence is limited to a few cases but if used in the treatment of women with life-threatening hypercalcaemia, infants should be monitored for hypocalcaemia during the first few days after birth.

Breast-feeding
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 breast-fed infant is not likely. However due to extremely limited experience and the potential of pamidronate to have an important impact on bone mineralisation breast-feeding during the therapy is not recommended.

Fertility
There are no data available.

4.7 Effects on ability to drive and use machines

Patients should be warned that somnolence and/or dizziness may occur following Medac Disodium Pamidronate 3 mg/ml 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 °C), typically occurring within the first 48 hours of infusion. Fever usually resolves spontaneously and does not require treatment.

Acute “influenza-like” reactions usually occur only with the first pamidronate infusion. Local soft tissue inflammation at the infusion site occurs commonly (≥ 1/100 to < 1/10), especially at the highest dose.

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 Medac Disodium Pamidronate 3 mg/ml (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.

Atrial fibrillation
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 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.

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

Adverse reactions (Table 2) are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

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
Uncommon:	Muscle cramps, osteonecrosis
Rare:	Atypical subtrochanteric and diaphyseal femoral fractures
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Not known:	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, glomerulonephropathy
General disorders and administration site conditions	
Very common:	Fever and influenza-like symptoms sometimes accompanied by malaise, rigors, fatigue, and flushes
Common:	Reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis), general body pain
Investigations	
Common:	Increase in serum creatinine
Uncommon:	Abnormal liver function tests, increase in serum urea

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. There is no available information for overdose of pamidronate disodium.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: medicinal products affecting bone structure and mineralisation, bisphosphonates, ATC code: M05 BA 03

Mechanism of action
Pamidronate disodium, active substance of Medac Disodium Pamidronate 3 mg/ml, 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 and the so induced transformation to mature absorbing osteoclasts. 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. A dose of 90 mg achieves normocalcaemia in more than 90 % of patients.
The normalisation of the plasma-calcium-level can also normalise the plasma-parathyroid-hormon-level in adequately rehydrated patients.
Serum levels of parathyroid hormone-related protein (PTHrP) inversely correlate with response to pamidronate. Medicinal products that inhibit tubular reabsorption of calcium or PTHrP secretion may help in patients who do not respond to pamidronate.

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.

When used in addition to systemic antineoplastic therapy pamidronate reduces skeletal complications of non-vertebral fracture, radiotherapy/surgery for bone complications and increases the time to first skeletal event.
Pamidronate may also reduce bone pain in about 50 % women with advanced breast cancer and clinically evident bone metastases. In women with abnormal bone scans but normal plain radiographs pain should be the primary guide to treatment.

Pamidronate has been shown to reduce pain, decrease the number of pathological fractures and the need for radiotherapy, correct hypercalcaemia and improve Quality of Life in patients with advanced multiple myeloma.

A meta-analysis of bisphosphonates in > 1,100 patients with multiple myeloma showed the NNT (number of patients needed to treat) to prevent one vertebral fracture was 10 and NNT to prevent one patient experiencing pain was 11 with best effects seen with pamidronate and clodronate.

5.2 Pharmacokinetic properties

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”.

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 distribution 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.

A similar percentage (approximately 50 %) of the dose is retained in the body after administration of different doses (30–90 mg) of pamidronate disodium independent of infusion time (4 or 24 hours) 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 (less than 50 %) 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. From the urinary elimination of pamidronate, two decay phases with apparent half-lives of about 1.6 and

27 hours can be observed. The total plasma and renal clearance has been reported to be 88–254 ml/min and 38– 60 ml/min, respectively. The apparent plasma clearance is about 180 ml/min. 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. Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate disodium, although as there are no clinical data available in patients with severe liver impairment, no specific recommendations can be given for this patient population**.** Medac Disodium Pamidronate 3 mg/ml displays little potential for interaction with other medicinal products both at the metabolic level and at the level of protein binding (see section 5.2 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

In pregnant rats, pamidronate has been shown to cross the placenta and accumulate in foetal 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 an increasing pup mortality when given orally at daily doses of 60 mg/kg (approximately equivalent to 1.2 mg/kg intravenously) 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 disodium 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 disodium doses (1-6 mg/kg/day) interfered (pre-partum distress and fetotoxicity) with normal parturition in the rat. These effects: foetal developmental abnormalities, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels.

Only low intravenous doses have been investigated in pregnant rabbits, because of maternal toxicity, but the highest dose used (1.5 mg/kg/day) was associated with an increased resorption rate and reduced ossification. However 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
Pamidronate disodium by daily oral administration was not carcinogenic in an 80-week or a 104-week study in mice.
Pamidronate disodium showed no genotoxic activity in a standard battery of assays for gene mutations and chromosomal damage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Pamidronate will form complexes with divalent cations and should not be added to calcium-containing intravenous solutions.
The medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Solutions of pamidronate disodium are not soluble in lipophilic nutrition solutions, e.g. soya-bean oil.

6.3 Shelf life

Unopened vial: 4 years

Shelf life after dilution in 5 % glucose solution or in 0.9 % sodium chloride solution:
chemical and physical in-use stability has been demonstrated for 96 hours at 25 °C.

From a microbiological point of view, the medicinal 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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless 5 ml/10 ml/20 ml/30 ml glass vials (Ph. Eur., Type 1) and bromobutylrubber stoppers (Ph. Eur., Type 1).
Pack sizes:
1, 4 or 10 vials containing 5 ml sterile concentrate. Also available as multipacks of 4 packs each containing 1 vial.
1, 4 or 10 vials containing 10 ml sterile concentrate. Also available as multipacks of 4 packs each containing 1 vial.
1, 4 or 10 vials containing 20 ml sterile concentrate. Also available as multipacks of 4 packs each containing 1 vial.
1, 4 or 10 vials containing 30 ml sterile concentrate. Also available as multipacks of 4 packs each containing 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Must be diluted with 5 % glucose solution or 0.9 % sodium chloride solution prior to administration.
The concentration of pamidronate disodium in the infusion solution should not exceed 90 mg/250 ml.
Do not use the solution if particles are present.
Any portion of the contents remaining after use should be discarded.
Medac Disodium Pamidronate 3 mg/ml, sterile concentrate is for single use only.
The diluted solution for infusion should be visually inspected and only clear solutions practically free from particles should be used.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische
Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER

PL 11587/0027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/03/2014

10. DATE OF REVISION OF THE TEXT

04/2022