

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 a 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

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

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.

Children and adolescents (< 18 years):

There is not enough clinical experience available for the use of pamidronate disodium in children and adolescents (< 18 years) (see section 4.4).

Use only freshly prepared and clear dilutions!

Tumour-induced hypercalcaemia:

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

| Initial plasma calcium level | | Recommended total dose of pamidronate disodium | Concentration of solution for infusion | Maximum infusion rate |
|------------------------------|----------------------|--|--|-----------------------|
| (mmol/l) | (mg %) (mg/100ml) | (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 2-4 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 24-48 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/2h every 4 weeks 90 mg/4h every 4 weeks | 90/ 250 | 45 |
| Multiple Myeloma | | 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).

Dose adjustment is not necessary in mild (creatinine clearance 61-90 ml/min) to moderate renal impairment (creatinine clearance 30-60 ml/min). In such patients, the infusion rate should not exceed 90 mg/4h (approximately 20-22 mg/h).

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 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.

Liver impairment:

There are no published data for the use of pamidronate disodium in patients with hepatic impairment available. Therefore no specific recommendations can be given for Pamidronate disodium in such patients (see section 5.2).

4.3 Contraindications

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

Breast feeding is contra-indicated (see also section 4.6).

4.4 Special warnings and precautions for use

Warnings

Medac Disodium Pamidronate 3 mg/ml is a sterile concentrate and must therefore always be diluted and then given as a slow intravenous infusion (see section 4.2). Medac Disodium Pamidronate 3 mg/ml should be given only as an intravenous infusion.

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.

Do not co-administer Medac Disodium Pamidronate 3 mg/ml with other bisphosphonates. If other calcium lowering agents are used in conjunction with pamidronate disodium, significant hypocalcaemia may result.

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

Precautions

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy with Medac Disodium Pamidronate 3 mg/ml. Patients with anaemia, leukopenia or thrombocytopenia should have regular haematology assessments.

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

Although pamidronate is excreted unchanged by the kidneys, the medicinal product has been used without apparent increase in adverse effects in patients with significantly elevated plasma creatinine levels (including patients undergoing renal replacement therapy with both haemodialysis and peritoneal dialysis). However, experience with pamidronate disodium in patients with severe renal impairment (serum creatinine: >440 micromol/l, or 5 mg/dl in TIH [Tumour-induced hypercalcaemia] patients; 180 micromol/l, or 2 mg/dl in multiple myeloma patients) is limited. If clinical judgement determines that the potential benefits outweigh the risk in such cases, Medac Disodium Pamidronate 3 mg/ml should be used cautiously and renal function carefully monitored.

Fluid balance (urine output, daily weights) should also be followed carefully. There is very little experience of the use of pamidronate disodium in patients receiving haemodialysis. No specific recommendation on patients with severe liver impairment can be given as there are no clinical data available.

Patients should have standard laboratory (serum creatinine and BUN [blood urea nitrogen]) and clinical renal function parameters periodically evaluated, especially those receiving frequent pamidronate disodium 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). 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 disodium in patients with multiple myeloma. However, underlying disease progression and/or concomitant complications were also present and therefore a causal relationship with pamidronate disodium is unproven.

It is essential in the initial treatment of tumour induced hypercalcaemia that intravenous rehydration be instituted to restore urine output. Patients should be hydrated adequately throughout treatment but overhydration must be avoided. In patients with cardiac disease, especially in the elderly, additional saline overload may precipitate cardiac failure (left ventricular failure or congestive heart failure). Fever (influenza-like symptoms) may also contribute to this deterioration.

The safety and efficacy of pamidronate disodium in children and adolescents (< 18 years) has not been established.

Osteonecrosis of the jaw

Osteonecrosis of the jaw has been reported in patients with cancer receiving treatment regimens including Pamidronate. Osteonecrosis of the jaw has multiple well documented risk factors including cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anemia, coagulopathies, infection, pre-existing oral disease).

The majority of reported cases have been associated with dental procedures such as tooth extraction. Many of these patients were also receiving chemotherapy or corticosteroids and had signs of local infection including osteomyelitis.

A dental examination with appropriate advice should be considered prior to treatment with Pamidronate.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pamidronate disodium has been administered concomitantly with commonly used anti-tumour medicinal products 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).

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

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

4.6 Pregnancy and lactation

Use in pregnancy:

There are no adequate data from the use of pamidronate disodium 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 whole period of gestation in animals, pamidronate can cause bone mineralization disorder especially of long bones resulting in angular distortion.

The potential risk for humans is unknown. Therefore, pamidronate disodium should not be used during pregnancy except in cases of life-threatening hypercalcaemia.

Use in lactation:

It is unknown whether Medac Disodium Pamidronate 3 mg/ml is excreted in human breast milk. Animal studies have shown excretion of pamidronate disodium in breast milk and a risk to the breast-fed child cannot be excluded.

Therefore, breast-feeding is contraindicated in women treated with pamidronate disodium (see also section 4.3).

4.7 Effects on ability to drive and use machines

Pamidronate disodium has minor or moderate influence on the 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 (>1/10) symptomatic adverse reactions are influenza-like symptoms and mild fever. This mild fever (an increase in body temperature of 1-2 °C) usually occurs within the first 48 hours as a first-dose, dose-related, self-limiting reaction, often without further concomitant symptoms, and usually lasts no longer than 24 hours.

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

Osteonecrosis primarily involving the jaws has been reported rarely (see 4.4 "Precautions"). Symptomatic hypocalcaemia is very rare (<1/10,000).

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.

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

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)

| | |
|--------------------------------------|---|
| Blood and lymphatic system disorders | Common (>1/100, <1/10) Lymphopenia Uncommon (>1/1,000, <1/100) Anaemia, leukopenia Very rare (<1/10,000), including isolated reports Thrombocytopenia |
| Immune system disorders | Uncommon (>1/1,000, <1/100) Hypersensitivity including anaphylactic reactions, bronchospasm, dyspnoea, angioneurotic oedema Very rare (<1/10,000), including isolated reports Anaphylactic shock, reactivation of herpes simplex and herpes zoster |
| Metabolism and nutrition disorders | Very common (>1/10) Hypocalcaemia, hypophosphataemia Common (>1/100, <1/10) Hypomagnesaemia Uncommon (>1/1,000, <1/100) Hyperkalaemia, hypokalaemia, hypernatraemia Very rare (<1/10,000), including isolated reports Hypernatraemia with confusional state |
| Nervous system disorders | Common (>1/100, <1/10) Headache Uncommon (>1/1,000, <1/100) Agitation, confusional state, dizziness, insomnia, somnolence, lethargy Very rare (<1/10,000), including isolated reports Seizures, visual hallucinations, symptomatic hypocalcaemia (paraesthesia, tetany, muscle cramps) |

| | |
|--|--|
| Eye disorders | <p>Uncommon (>1/1,000, <1/100) Uveitis (iritis, iridocyclitis), scleritis, episcleritis, conjunctivitis</p> <p>Very rare (<1/10,000), including isolated reports Xanthopsia, orbital inflammation</p> |
| Cardiac disorders/ Vascular disorders | <p>Uncommon (>1/1,000, <1/100) Hypertension</p> <p>Very rare (<1/10,000), including isolated reports Hypotension, heart disease aggravated (left ventricular failure / congestive cardiac failure) with dyspnoea, pulmonary oedema due to fluid overload</p> <p>Not known (cannot be estimated from the available data) Atrial fibrillation</p> |
| Gastrointestinal disorders | <p>Common (>1/100, <1/10) Nausea, vomiting</p> <p>Uncommon (>1/1,000, <1/100) Abdominal pain, anorexia, diarrhoea, constipation, dyspepsia</p> <p>Very rare (<1/10,000), including isolated reports Gastritis</p> |
| Skin and subcutaneous tissue disorders | <p>Uncommon (>1/1,000, <1/100) Rash, pruritus</p> |
| Musculoskeletal and connective tissue disorders | <p>Common (>1/100, <1/10) Transient bone pain, arthralgia, myalgia</p> <p>Uncommon (>1/1,000, <1/100) Muscle cramp</p> <p>Rare (>1/10,000, <1/1,000) Osteonecrosis primarily involving the jaws, atypical subtrochanteric and diaphyseal femoral fractures</p> |
| Renal and urinary disorders | <p>Rare (>1/10,000, <1/1,000) Focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome, renal tubular disorder, glomerulonephropathy, tubulointerstitial nephritis</p> <p>Very rare (<1/10,000), including isolated reports Renal function aggravated in patients with multiple myeloma, haematuria, renal failure acute, renal function aggravated in patients with pre-existing renal disease.</p> |
| General disorders and administration site conditions | <p>Very common (>1/10) Fever and influenza like symptoms sometimes accompanied by malaise, rigors, fatigue and flushing</p> <p>Common (>1/100, <1/10) Infusion site reactions like infusion site pain, infusion site rash, infusion site swelling, infusion site induration, infusion site phlebitis, thrombophlebitis, general body pain</p> |
| Investigations | <p>Very rare (<1/10,000), including isolated reports Liver function test abnormal, blood creatinine increased, blood urea increased</p> |

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

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: M05 BA 03

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 90mg 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 >1100 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

General characteristics:

Pamidronate has a strong affinity for calcified tissues, and total elimination of pamidronate from the body is not observed within the time-frame of experimental studies. Calcified tissues are therefore regarded as 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 drug-drug interactions 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 should not be mixed with other 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 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.

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
- 1, 4 or 10 vials containing 10 ml sterile concentrate
- 1, 4 or 10 vials containing 20 ml sterile concentrate
- 1, 4 or 10 vials containing 30 ml sterile concentrate

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 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
Fehlandtstraße 3
D-20354 Hamburg

8. MARKETING AUTHORISATION NUMBER

PL 11587/0027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2004; 09/03/2009

10. DATE OF REVISION OF THE TEXT

26/07/2011