Package leaflet: Information for the patient

Medac Disodium Pamidronate 3 mg/ml, sterile concentrate
Pamidronate disodium

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Medac Disodium Pamidronate 3 mg/ml is and what it is used for

Medac Disodium Pamidronate 3 mg/ml is a medicine which affects the formation and destruction of bone in the form of a solution which can be given as a slow injection via a drip.

Medac Disodium Pamidronate 3 mg/ml is used in three ways:
- It reduces high levels of calcium in the blood caused by cancers.
- It inhibits bone destruction in patients with spread of breast cancer to the bones.
- It is used in patients with advanced multiple myeloma (a tumour of bone marrow cells).

2. What you need to know before Medac Disodium Pamidronate 3 mg/ml is administered to you

Medac Disodium Pamidronate 3 mg/ml will not be used
- if you are allergic to pamidronate disodium, other bisphosphonate medicines or to any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor or pharmacist before you are given Medac Disodium Pamidronate 3 mg/ml
- if you are pregnant.
- if you are on a controlled sodium diet.
- if you have low levels of blood cells (red blood cells, white blood cells or platelets).
- if you have undergone thyroid surgery.
- if you have heart problems.
- if you have liver problems.
- if you suffer from kidney disease.
- if you are taking other medicines that can affect the kidneys.
- if you are taking other similar medicines that reduce the calcium level in blood.
- if you have or have had pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth. Your doctor may recommend a dental examination before you start treatment with Medac Disodium Pamidronate 3 mg/ml.

- if you are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Medac Disodium Pamidronate 3 mg/ml and inform your doctor about your dental treatment.

While being treated with Medac Disodium Pamidronate 3 mg/ml, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of a condition called osteonecrosis of the jaw.

Patients who are undergoing chemotherapy and/or radiotherapy, who are taking steroids, who are undergoing dental surgery, who do not receive routine dental care, who have gum disease, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing osteonecrosis of the jaw.

Your doctor will monitor serum electrolytes, calcium and phosphate following the initiation of your therapy with Medac Disodium Pamidronate 3 mg/ml and he/she will ensure that you are well hydrated.

Pamidronate should not be prescribed to you if you are pregnant unless absolutely necessary.

Pamidronate may interfere with the results of bone scans. Please tell your doctor or nurse if you are due to have a bone scan.

Other medicines and Medac Disodium Pamidronate 3 mg/ml
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines can interfere with your treatment. Please inform your doctor or pharmacist if you are taking any of the following:
- Other medicines for high calcium levels such as calcitonin.
- Other bisphosphonates.
- Other medicines that may affect the kidneys (your doctor or pharmacist will know which medicines these are).
- Thalidomide (used to treat some cancers).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
If you are pregnant or likely to become pregnant, you should inform your doctor before you take pamidronate disodium.

Breast-feeding
If you are breast-feeding you must not take pamidronate disodium.

Driving and using machines
Do not drive or use machines
- if you feel sleepy or dizzy following Medac Disodium Pamidronate 3 mg/ml infusion.
- if you experience any effect that may impair your ability to drive or use machines.

Medac Disodium Pamidronate 3 mg/ml contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium-free”.

3. How Medac Disodium Pamidronate 3 mg/ml is administered to you

Method and routes of administration
Medac Disodium Pamidronate 3 mg/ml is a solution which must be diluted and is then given to you as a slow injection via a drip.

Medac Disodium Pamidronate 3 mg/ml is administered to you in a prepared solution given very slowly into the vein via the drip (intravenous infusion). Your doctor will only use freshly prepared and clear dilutions and will not use the solution if particles are present.

Pamidronate disodium is given only to adults of 18 years and above under the supervision of a physician with the facilities to monitor its effects.

Dose
The dose of medicine given to you will depend upon your medical condition, the levels of calcium in your blood and how well your kidneys are working. The usual dose per treatment course is between 15 mg and 90 mg. Your doctor will decide how many infusions you need, how often they will be given and how long the therapy will be continued.

During treatment you will have blood tests and may be asked to provide urine samples.

If you have received more Medac Disodium Pamidronate 3 mg/ml than you should
As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much.
If you experience paraesthesia (pins and needles), tetany (muscle spasm particularly of the jaw or limbs) and hypotension (feeling light-headed) during treatment with Medac Disodium Pamidronate 3 mg/ml, you should inform the medical staff who will give you calcium into the vein to reverse the symptoms. It is unlikely that these symptoms would occur however during the infusion.

If nevertheless you have received doses higher than those recommended you will be carefully monitored by your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the following side effects may have been related to your underlying disease.

- Very common (may affect more than 1 in 10 people) side effects are **flu-like symptoms** and a **mild fever** (increase in body temperature of 1 – 2 °C) which occur within the first 48 hours and usually last no longer than 24 hours. Acute “influenza-like” reactions usually occur only with the first Medac Disodium Pamidronate 3 mg/ml infusion given to you.

If these effects happen to you they will usually disappear after you have received Medac Disodium Pamidronate 3 mg/ml for a while, so you should be able to continue the therapy. Tell your doctor if any effect becomes troublesome or lasts a long time.

- Not known (frequency cannot be estimated from the available data): Pain in the mouth, teeth and/or jaw, swelling or non-healing sores inside the mouth or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience such symptoms while being treated with Medac Disodium Pamidronate 3 mg/ml or after stopping treatment.

Cases of **bone damage (osteonecrosis)** - **primarily of the jaw** - have been reported predominantly in cancer patients treated with bisphosphonates including Medac Disodium Pamidronate 3 mg/ml. Many of these patients had signs of local infection including bone marrow inflammation (osteomyelitis) and

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, blood-clotting disorders [coagulopathies], infection, pre-existing oral disease). You should avoid dental surgery while you are treated with Medac Disodium Pamidronate 3 mg/ml. If you have developed osteonecrosis of jaw the dental surgery may exacerbate the condition. It is unknown whether the discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of jaw in patients requiring dental procedure.

If you develop symptoms such as sudden **itchy rash, swelling** of the hands, feet, ankles, face, lips, mouth or throat, **difficulty in swallowing or breathing**, this can be a severe allergic reaction. **If any of this happens, tell your doctor immediately.**

Pamidronate disodium may affect your blood. Your doctor will monitor for this with blood tests.

Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving pamidronate. It is currently unclear whether pamidronate causes this irregular heart rhythm. You should report to your doctor if you experience irregular heart rhythm during treatment with pamidronate.

Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

Very common (may affect more than 1 in 10 people)**:**
- Low level of calcium and phosphate in the blood.
- Fever and influenza-like symptoms sometimes accompanied by tiredness, shivering, fatigue and flushing.

Common (may affect up to 1 in 10 people)**:**
- Low level of red blood cells (anaemia).
- Low level of platelets in the blood (thrombocytopenia).
- Low level of lymphocytes (type of white blood cells) in the blood.
- Low level of potassium in the blood.
- Low level of magnesium in the blood.
- Symptoms from low blood calcium levels (pins and needles, muscle cramps or muscle spasm).
- Headache.
- Inability to sleep (insomnia).
- Condition of being sleepy (somnolence).
- Conjunctivitis (“pinkeye”).
- High blood pressure (hypertension).
- Gastrointestinal reactions such as nausea, vomiting, loss of appetite (anorexia), abdominal pain, diarrhoea, constipation as well as inflammation of the stomach (gastritis).
- Rash.
- Episodes of bone, joint or muscle pain.
- Pain, rash and swelling at the drip site, inflammation or thrombosis of the arm vein, general body pain.
- High levels of serum creatinine.

Uncommon (may affect up to 1 in 100 people)**:**
- Hypersensitivity including wheezing (bronchospasm), difficulty in breathing (dyspnoea), acute swelling of the eyelids, lips and tongue (angioneurotic oedema).
- Seizures.
- State of restlessness (agitation).
- Dizziness.
- State of being apathetic (lethargy).
- Inflammation of the uvea of the eye (uveitis).
- Low blood pressure (hypotension).

- Indigestion.
- Skin itching.
- Muscle cramps.
- Death of bone tissue (osteonecrosis).
- Reduction in the amount of urine produced (kidney failure).
- Abnormal liver and kidney blood tests.

Rare (may affect up to 1 in 1,000 people)**:**
- Unusual fracture of the thigh bone.
- Change in kidney function known as glomerulosclerosis, some of the symptoms of this condition may be fluid retention, nausea and fatigue.
- Protein leak into the urine associated with swelling of the legs and abdomen (nephrotic syndrome).

Very rare (may affect up to 1 in 10,000 people):
- Further episodes of past infection with cold sores or shingles.
- Decreased number of white blood cells in the blood (leukopenia).
- Anaphylactic shock (life-threatening allergy with immediate restlessness, lightheadedness or fainting, breathlessness, drop in blood pressure or itching).
- Elevated level of potassium in the blood.
- High levels of sodium in the blood (hypernatraemia).
- Confusional state (state of disorientation) due to high blood sodium levels.
- Confusion or visual hallucinations (seeing things that are not there).
- Irritation/inflammation of the episclera of the eye which causes pain and redness (episcleritis).
- Inflammation of the sclera of the eye which causes pain and redness (scleritis).
- Abnormal visual condition in which everything appears to have a yellow hue (xanthopsia).
- Worsening of heart failure with difficulty in breathing.
- Severe lung disease (acute respiratory distress syndrome).
- Inflammation of the lung (interstitial lung disease).
- Worsening of existing kidney disease.
- Blood in the urine.
- Kidney inflammation.
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Not known (frequency cannot be estimated from the available data)**:**
- Irregular heart rhythm (atrial fibrillation).
- Inflammation of structures within the orbit (orbital inflammation).
- Pain in the mouth, teeth and/or jaw, swelling or non-healing sores inside the mouth or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Medac Disodium Pamidronate 3 mg/ml

Keep this medicine out of the sight and reach of children.

This medicine is not used after the expiry date which is stated on the vial label and carton after “EXP”.

This medicine does not require any special storage conditions.

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.
Following dilution, 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. Contents of the pack and other information

What Medac Disodium Pamidronate 3 mg/ml contains
- The active substance is pamidronate disodium (from the group of bisphosphonates).
- The other ingredients are: Sodium hydroxide, hydrochloric acid and water for injections.

What Medac Disodium Pamidronate 3 mg/ml looks like and contents of the pack
Medac Disodium Pamidronate 3 mg/ml is presented in glass containers called vials.
Each millilitre (ml) of solution contains 3 milligrams (mg) of pamidronate disodium as pamidronic acid 2.527 mg.
The 5 ml vial (available in packs of 1, 4 or 10 vials and in multipacks of 4 packs each containing 1 vial) contains 15 mg of pamidronate disodium.
The 10 ml vial (available in packs of 1, 4 or 10 vials and in multipacks of 4 packs each containing 1 vial) contains 30 mg of pamidronate disodium.
The 20 ml vial (available in packs of 1, 4 or 10 vials and in multipacks of 4 packs each containing 1 vial) contains 60 mg of pamidronate disodium.
The 30 ml vial (available in packs of 1, 4 or 10 vials and in multipacks of 4 packs each containing 1 vial) contains 90 mg of pamidronate disodium.

Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer
medac
Gesellschaft für klinische
Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Czech Republic:
Pamidronate medac

Denmark, Finland, Germany, Slovak Republic, Sweden:
Pamifos

Netherlands:
Pamipro

United Kingdom (Northern Ireland):
Medac Disodium Pamidronate

This leaflet was last revised in 04/2022.

The following information is intended for medical or healthcare professionals only:

Method of administration

Medac Disodium Pamidronate 3 mg/ml is a concentrate for solution for infusion 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.

Tumour-induced hypercalcaemia
Patients must be adequately rehydrated with 0.9 % w/v sodium chloride solution before or and during administration of pamidronate disodium.
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 Multiple Myeloma	90 mg/2 h every 4 weeks 90 mg/4 h every 4 weeks	90/250 90/500	45 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.

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.

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

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.

Use only freshly prepared and clear dilutions!

Incompatibilities

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

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

The medicinal product must not be mixed with other medicinal products except those mentioned below.

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, concentrate for solution for infusion 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.

Shelf life and special precautions for storage

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.

This medicinal product does not require any special storage conditions.