Package leaflet: Information for the user
Disodium Pamidronate 15mg/ml Concentrate for Solution for Infusion

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Disodium Pamidronate 15mg/ml Concentrate for Solution for Infusion. In the rest of this leaflet it is called Disodium Pamidronate.

What is in this leaflet:

1. What Disodium Pamidronate is and what it is used for
The active ingredient is called Disodium Pamidronate.
Disodium pamidronate belongs to a group of medicines called bisphosphonates, which prevent bones from weakening and breaking.
Disodium Pamidronate is used to treat:
• high blood calcium levels (hypercalcaemia) due to tumours
• holes in the bone and bone pain due to the spread of breast cancer or bone marrow cancer (myeloma)
• Paget's disease of the bone (a chronic bone disorder)

2. What you need to know before you are given Disodium Pamidronate
You should not be given Disodium Pamidronate:
• if you are allergic to Disodium Pamidronate, any other bisphosphonate, or any of the other ingredients of this medicine (listed in section 6.)
• if you are pregnant
• if you are breast feeding

Warnings and precautions
Talk to your doctor or nurse before being given Disodium Pamidronate if you:
• are receiving dental treatment or will be undergoing dental surgery such as a tooth extraction (see information on osteonecrosis of the jaw below). Tell your dentist that you are being treated with Disodium Pamidronate
• suffer from kidney disease or any other kidney problems
• have had an operation for thyroid problems
• suffer from liver disease or any other liver problems
• suffer from heart disease

• suffer from calcium or vitamin D deficiency which may have been caused by not absorbing your food properly or by lack of exposure to the sun.
• are under 18 years of age.
• 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 Disodium Pamidronate.
• are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Disodium Pamidronate and inform your doctor about your dental treatment.

While being treated with Disodium Pamidronate , 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.

If any of the above statements apply to you, speak to your doctor or nurse before you are given Disodium Pamidronate.

If you have frequent infusions of Disodium Pamidronate over a prolonged period of time your doctor may perform blood tests during your treatment to monitor calcium and phosphate levels in the blood and to check your kidneys are working properly. Your doctor will test your kidney function before each course of treatment.

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

You should drink plenty of fluids during treatment so that you do not dehydrate.

Other medicines and Disodium Pamidronate
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. Taking another medicine while you are being given Disodium Pamidronate can affect how it or the other medicine works.

Please particularly check with your doctor if you are taking or need to take any of the following:
• any other bisphosphonates
• calcitonin, used to control the levels of calcium in the blood
• aminoglycoside antibiotics such as gentamicin and amikacin

If you are suffering from Paget's disease of the bone, you may be advised to take calcium and vitamin D tablets while you are being treated with Disodium Pamidronate.

Pregnancy and breast-feeding

You should not be given Disodium Pamidronate during pregnancy except when your calcium level is so high that it is life-threatening. You should let your doctor know immediately if you are pregnant or trying for a baby, before this medicine is given to you.

You should not breast feed whilst receiving Disodium Pamidronate as the active ingredient can enter breast milk. You should let your doctor know if you are breastfeeding or want to start breast-feeding while you are having treatment with Disodium Pamidronate.

Driving and using machines
Sleepiness and dizziness may rarely occur with Disodium Pamidronate. If these side effects are experienced whilst being given Disodium Pamidronate, you should not drive or operate machinery.

Disodium Pamidronate contains sodium
Disodium Pamidronate 1ml and 2ml ampoules contain less than 1mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

Disodium Pamidronate 4ml ampoules contain 24mg sodium (main component of cooking/table salt) in each ampoule. This is equivalent to 1.2% of the recommended maximum daily dietary intake of sodium for an adult.

Disodium Pamidronate 6ml ampoules contain 36mg sodium (main component of cooking/table salt) in each ampoule. This is equivalent to 1.8% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Disodium Pamidronate should be given
You will only be given Disodium Pamidronate under the supervision of a doctor and in suitable premises. Your doctor or nurse will prepare your injection by diluting it with a calcium free solution in a larger container (e.g. a salt solution). The mixture is given by a slow injection into a vein (intravenous infusion).

Disodium Pamidronate must never be given as a single short injection.

The total dose of Disodium Pamidronate may be given either in a single infusion or in several infusions over 2 to 4 consecutive days. The maximum dose per treatment course is 90mg. The recommended infusion rate should not be greater than 60mg/hour (1mg/minute) and the amount of Disodium Pamidronate in the infusion solution should not be greater than 90mg/250ml.

To treat high blood calcium levels due to tumours
The recommended total dose for adults is 15 to 90mg, depending on your blood calcium levels.

To treat holes in the bones and bone pain due to cancer spread
The recommended adult dose is 90mg every four weeks. For patients with breast cancer this may be given at three week intervals to coincide with chemotherapy.

To treat Paget's disease

The recommended adult dose is 30mg once a week for six weeks (total 180mg), or 30mg once and then 60mg every other week over 6 weeks (total 210mg). Treatment may be repeated every six months.

If you have kidney disease
Although you will be given the same dose as described above, if you have kidney disease your infusion will be given more slowly (the fastest infusion rate should be 20mg/hour).

If you have liver disease
No changes in the doses described above are required.

Your doctor will decide the dose that is best for you. If you do not understand, or are in any doubt, ask your doctor or nurse.

If you stop treatment with Disodium Pamidronate
Your doctor will decide when you can stop treatment with Disodium Pamidronate.

If you are given more Disodium Pamidronate than you should
A doctor or a nurse will give you this medicine. If you think you may have received too much Disodium Pamidronate, please tell your doctor or nurse immediately. Signs that you may have been given too much medicine include 'pins and needles', a locked jaw and low blood pressure due to low calcium levels.

If you think you have missed a dose of Disodium Pamidronate
A doctor or a nurse will give you this medicine. If you think you have missed a dose, please tell your doctor or nurse.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects of Disodium Pamidronate usually occur within the first 48 hours of treatment and then go away again.

Allergic reactions occur uncommonly. If you experience difficulty breathing, shortness of breath, swelling of the face, lips or eyes or anaphylactic shock (allergic shock) with a sudden decrease in blood pressure, contact your doctor immediately.

Other side effects include:
Very common: may affect more than 1 in 10 people
• fever and flu-like symptoms, such as feeling unwell, shivering, tiredness and hot flushes
• low calcium or low phosphate levels in the blood

Common: may affect up to 1 in 10 people
• reactions at the infusion site - pain, inflamed veins, swelling or redness
• bone pain, joint or muscle pain or general aches and pains
• nausea or vomiting
• headache
• reduction of lymphocytes (white cells) in the blood
• low magnesium levels in the blood

Uncommon: may affect up to 1 in 100 people
The following are uncommon symptoms, but if you do get any you must tell your doctor or nurse:
Muscle cramps, stomach pain, diarrhoea, constipation, loss of appetite, indigestion, feeling agitated, confusion, dizziness, difficulty sleeping, sleepiness, feeling lethargic, anaemia, a decrease of white blood cells, high or low blood pressure, rash, itching, eye pain or irritation, a yellow tinge to your vision or changes in various salts in the blood.

Very rare: may affect up to 1 in 10,000 people
Inflammation of the stomach, fits, hallucinations (seeing things that are not there), a tendency to bruise or bleed easily, cold sores or shingles, blood in the urine, worsening of kidney disease or changes in liver or kidney tests.

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.

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

- 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 Disodium Pamidronate or after stopping treatment.

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 tell your doctor if you experience irregular heart rhythm during treatment with pamidronate.

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 national reporting systems listed below.

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Disodium Pamidronate

Keep this medicine out of the sight and reach of children.
• Disodium Pamidronate should not be used after the expiry date given on the ampoule. The expiry date refers to the last day of that month.
• Your doctor, nurse or pharmacist will be responsible for storing and preparing Disodium Pamidronate before use and for checking that the ampoules have not passed their expiry date.
• The medicine should not be used if it shows any signs of deterioration such as going cloudy.
• Disodium Pamidronate should not be stored above 25°C.
• Once the solution has been diluted the product should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information
What Disodium Pamidronate contains
Each 1ml of solution contains 15mg disodium pamidronate.
The other ingredients are sodium chloride, sodium hydroxide (E524), hydrochloric acid (E507) and water for injections.

What Disodium Pamidronate looks like and contents of the pack
The injection is a clear, colourless solution.
1 ampoule of 1ml contains 15mg disodium pamidronate.
1 ampoule of 2ml contains 30mg disodium pamidronate.
1 ampoule of 4ml contains 60mg disodium pamidronate.
1 ampoule of 6ml contains 90mg disodium pamidronate.
Packs may contain 1, 2 or 4 ampoules. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Pinewood Laboratories Limited, Ballymacarbry, Clonmel, Co. Tipperary, Ireland
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

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INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Disodium pamidronate 15mg/ml concentrate for solution for infusion
Please refer to the Summary of Product Characteristics (SmPC) for further details on this product.

Qualitative and Quantitative Composition
1ml of concentrate contains 15mg disodium pamidronate.
One ampoule of 1ml contains 15mg disodium pamidronate.
One ampoule of 2ml contains 30mg disodium pamidronate.
One ampoule of 4ml contains 60mg disodium pamidronate.
One ampoule of 6ml contains 90mg disodium pamidronate.

Excipient with known effect

One ampoule of 1ml contains 6mg sodium.
One ampoule of 2ml contains 12mg sodium.
One ampoule of 4ml contains 24mg sodium.
One ampoule of 6ml contains 36mg sodium.
For a full list, see below under 'List of excipients'.

Pharmaceutical Form
Concentrate for solution for infusion.

Colourless solution, free from particles.

Therapeutic indications
Treatment of conditions associated with increased osteoclast activity:
- Tumour-induced hypercalcaemia
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer or multiple myeloma
- Paget's disease of bone.

Posology and method of administration

Disodium pamidronate concentrate must never be given as a bolus injection (see SmPC). The concentrate of disodium pamidronate concentrate in ampoules should be diluted in a calcium-free infusion solution (0.9 % Sodium Chloride Intravenous Infusion B.P. is recommended) and infused slowly.

The infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of disodium pamidronate concentrate in the infusion solution should not exceed 90mg/250ml. A dose of 90mg should normally be administered as a 2-hour infusion in 250mL infusion solution. However, in patients with multiple myeloma and in patients with tumour-induced hypercalcaemia, it is recommended not to exceed 90mg in 500mL over 4 hours.

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 20mg/h (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.

Until further experience is gained, disodium pamidronate concentrate is only recommended for use in adult patients.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Disodium Pamidronate on an individual patient basis, particularly after 5 or more years of use.

Tumour-induced hypercalcaemia
It is recommended that patients be rehydrated with 0.9% w/v sodium chloride solution before or during treatment.

The total dose of disodium pamidronate concentrate 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 serum calcium		**Recommended total**
(mmol/l)	**(mg %)**	**dose (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 disodium pamidronate concentrate 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 repeated courses.

A significant decrease in serum calcium is generally observed 24-48 hours after administration of Disodium Pamidronate Injection, and normalisation is usually achieved within three to seven 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 disodium pamidronate concentrate may become less effective as the number of treatments increases.

Adults and Elderly
Predominantly lytic bone metastases and multiple myeloma

The recommended dose of disodium pamidronate for the treatment of predominantly lytic bone metastases and multiple myeloma is 90mg administered as a single infusion every 4 weeks.

In patients with bone metastases who receive chemotherapy at 3-weekly intervals, disodium pamidronate 90mg may also be given on a 3-weekly schedule.

Osteolytic lesions and bone pain in bone metastases associated with breast cancer

The recommended dose is 90mg every four weeks. This dose may also be administered at three weekly intervals to coincide with chemotherapy if desired.

Paget's disease of Bone

The recommended total dose of disodium pamidronate for a treatment course is 180 to 210mg. This can be administered either in 6 unit doses of 30mg once a week (total dose of 180mg), or in 3 unit doses of 60mg every other week. Experience to date suggests that any mild and transient unwanted effects tend to occur after the first dose. For this reason if unit doses of 60mg are used it is recommended that treatment be started with an initial additional

dose of 30mg (i.e. total dose 210mg). Each dose of 30 or 60mg should be diluted in 125 or 250 ml 0.9% w/v Sodium Chloride Intravenous Infusion B.P. respectively, and the infusion rate should not exceed 60mg/hour (1mg/min). This regimen or increased dose levels according to disease severity, up to a maximum total dose of 360mg (in divided doses of 60mg) can be repeated every six months until remission of disease is achieved, and if relapse occurs.

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

As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of disodium pamidronate. In patients receiving disodium pamidronate for bone metastases or multiple myeloma who show evidence of deterioration in renal function, disodium pamidronate 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.
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/4h (approximately 20 to 22 mg/h).

Hepatic impairment
Although patients with hepatic impairment exhibited higher mean AUC and Cmax values compared to patients with normal hepatic function, this is not perceived as being clinically relevant. As pamidronate is still rapidly cleared from the plasma almost entirely into the bone, and as is administered on a monthly basis for chronic treatment, drug accumulation is not expected. Therefore no dose adjustment is necessary in patients with mild to moderate abnormal hepatic function (see Pharmacokinetic properties - Hepatic impairment). Clinical data in patients with severe hepatic impairment is not available. Pamidronate should be administered to this patient population with caution.

Children
There is no clinical experience of the use of disodium pamidronate in children.

Pharmaceutical Particulars

List of excipients
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for Injections

Incompatibilities

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

Shelf life
Three years
Reconstituted solutions that have been further diluted with one of the recommended diluents for intravenous infusion should be used immediately. Discard the unused portion.

Special precautions for storage
Do not store above 25°C.

Chemical and physical in-use stability has been demonstrated for 48 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.

Also refer to the information above, under 'Shelf life'.

Nature and contents of container

1ml, 2ml, 4ml or 6ml polyethylene ampoules in packs of 1, 2 or 4 ampoules.

Not all pack sizes may be marketed.

Special precautions for disposal

The concentrate should be diluted with a calcium-free infusion solution (0.9% w/v Sodium Chloride Intravenous Infusion BP is recommended) before administration.

Marketing Authorisation Holder
Pinewood Laboratories Limited., Ballymacarbry, Clonmel, Co. Tipperary, Ireland

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12/2020