PAMIDRONATE DISODIUM 3MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0029
PAMIDRONATE DISODIUM 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0030
PAMIDRONATE DISODIUM 9MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0031

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PAMIDRONATE DISODIUM 3MG/ML, 6MG/ML AND 9MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0029-31

LAY SUMMARY

On 10 June 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) granted APSLA Limited licences for the medicinal products Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for solution for infusion (PL 33410/0029, 0030 and 0031). These are prescription-only medicines (POM) to treat high blood calcium levels caused by some cancers. In some patients with cancer, it is also used to treat bone disease and to help relieve bone pain. Pamidronate is also used to treat Paget’s disease.

The active ingredient is pamidronate disodium. This is one of a group of medicines called bisphosphonates. Pamidronate helps to regulate the amount of calcium in the blood. High blood calcium levels (hypercalcaemia) occur in a number of conditions, including some types of cancer. Often, hypercalcaemia is caused by the release of calcium from bones. Pamidronate sticks to the bones and helps to reduce the release of calcium into the blood. If untreated, hypercalcaemia can cause symptoms such as nausea, tiredness and confusion.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for solution for infusion outweigh the risks; hence Marketing Authorisations have been granted.
PAMIDRONATE DISODIUM 3MG/ML, 6MG/ML AND 9MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0029-31

SCIENTIFIC DISCUSSION

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**INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted APSLA Limited marketing authorisations for the medicinal products Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for solution for infusion (PL 33410/0029-31) on 10 June 2010. Pamidronate is indicated for the treatment of conditions associated with increased osteoclast activity:

- The treatment of 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.

The application was submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Aredia Dry Powder 15mg, 30mg and 90mg, which were originally licensed to Ciba-Geigy PLC MOD in October 1992 (they are currently licensed to Novartis Pharmaceuticals UK Limited).

Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for solution for infusion contain the active ingredient pamidronate disodium. Pamidronate is an intravenously active amino-substituted bisphosphonate which produces potent and specific inhibition of bone resorption at doses devoid of any significant detrimental effect on bone growth and mineralisation. Clinical trials indicate that pamidronate is effective in a variety of conditions characterised by pathologically enhanced bone turnover, including Paget's disease, hypercalcaemia of malignancy, osteolytic bone metastasis, steroid-induced osteoporosis and idiopathic osteoporosis. Pamidronate is highly effective in restoring normocalcaemia in patients with hypercalcaemia of malignancy associated with bone metastases but, in common with other bisphosphonates, is marginally less effective against humoral hypercalcaemia of malignancy.

The principal pharmacologic action of pamidronate is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Pamidronate binds to calcium phosphate (hydroxyapatite) crystals in bone and may directly block dissolution of this mineral component of bone. Pamidronate inhibits bone resorption apparently without inhibiting bone formation and mineralization. Of relevance to the treatment of hypercalcaemia of malignancy is the finding that pamidronate inhibits the accelerated bone resorption that results from osteoclast hyperactivity induced by various tumours in animal studies.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Pamidronate disodium
Chemical Name: Disodium 3-amino-1-hydroxypropylidenebis (phosphonate) pentahydrate (IUPAC).

Molecular Formula: $\text{C}_3\text{H}_9\text{NNa}_2\text{O}_7\text{P}_2 \cdot 5 \text{H}_2\text{O}$

Structure:

![Molecular Structure of Pamidronate Disodium](image)

Molecular weight: 369.1

Appearance: A white or almost white crystalline powder. Soluble in water, practically insoluble in methylene chloride. It is sparingly soluble in dilute mineral acids and dissolves in dilute alkaline solutions.

Pamidronate disodium pentahydrate is the subject of a European Pharmacopeia monograph.

All aspects of the manufacture and control of pamidronate disodium pentahydrate are controlled by a Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients, mannitol, phosphoric acid (for pH adjustment) and water for injections.

All excipients comply with their respective European Pharmacopoeia monographs. Suitable certificates of analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients are sourced from materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.
Pharmaceutical Development
Based on the data provided, the applicant’s Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for solution for infusion are considered bioequivalent to Aredia Dry Powder 15mg, 30 mg, and 90 mg (Novartis Pharmaceuticals UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparable impurity profiles have been provided for the proposed and originator products.

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The finished products (3mg/ml, 6mg/ml and 9mg/ml) are supplied in a 10ml Type I moulded flint glass vial with a butyl rubber stopper and coloured (light blue, red and dark-green, respectively) flip-off, tear-off aluminium seal. Pack size is 1 vial.

Specifications and certificates of analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

Stability
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions, “Store below 25°C. Store in the original package in order to protect from light.”

The following storage conditions are stipulated for the diluted product:
Following dilution in 0.9% sodium chloride and 5% glucose infusion solutions, chemical and physical in-use stability has been demonstrated for 24 hours at temperatures not exceeding 25°C.

If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between dilution and storage in a refrigerator at 2 to 8°C and end of administration must not exceed 24 hours.
Bioequivalence/bioavailability
A bioequivalence study is not necessary to support these applications for parenteral products.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
All aspects of the MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of pamidronate disodium are well-known, no further studies are required and none have been provided.

PRECLINICAL EXPERT REPORT
The preclinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an environmental risk assessment.

CONCLUSION
There are no objections to the approval of these products from a preclinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY, EFFICACY AND SAFETY
No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study is not necessary to support these applications for parenteral products.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, sub-point 5.1.6, Parenteral solutions).

CLINICAL EXPERT REPORT
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

SPC, PIL AND LABELLING
The SPCs, PIL and labelling are medically acceptable. The SPCs are consistent with those for the originator products.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT
QUALITY
The important quality characteristics of Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
No bioequivalence studies were submitted or required for these applications. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with pamidronate disodium is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
PAMIDRONATE DISODIUM 3MG/ML, 6MG/ML AND 9MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0029-31

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 04 November 2008.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 11 November 2008.

3 Following assessment of the application the MHRA requested further information relating to the clinical dossiers on 03 March 2009 and the quality dossiers on 19 February 2009.

4 The applicant responded to the MHRA’s requests, providing further information on the clinical dossiers on 29 June 2009 and the quality dossiers on 09 December 2009.

5 The applications were determined on 10 June 2010.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pamidronate Disodium 3 mg/ml Concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of concentrate for solution for infusion contains 3.97mg/ml of pamidronate disodium pentahydrate, which is equivalent to 3mg/ml of pamidronate disodium anhydrous.

1 vial of 10 ml of Concentrate for solution for infusion contains 30 mg of pamidronate disodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Pamidronate Disodium 3 mg/ml is a clear colourless solution in flint glass vial.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of conditions associated with increased osteoclast activity:
- The treatment of 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.

4.2 Posology and method of administration
Pamidronate disodium must never be given as a bolus injection (see section 4.4). The solution must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to 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 60 mg/250 ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20 mg/hour (see also “Renal Impairment”). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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 pamidronate disodium to be used for a treatment course depends on the patient's initial serum calcium levels. The following guidelines are derived from clinical data on uncorrected calcium values. However, doses within the ranges given are also applicable for calcium values corrected for serum or albumin in rehydrated patients.
### Initial serum calcium

<table>
<thead>
<tr>
<th>Initial serum calcium (mmol/litre)</th>
<th>Recommended total dose (mg %) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 3.0</td>
<td>up to 12.0</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>12.0-14.0</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>14.0-16.0</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>&gt;16.0</td>
</tr>
</tbody>
</table>

The total dose of pamidronate disodium may be administered either in a single infusion or in multiple infusions over 2-4 consecutive days. The maximum dose per treatment course is 90 mg for both initial and repeat courses.

A significant decrease in serum calcium is generally observed 24-48 hours after administration of pamidronate disodium, and normalisation is usually achieved within 3 to 7 days. If normocalcaemia is not achieved within this time, a further dose may be given. The duration of the response may vary from patient to patient, and treatment can be repeated whenever hypercalcaemia recurs. Clinical experience to date suggests that pamidronate disodium may become less effective as the number of treatments increases.

**Osteolytic lesions and bone pain in multiple myeloma**

The recommended dose is 90 mg every 4 weeks.

**Osteolytic lesions and bone pain 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.

**Paget's disease of bone**

The recommended treatment course consists of a total dose of 180 mg administered in unit doses of either 30 mg once a week for 6 consecutive weeks, or 60 mg every other week over 6 weeks. Experience to date suggests that any mild and transient unwanted effects (see section 4.8) tend to occur after the first dose. For this reason if unit doses of 60 mg are used it is recommended that treatment be started with an initial additional dose of 30 mg (i.e. total dose 210 mg). Each dose of 30 or 60 mg should be diluted in 125 or 250 ml 0.9 % w/v Sodium Chloride Intravenous Infusion BP respectively, and the infusion rate should not exceed 60 mg/hour (1 mg/min). This regimen or increased dose levels according to disease severity, up to a maximum total does of 360 mg (in divided doses of 60 mg) can be repeated every 6 months until remission of disease is achieved, and if relapse occurs.

**Renal Impairment**

Pamidronate disodium should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. Because there is only limited clinical experience in patients with severe renal impairment no dose recommendations for this patient population can be made (see Section 4.4 “Special warnings and special precautions for use” and Section 5.2 “Pharmacokinetic properties”).

As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of pamidronate disodium. In patients receiving pamidronate disodium for bone metastases or multiple myeloma who show evidence of deterioration in renal function, pamidronate disodium treatment should be withheld until renal function returns to within 10% of the baseline value. This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5mg/dL.
- For patients with abnormal baseline creatinine, increase of 1.0mg/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 61-90 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).

**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 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 Section 5.2 Pharmacokinetic properties “Hepatic impairment”). Clinical data in patients with severe hepatic impairment is not available (see Section 4.4 Special warnings and special precautions for use). Pamidronate should be administered to this patient population with caution.

**Children**

There is no clinical experience with pamidronate disodium in children. Therefore until further experience is gained, pamidronate disodium is only recommended for use in adult patients.

### 4.3 Contraindications

Pamidronate disodium is contraindicated in:
- patients with known hypersensitivity to pamidronate or to other bisphosphonates, or to any of the excipients of Aredia,
- pregnancy,
- breast feeding women.

### 4.4 Special warnings and precautions for use

Pamidronate must never be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see Section 4.2 Posology and method of administration).

Patients must be assessed prior to administration of Pamidronate 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 Pamidronate. Patients who have undergone thyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.

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.

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

**Renal Insufficiency**

Bisphosphonates, including Pamidronate, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Pamidronate. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate in patients with multiple myeloma.

Pamidronate is excreted intact primarily via the kidney (see Section 5.2 Pharmacokinetic properties), 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 Pamidronate should not exceed 90mg, and the recommended infusion time should be observed (See Section 4.2. Posology and method of administration).
As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Pamidronate.

Patients treated with Pamidronate for bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see Section 4.2. Posology and method of administration).

Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. (See section 4.2 Posology and method of administration “Renal impairment”). Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made (See Section 4.2 “Posology and method of administration” and Section 5.2 “Pharmacokinetic properties”). Pamidronate 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 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 Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

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 (e.g. through malabsorption or lack of exposure to sunlight) and patients with Paget's disease of the bone should take oral calcium and vitamin D supplementation in order to minimise the potential risk of hypocalcaemia.

Osteonecrosis of the jaw
Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. 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. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes pamidronate disodium for infusion. The time to onset of symptoms varied from one day to several months after starting the drug with the majority occurring within a few days. Most patients had relief or improvement of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.
4.5 Interaction with other medicinal products and other forms of interaction

Pamidronate disodium has been administered concomitantly with commonly used anti-cancer agents without significant interactions.

Pamidronate 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 is used with other potentially nephrotoxic drugs.

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

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

4.6 Pregnancy and lactation

There are no adequate data from the use of pamidronate in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. Therefore, Pamidronate should not be used during pregnancy (see Section 4.3 Contraindications).

It is not known whether Pamidronate is excreted into human milk. Study in lactating rats has shown that pamidronate will pass into the milk. Mothers treated with Pamidronate should therefore not breast-feed their infants (see Section 4.3 Contraindications).

4.7 Effects on 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 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.

One case of acute lymphoblastic leukaemia has been reported in a patient with Paget’s disease. The causal relationship to the treatment or the underlying disease is unknown.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ System</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>reactivation of Herpes simplex, reactivation of Herpes zoster</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Blood and lymphatic system Disorders</td>
<td>Anaemia, thrombocytopenia, lymphocytopenia</td>
<td></td>
<td></td>
<td></td>
<td>leukopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Allergic reactions including anaphylactoid</td>
<td></td>
<td></td>
<td>anaphylactic shock</td>
</tr>
<tr>
<td>Frequency</td>
<td>Organ System</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
<td>Very rare (&lt;1/10,000) not known (cannot be estimated from the available data)</td>
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<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Very Common (≥1/10)</td>
<td>Metabolism and nutrition Disorders</td>
<td>Hypocalcaemia, hypophosphataemia</td>
<td>hypokalaemia, hypomagnesaemia, increase in serum creatinine.</td>
<td>abnormal liver function tests, increase in serum urea.</td>
<td>hyperkalaemia, hypernatraemia</td>
</tr>
<tr>
<td></td>
<td>Nervous system disorders</td>
<td>symptomatic hypocalcaemia (paraesthesia, tetany), headache, insomnia, somnolence.</td>
<td>seizures, agitation, dizziness, lethargy</td>
<td>confusion, visual hallucinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye disorders</td>
<td>conjunctivitis</td>
<td>uveitis (iritis, iridocyclitis).</td>
<td>scleritis, episcleritis, xanthopsia.</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac disorders / Vascular Disorders</td>
<td>hypertension</td>
<td>hypotension</td>
<td>left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.</td>
<td></td>
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<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, gastritis.</td>
<td>dyspepsia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue Disorders</td>
<td>rash</td>
<td>pruritus.</td>
<td></td>
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<tr>
<td></td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>transient bone pain, arthralgia, myalgia, generalised pain.</td>
<td>muscle cramps.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Renal and urinary disorders</td>
<td>acute renal failure.</td>
<td>focal segmental glomerulosclerosis</td>
<td>deterioration of pre-existing renal disease, haematuria.</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Organ System</td>
<td>Tissue</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------</td>
<td>---------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Common (≥1/10)</td>
<td>Frequency</td>
<td>Fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue and flushes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Organ System</td>
<td>Reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon (≥1/10,000 to &lt;1/1000)</td>
<td>System</td>
<td>Including the collapsing variant, nephrotic syndrome.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>Postmarketing experience: Commonly, cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including Pamidronate. Many of these patients had signs of local infection including 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, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4 Special warnings and special precautions for use).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Inhibitor of bone resorption

ATC code: M05BA03

Pamidronate disodium, is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals in vitro. Inhibition of osteoclastic bone resorption in vivo may be at least partly due to binding of the drug to the bone mineral.

Pamidronate suppresses the accesion of osteoclast precursors onto the bone. 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.

Hypercalcaemia can lead to a depletion in the volume of extracellular fluid and a reduction in the glomerular filtration rate (GFR). By controlling hypercalcaemia, pamidronate disodium improves GFR and lowers elevated serum creatinine levels in most patients.
Clinical trials in patients with breast cancer and predominantly lytic bone metastases or with multiple myeloma showed that pamidronate disodium prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain.

Paget's disease of bone, which is characterised by local areas of increased bone resorption and formation with qualitative changes in bone remodelling, responds well to treatment with pamidronate disodium. Clinical and biochemical remission of the disease has been demonstrated by bone scintigraphy, decreases in urinary hydroxyproline and serum alkaline phosphatase, and by symptomatic improvement.

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 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.

In animals and in man, a similar percentage of the dose is retained in the body after each dose of pamidronate disodium. Thus the accumulation of pamidronate in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

The percentage of circulating pamidronate bound to plasma proteins is relatively low (about 54 %) and increases when calcium concentrations are pathologically elevated.

Elimination
Pamidronate does not appear to be eliminated by biotransformation and it is almost exclusively eliminated by renal excretion. 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. The percentage of the dose retained in the body is independent of both the dose (range 15-180 mg) and the infusion rate (range 1.25-60 mg/h). From the urinary elimination of pamidronate, two decay phases with apparent half-lives of about 1.6 and 27 hours, can be observed. The apparent total plasma clearance is about 180mL/min and the apparent renal clearance is about 54 ml/min, There is a tendency for the renal clearance to correlate with creatinine clearance.

Characteristics in patients
Hepatic and metabolic clearance of pamidronate are insignificant. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).
Hepatic impairment
The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=9). Each patient received a single 90mg dose of Pamidronate infused over 4 hours. There was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function. Patients with hepatic impairment exhibited higher mean AUC (39.7%) and Cmax (28.6%) values. The difference was not considered clinically relevant. The mean ratio based on log transformed parameters of impaired versus normal patients was 1.38 (90% C.I. 1.12 – 1.70, P=0.02) for AUC and 1.23 (90% C.I. 0.89 – 1.70, P=0.27) for Cmax. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because pamidronate is administered on a monthly basis, drug accumulation is not expected. No changes in pamidronate dosing regimen are recommended for patients with mild to moderate abnormal hepatic function (see Section 4.2 Posology and method of administration).

Renal impairment
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 <30mL/min), the AUC of pamidronate was approximately 3 times higher than in patients with normal renal function (creatinine clearance >90mL/min). Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made (See Section 4.2 “Posology and method of administration” and Section 4.4 “Special warnings and special precautions for use”).

5.3 Preclinical safety data
The toxicity of pamidronate is characterised by direct (cytotoxic) effects on organs with a copious blood supply, particularly the kidneys following i.v. exposure. The compound is not mutagenic and does not appear to have carcinogenic potential.

Studies in rats and rabbits determined that pamidronate disodium produces maternal toxicity and embryo/fetal effects when administered at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion. The effects include protracted parturition leading to dystocia, and shortened long bones in the foetus. Animal data suggest that uptake of bisphosphonates into foetal bone is greater than into maternal bone.
6.4 Special precautions for storage
Following dilution in 0.9% sodium chloride and 5% glucose infusion solutions, chemical and physical in-use stability has been demonstrated for 24 hours at temperatures not exceeding 25°C.

If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between dilution and storage in a refrigerator at 2 to 8°C and end of administration must not exceed 24 hours.

Prior to first use: Store below 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container
10 ml Type I moulded flint glass vial with butyl rubber stopper and light blue coloured flip-off, tear-off aluminium seals in packs of 1 vial.

6.6 Special precautions for disposal
Must be diluted prior to administration.

The concentration of pamidronate disodium in the infusion solution should not exceed 60 mg/250 ml.

Do not use solution if particles are present.

Any portion of the contents remaining after use should be discarded.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/06/2010

10 DATE OF REVISION OF THE TEXT
10/06/2010
1 NAME OF THE MEDICINAL PRODUCT
Pamidronate Disodium 6 mg/ml Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of concentrate for solution for infusion contains 7.93mg/ml of pamidronate disodium pentahydrate, which is equivalent to 6mg/ml of pamidronate disodium anhydrous.

1 vial of 10 ml of Concentrate for solution for infusion contains 60 mg of pamidronate disodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.

Pamidronate Disodium 6 mg/ml is a clear colourless solution in flint glass vial.

4 CLINICAL PARTICULARS
Treatment of conditions associated with increased osteoclast activity:
• The treatment of 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.

4.2 Posology and method of administration
Pamidronate disodium must never be given as a bolus injection (see section 4.4). The solution must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to 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 60 mg/250 ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20 mg/hour (see also “Renal Impairment”). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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 pamidronate disodium to be used for a treatment course depends on the patient's initial serum calcium levels. The following guidelines are derived from clinical data on uncorrected calcium values. However, doses within the ranges given are also applicable for calcium values corrected for serum or albumin in rehydrated patients.

<table>
<thead>
<tr>
<th>Initial serum calcium (mmol/litre)</th>
<th>(mg %)</th>
<th>Recommended total dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 3.0</td>
<td>up to 12.0</td>
<td>15-30</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>12.0-14.0</td>
<td>30-60</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>14.0-16.0</td>
<td>60-90</td>
</tr>
<tr>
<td>&gt;=4.0</td>
<td>&gt;16.0</td>
<td>90</td>
</tr>
</tbody>
</table>
The total dose of pamidronate disodium may be administered either in a single infusion or in multiple infusions over 2-4 consecutive days. The maximum dose per treatment course is 90 mg for both initial and repeat courses.

A significant decrease in serum calcium is generally observed 24-48 hours after administration of pamidronate disodium, and normalisation is usually achieved within 3 to 7 days. If normocalcaemia is not achieved within this time, a further dose may be given. The duration of the response may vary from patient to patient, and treatment can be repeated whenever hypercalcaemia recurs. Clinical experience to date suggests that pamidronate disodium may become less effective as the number of treatments increases.

Osteolytic lesions and bone pain in multiple myeloma
The recommended dose is 90 mg every 4 weeks.

Osteolytic lesions and bone pain 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.

Paget's disease of bone
The recommended treatment course consists of a total dose of 180 mg administered in unit doses of either 30 mg once a week for 6 consecutive weeks, or 60 mg every other week over 6 weeks. Experience to date suggests that any mild and transient unwanted effects (see section 4.8) tend to occur after the first dose. For this reason if unit doses of 60 mg are used it is recommended that treatment be started with an initial additional dose of 30 mg (i.e. total dose 210 mg). Each dose of 30 or 60 mg should be diluted in 125 or 250 ml 0.9 % w/v Sodium Chloride Intravenous Infusion BP respectively, and the infusion rate should not exceed 60 mg/hour (1 mg/min). This regimen or increased dose levels according to disease severity, up to a maximum total does of 360 mg (in divided doses of 60 mg) can be repeated every 6 months until remission of disease is achieved, and if relapse occurs.

Renal Impairment
Pamidronate disodium should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. Because there is only limited clinical experience in patients with severe renal impairment no dose recommendations for this patient population can be made (see Section 4.4 “Special warnings and special precautions for use” and Section 5.2 “Pharmacokinetic properties”).

As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of pamidronate disodium. In patients receiving pamidronate disodium for bone metastases or multiple myeloma who show evidence of deterioration in renal function, pamidronate disodium treatment should be withheld until renal function returns to within 10% of the baseline value. This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

• For patients with normal baseline creatinine, increase of 0.5mg/dL.
• For patients with abnormal baseline creatinine, increase of 1.0mg/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 61-90 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).

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 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 Section 5.2 Pharmacokinetic properties “Hepatic impairment”). Clinical data in patients with severe hepatic impairment is not available (see Section 4.4
Special warnings and special precautions for use). Pamidronate should be administered to this patient population with caution.

**Children**
There is no clinical experience with pamidronate disodium in children. Therefore until further experience is gained, pamidronate disodium is only recommended for use in adult patients.

### 4.3 Contraindications
Pamidronate disodium is contraindicated in:
- patients with known hypersensitivity to pamidronate or to other bisphosphonates, or to any of the excipients of Aredia,
- pregnancy,
- breast feeding women.

### 4.4 Special warnings and precautions for use
Pamidronate must never be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see Section 4.2 Posology and method of administration).

Patients must be assessed prior to administration of Pamidronate 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 Pamidronate. Patients who have undergone thyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.

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.

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

#### Renal Insufficiency
Bisphosphonates, including Pamidronate, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Pamidronate. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate in patients with multiple myeloma.

Pamidronate is excreted intact primarily via the kidney (see Section 5.2 Pharmacokinetic properties), 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 Pamidronate should not exceed 90mg, and the recommended infusion time should be observed (See Section 4.2. Posology and method of administration).

As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Pamidronate.

Patients treated with Pamidronate for bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see Section 4.2. Posology and method of administration).

Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. (See section 4.2 Posology and method of administration “Renal Impairment”). Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made.
(See Section 4.2 “Posology and method of administration” and Section 5.2 “Pharmacokinetic properties”). Pamidronate 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 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 Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

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 (e.g. through malabsorption or lack of exposure to sunlight) and patients with Paget's disease of the bone should take oral calcium and vitamin D supplementation in order to minimise the potential risk of hypocalcaemia.

Osteonecrosis of the jaw
Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. 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. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes pamidronate disodium for infusion. The time to onset of symptoms varied from one day to several months after starting the drug with the majority occurring within a few days. Most patients had relief or improvement of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

4.5 Interaction with other medicinal products and other forms of interaction
Pamidronate disodium has been administered concomitantly with commonly used anti-cancer agents without significant interactions.

Pamidronate 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 is used with other potentially nephrotoxic drugs.

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

Since pamidronate binds to bone, it could in theory interfere with bone scintigraphy examinations.
4.6 Pregnancy and lactation

There are no adequate data from the use of pamidronate in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. Therefore, Pamidronate should not be used during pregnancy (see Section 4.3 Contraindications).

It is not known whether Pamidronate is excreted into human milk. Study in lactating rats has shown that pamidronate will pass into the milk. Mothers treated with Pamidronate should therefore not breast-feed their infants (see Section 4.3 Contraindications).

4.7 Effects on 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 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.

One case of acute lymphoblastic leukaemia has been reported in a patient with Paget’s disease. The causal relationship to the treatment or the underlying disease is unknown.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ System</th>
<th>Syndrome/Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common</td>
<td>Infection</td>
<td>reactivation of Herpes simplex, reactivation of Herpes zoster</td>
</tr>
<tr>
<td>(≥1/10)</td>
<td>Blood and</td>
<td>Anaemia, thrombocytopenia, lymphocytopenia</td>
</tr>
<tr>
<td></td>
<td>lymphatic</td>
<td>leukopenia</td>
</tr>
<tr>
<td></td>
<td>system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Immune system disorders</td>
<td>Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke’s (angioneurotic) oedema.</td>
</tr>
<tr>
<td>(≥1/100 to &lt;1/10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Metabolism and nutrition Disorders</td>
<td>hypocalcaemia, hypophosphataemia, increase in serum creatinine.</td>
</tr>
<tr>
<td>(≥1/1000 to &lt;1/100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
<td>abnormal liver function tests, increase in serum urea.</td>
</tr>
<tr>
<td>(≥1/10,000 to &lt;1/1000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Nervous system disorders</td>
<td>hyperkalaemia, hypernatraemia</td>
</tr>
<tr>
<td>(&lt;1/10,000), not known (cannot be estimated from the available data)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptomatic hypocalcaemia (paraesthesia, seizures, agitation, dizziness, confusion, visual hallucinations</td>
</tr>
<tr>
<td>Organ System</td>
<td>Frequency</td>
<td>Very Common (≥1/10)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders / Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue and flushes</td>
<td>reactions at the infusion site; pain, redness, swelling, induration, phlebitis, thrombophlebitis</td>
</tr>
</tbody>
</table>

Postmarketing experience: Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including Pamidronate. Many of these patients had signs of local infection including 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, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4 Special warnings and special precautions for use).

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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Inhibitor of bone resorption
ATC code: M05BA03

Pamidronate disodium, is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals \textit{in vitro}. Inhibition of osteoclastic bone resorption \textit{in vivo} may be at least partly due to binding of the drug to the bone mineral.

Pamidronate suppresses the accession of osteoclast precursors onto the bone. However, the local and direct antiresorptive effect of bone-bound biphosphonate appears to be the predominant mode of action \textit{in vitro} and \textit{in vivo}.

Experimental studies have demonstrated that pamidronate inhibits tumour-induced osteolysis when given prior to or at the time of inoculation or transplantation with tumour cells. Biochemical changes reflecting the inhibitory effect of pamidronate disodium on tumour-induced hypercalcaemia, are characterised by a decrease in serum calcium and phosphate and secondarily by decreases in urinary excretion of calcium, phosphate and hydroxyproline.

Hypercalcaemia can lead to a depletion in the volume of extracellular fluid and a reduction in the glomerular filtration rate (GFR). By controlling hypercalcaemia, pamidronate disodium improves GFR and lowers elevated serum creatinine levels in most patients.

Clinical trials in patients with breast cancer and predominantly lytic bone metastases or with multiple myeloma showed that pamidronate disodium prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain.

Paget's disease of bone, which is characterised by local areas of increased bone resorption and formation with qualitative changes in bone remodelling, responds well to treatment with pamidronate disodium. Clinical and biochemical remission of the disease has been demonstrated by bone scintigraphy, decreases in urinary hydroxyproline and serum alkaline phosphatase, and by symptomatic improvement.

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 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.

In animals and in man, a similar percentage of the dose is retained in the body after each dose of pamidronate disodium. Thus the accumulation of pamidronate in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered. The percentage of circulating pamidronate bound to plasma proteins is relatively low (about 54%) and increases when calcium concentrations are pathologically elevated.

**Elimination**

Pamidronate does not appear to be eliminated by biotransformation and it is almost exclusively eliminated by renal excretion. 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. The percentage of the dose retained in the body is independent of both the dose (range 15-180 mg) and the infusion rate (range 1.25-60 mg/h). From the urinary elimination of pamidronate, two decay phases with apparent half-lives of about 1.6 and 27 hours, can be observed. The apparent total plasma clearance is about 180 mL/min and the apparent renal clearance is about 54 mL/min. There is a tendency for the renal clearance to correlate with creatinine clearance.

**Characteristics in patients**

Hepatic and metabolic clearance of pamidronate are insignificant. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).

**Hepatic impairment**

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=9). Each patient received a single 90mg dose of Pamidronate infused over 4 hours. There was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function. Patients with hepatic impairment exhibited higher mean AUC (39.7%) and Cmax (28.6%) values. The difference was not considered clinically relevant. The mean ratio based on log transformed parameters of impaired versus normal patients was 1.38 (90% C.I. 1.12 – 1.70, P=0.02) for AUC and 1.23 (90% C.I. 0.89 – 1.70, P=0.27) for Cmax. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because pamidronate is administered on a monthly basis, drug accumulation is not expected. No changes in pamidronate dosing regimen are recommended for patients with mild to moderate abnormal hepatic function (see Section 4.2 “Posology and method of administration”).

**Renal impairment**

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 <30mL/min), the AUC of pamidronate was approximately 3 times higher than in patients with normal renal function (creatinine clearance >90mL/min). Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made (See Section 4.2 “Posology and method of administration” and Section 4.4 “Special warnings and special precautions for use”).

**5.3 Preclinical safety data**

The toxicity of pamidronate is characterised by direct (cytotoxic) effects on organs with a copious blood supply, particularly the kidneys following i.v. exposure. The compound is not mutagenic and does not appear to have carcinogenic potential.

Studies in rats and rabbits determined that pamidronate disodium produces maternal toxicity and embryo/foetal effects when administered at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion. The effects include protracted
parturition leading to dystocia, and shortened long bones in the foetus. Animal data suggest
that uptake of bisphosphonates into foetal bone is greater than into maternal bone

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Phosphoric acid
Water for Injections

6.2 Incompatibilities
Pamidronate must not be mixed with calcium-containing solution such as Ringer's solution.

To avoid potential incompatibilities, Pamidronate is to be diluted with 0.9% w/v sodium
chloride solution or 5% w/v glucose solution.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Following dilution in 0.9% sodium chloride and 5% glucose infusion solutions, chemical and
physical in-use stability has been demonstrated for 24 hours at temperatures not exceeding
25°C.

If not used immediately, the duration and conditions of storage prior to use are the care
provider's responsibility. The total time between dilution and storage in a refrigerator at 2 to
8°C and end of administration must not exceed 24 hours.

Prior to first use: Store below 25°C. Store in the original package in order to protect from
light.

6.5 Nature and contents of container
10 ml Type I moulded flint glass vial with butyl rubber stopper and red coloured flip-off, tear-
off aluminium seals in packs of 1 vial.

6.6 Special precautions for disposal
Must be diluted prior to administration.

The concentration of pamidronate disodium in the infusion solution should not exceed 60 mg/
250 ml.

Do not use solution if particles are present.

Any portion of the contents remaining after use should be discarded.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/06/2010

10 DATE OF REVISION OF THE TEXT
10/06/2010
1 **NAME OF THE MEDICINAL PRODUCT**
Pamidronate Disodium 9 mg/ml Concentrate for solution for infusion.

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each ml of concentrate for solution for infusion contains 11.90 mg/ml of pamidronate disodium pentahydrate, which is equivalent to 9 mg/ml of pamidronate disodium anhydrous.

1 vial of 10 ml of Concentrate for solution for infusion contains 90 mg of pamidronate disodium.

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Concentrate for solution for infusion.

Pamidronate Disodium 9 mg/ml is a clear colourless solution in flint glass vial.

4 **CLINICAL PARTICULARS**

*Treatment of conditions associated with increased osteoclast activity:*
- The treatment of 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.

4.2 **Posology and method of administration**
Pamidronate disodium must never be given as a bolus injection (see section 4.4). The solution must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to 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 60 mg/250 ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20 mg/hour (see also “Renal Impairment”). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

**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 pamidronate disodium to be used for a treatment course depends on the patient's initial serum calcium levels. The following guidelines are derived from clinical data on uncorrected calcium values. However, doses within the ranges given are also applicable for calcium values corrected for serum or albumin in rehydrated patients.

<table>
<thead>
<tr>
<th>Initial serum calcium</th>
<th>Recommended total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mmol/litre)</td>
<td>(mg %)</td>
</tr>
<tr>
<td>up to 3.0</td>
<td>up to 12.0</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>12.0-14.0</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>14.0-16.0</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>&gt;16.0</td>
</tr>
</tbody>
</table>
The total dose of pamidronate disodium may be administered either in a single infusion or in multiple infusions over 2-4 consecutive days. The maximum dose per treatment course is 90 mg for both initial and repeat courses.

A significant decrease in serum calcium is generally observed 24-48 hours after administration of pamidronate disodium, and normalisation is usually achieved within 3 to 7 days. If normocalcaemia is not achieved within this time, a further dose may be given. The duration of the response may vary from patient to patient, and treatment can be repeated whenever hypercalcaemia recurs. Clinical experience to date suggests that pamidronate disodium may become less effective as the number of treatments increases.

Osteolytic lesions and bone pain in multiple myeloma
The recommended dose is 90 mg every 4 weeks.

Osteolytic lesions and bone pain 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.

Paget’s disease of bone
The recommended treatment course consists of a total dose of 180 mg administered in unit doses of either 30 mg once a week for 6 consecutive weeks, or 60 mg every other week over 6 weeks. Experience to date suggests that any mild and transient unwanted effects (see section 4.8) tend to occur after the first dose. For this reason if unit doses of 60 mg are used it is recommended that treatment be started with an initial additional dose of 30 mg (i.e. total dose 210 mg). Each dose of 30 or 60 mg should be diluted in 125 or 250 ml 0.9 % w/v Sodium Chloride Intravenous Infusion BP respectively, and the infusion rate should not exceed 60 mg/hour (1 mg/min). This regimen or increased dose levels according to disease severity, up to a maximum total does of 360 mg (in divided doses of 60 mg) can be repeated every 6 months until remission of disease is achieved, and if relapse occurs.

Renal Impairment
Pamidronate disodium should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. Because there is only limited clinical experience in patients with severe renal impairment no dose recommendations for this patient population can be made (see Section 4.4 “Special warnings and special precautions for use” and Section 5.2 “Pharmacokinetic properties”).

As with other i.v. bisphosphonates, renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of pamidronate disodium. In patients receiving pamidronate disodium for bone metastases or multiple myeloma who show evidence of deterioration in renal function, pamidronate disodium treatment should be withheld until renal function returns to within 10% of the baseline value. This recommendation is based on a clinical study, in which renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5mg/dL.
- For patients with abnormal baseline creatinine, increase of 1.0mg/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 61-90 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).

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 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 Section 5.2 Pharmacokinetic properties “Hepatic impairment”).
Clinical data in patients with severe hepatic impairment is not available (see Section 4.4 Special warnings and special precautions for use). Pamidronate should be administered to this patient population with caution.

Children
There is no clinical experience with pamidronate disodium in children. Therefore until further experience is gained, pamidronate disodium is only recommended for use in adult patients.

4.3 Contraindications
Pamidronate disodium is contraindicated in:

- patients with known hypersensitivity to pamidronate or to other bisphosphonates, or to any of the excipients of Aredia,
- pregnancy,
- breast feeding women.

4.4 Special warnings and precautions for use
Pamidronate must never be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see Section 4.2 Posology and method of administration).

Patients must be assessed prior to administration of Pamidronate 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 Pamidronate. Patients who have undergone thyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.

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.

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

Renal Insufficiency
Bisphosphonates, including Pamidronate, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Pamidronate. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate in patients with multiple myeloma.

Pamidronate is excreted intact primarily via the kidney (see Section 5.2 Pharmacokinetic properties), 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 Pamidronate should not exceed 90mg, and the recommended infusion time should be observed (See Section 4.2. Posology and method of administration).

As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of Pamidronate.

Patients treated with Pamidronate for bone metastases or multiple myeloma should have the dose withheld if renal function has deteriorated (see Section 4.2. Posology and method of administration).

Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. (See section 4.2 Posology and method of
administration “Renal impairment”). Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made (See Section 4.2 “Posology and method of administration” and Section 5.2 “Pharmacokinetic properties”). Pamidronate 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 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 Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

**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 (e.g. through malabsorption or lack of exposure to sunlight) and patients with Paget's disease of the bone should take oral calcium and vitamin D supplementation in order to minimise the potential risk of hypocalcaemia.

**Osteonecrosis of the jaw**

Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. 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. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**Musculoskeletal Pain**

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes pamidronate disodium for infusion. The time to onset of symptoms varied from one day to several months after starting the drug with the majority occurring within a few days. Most patients had relief or improvement of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

### 4.5 Interaction with other medicinal products and other forms of interaction

Pamidronate disodium has been administered concomitantly with commonly used anti-cancer agents without significant interactions.

Pamidronate 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 is used with other potentially nephrotoxic drugs.

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

Since pamidronate binds to bone, it could in theory interfere with bone scintigraphy examinations.
4.6 **Pregnancy and lactation**

There are no adequate data from the use of pamidronate in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. Therefore, Pamidronate should not be used during pregnancy (see Section 4.3 Contraindications).

It is not known whether Pamidronate is excreted into human milk. Study in lactating rats has shown that pamidronate will pass into the milk. Mothers treated with Pamidronate should therefore not breast-feed their infants (see Section 4.3 Contraindications).

4.7 **Effects on 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 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.

One case of acute lymphoblastic leukaemia has been reported in a patient with Paget’s disease. The causal relationship to the treatment or the underlying disease is unknown.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reactivation of Herpes simplex, reactivation of Herpes zoster</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia, thrombocytopenia, lymphocytopenia</td>
<td></td>
<td></td>
<td></td>
<td>leukopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke’s (angioneurotic) oedema.</td>
</tr>
<tr>
<td>Metabolism and nutrition Disorders</td>
<td>Hypocalcaemia, hypophosphataemia</td>
<td>hypokalaemia, hypomagnesaemia, increase in serum creatinine.</td>
<td>abnormal liver function tests, increase in serum urea.</td>
<td>hyperkalaemia, hypernatraemia</td>
<td></td>
</tr>
<tr>
<td>Organ System</td>
<td>Frequency</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------</td>
<td>---------------------</td>
<td>--------------------------</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very Common</td>
<td>symptomatic hypocalcaemia (paraesthesia, tetany), headache, insomnia, somnolence.</td>
<td>seizures, agitation, dizziness, lethargy</td>
<td>confusion, visual hallucinations</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>conjunctivitis</td>
<td>uveitis (iritis, iridocyclitis).</td>
<td>scleritis, episcleritis, xanthopsia.</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders / Vascular Disorders</td>
<td></td>
<td>hypertension</td>
<td>hypotension</td>
<td>left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, gastritis.</td>
<td>dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue Disorders</td>
<td></td>
<td>rash</td>
<td>pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>transient bone pain, arthralgia, myalgia, generalised pain.</td>
<td>muscle cramps.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>acute renal failure.</td>
<td></td>
<td>focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome.</td>
<td>deterioration of pre-existing renal disease, haematuria.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue and flushes</td>
<td>reactions at the infusion site; pain, redness, swelling, induration, phlebitis, thrombophlebitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Postmarketing experience: Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including Pamidronate. Many of these patients had signs of local infection including 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, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4 Special warnings and special precautions for use).

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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Inhibitor of bone resorption
ATC code: M05BA03

Pamidronate disodium, is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals in vitro. Inhibition of osteoclastic bone resorption in vivo may be at least partly due to binding of the drug to the bone mineral.

Pamidronate suppresses the accession of osteoclast precursors onto the bone. 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.

Hypercalcaemia can lead to a depletion in the volume of extracellular fluid and a reduction in the glomerular filtration rate (GFR). By controlling hypercalcaemia, pamidronate disodium improves GFR and lowers elevated serum creatinine levels in most patients.

Clinical trials in patients with breast cancer and predominantly lytic bone metastases or with multiple myeloma showed that pamidronate disodium prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain.

Paget's disease of bone, which is characterised by local areas of increased bone resorption and formation with qualitative changes in bone remodelling, responds well to treatment with pamidronate disodium. Clinical and biochemical remission of the disease has been demonstrated by bone scintigraphy, decreases in urinary hydroxyproline and serum alkaline phosphatase, and by symptomatic improvement.

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”.

37
Absorption
Pamidronate disodium is given by intravenous infusion. By definition, absorption is complete at the end of the infusion.

Distribution
Plasma concentrations of pamidronate rise rapidly after the start of an infusion and fall rapidly when the infusion is stopped. The apparent half-life in plasma is about 0.8 hours. Apparent steady-state concentrations are therefore achieved with infusions of more than about 2-3 hours duration. Peak plasma pamidronate concentrations of about 10 nmol/ml are achieved after an intravenous infusion of 60 mg given over 1 hour.

In animals and in man, a similar percentage of the dose is retained in the body after each dose of pamidronate disodium. Thus the accumulation of pamidronate in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered. The percentage of circulating pamidronate bound to plasma proteins is relatively low (about 54%) and increases when calcium concentrations are pathologically elevated.

Elimination
Pamidronate does not appear to be eliminated by biotransformation and it is almost exclusively eliminated by renal excretion. After an intravenous infusion, about 20-55% of the dose is recovered in the urine within 72 hours as unchanged pamidronate. Within the timeframe of experimental studies the remaining fraction of the dose is retained in the body. The percentage of the dose retained in the body is independent of both the dose (range 15-180 mg) and the infusion rate (range 1.25-60 mg/h). From the urinary elimination of pamidronate, two decay phases with apparent half-lives of about 1.6 and 27 hours, can be observed. The apparent total plasma clearance is about 180 mL/min and 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. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).

Hepatic impairment
The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=9). Each patient received a single 90mg dose of Pamidronate infused over 4 hours. There was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function. Patients with hepatic impairment exhibited higher mean AUC (39.7%) and Cmax (28.6%) values. The difference was not considered clinically relevant. The mean ratio based on log transformed parameters of impaired versus normal patients was 1.38 (90% C.I. 1.12 – 1.70, P=0.02) for AUC and 1.23 (90% C.I. 0.89 – 1.70, P=0.27) for Cmax. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because pamidronate is administered on a monthly basis, drug accumulation is not expected. No changes in pamidronate dosing regimen are recommended for patients with mild to moderate abnormal hepatic function (see Section 4.2 Posology and method of administration).

Renal impairment
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). Because there is only limited pharmacokinetic data with severe renal impairment no dose recommendations for this patient population can be made (see Section 4.2 “Posology and method of administration” and Section 4.4 “Special warnings and special precautions for use”).
5.3 Preclinical safety data
The toxicity of pamidronate is characterised by direct (cytotoxic) effects on organs with a copious blood supply, particularly the kidneys following i.v. exposure. The compound is not mutagenic and does not appear to have carcinogenic potential.

Studies in rats and rabbits determined that pamidronate disodium produces maternal toxicity and embryo/foetal effects when administered at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion. The effects include protracted parturition leading to dystocia, and shortened long bones in the foetus. Animal data suggest that uptake of bisphosphonates into foetal bone is greater than into maternal bone.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Phosphoric acid
Water for Injections

6.2 Incompatibilities
Pamidronate must not be mixed with calcium-containing solution such as Ringer's solution.

To avoid potential incompatibilities, Pamidronate is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Following dilution in 0.9% sodium chloride and 5% glucose infusion solutions, chemical and physical in-use stability has been demonstrated for 24 hours at temperatures not exceeding 25°C.

If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between dilution and storage in a refrigerator at 2 to 8°C and end of administration must not exceed 24 hours.

Prior to first use: Store below 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container
10 ml Type I moulded flint glass vial with butyl rubber stopper and dark green coloured flip-off, tear-off aluminium seals in packs of 1 vial.

6.6 Special precautions for disposal
Must be diluted prior to administration.

The concentration of pamidronate disodium in the infusion solution should not exceed 60 mg/250 ml.

Do not use solution if particles are present.

Any portion of the contents remaining after use should be discarded.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland
MARKETING AUTHORISATION NUMBER(S)
PL 33410/0031

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/06/2010

DATE OF REVISION OF THE TEXT
10/06/2010
PATIENT INFORMATION LEAFLET

PAR Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Conc for sol for inf

PL 33410/0029-31

PACKAGING AND LABELLING INFORMATION FOR THE USER

Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Conc for sol for inf

1. WHAT PAMIDRONATE IS AND WHAT IT IS USED FOR

The name of the medicine is Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Conc for sol for inf. Pamidronate is a medicine which is to be given in a single injection via a drip. Throughout this leaflet the medicine will be referred to as Pamidronate.

The active ingredient in Pamidronate is called pamidronate disodium. This is a group of medicines called bisphosphonates which help protect the bone from being eaten away by the body. High blood calcium levels (hypercalcaemia) occurs in a number of conditions, including some types of cancer. Other bisphosphonates are used in the treatment of colorectal cancer in order to reduce the release of silicones into the blood. If uncontrolled, hypercalcaemia can cause symptoms such as: nausea, fever, vomiting, confusion and delirium.

Pamidronate is used to treat high blood calcium levels caused by some cancers. In some patients with cancer, it is also used to treat bone disease and to help reduce bone pain. Pamidronate is also used to treat Paget’s disease of bone.

2. BEFORE YOU USE PAMIDRONATE

Do not use Pamidronate
- if you have severe signs of hypocalcaemia (severe shaking) which require Pamidronate or previous treatment
- if you are pregnant or breastfeeding
- if you have liver problems
- if you have kidney problems
- if you receive irradiation to sections of the body
- if you receive chemotherapy
- if you receive other cancer medications that reduce the levels of calcium
- if you have or have ever had, claustraphobia or claustrophobia or the fear of confined spaces or narrow spaces
- if you suffer from mental illness
- if you are allergic to pamidronate or any other bisphosphonate

Tell your doctor how to prepare an examination of your bones, as Pamidronate could interfere with the examination.

3. HOW PAMIDRONATE IS USED

Your doctor will have discussed the right time depending on your condition.

A dose of 3mg/ml, 6mg/ml and 9mg/ml Conc for sol for inf

4. POSSIBLE SIDE EFFECTS

Like all medicines, pamidronate can cause side effects, although not everybody gets them.

If any of the following happen, tell your doctor immediately:
- severe allergic reactions, including anaphylaxis or sudden, unexpected, life-threatening or severe, multi-system reaction, which may cause death or serious disability, due to swelling of the lips, face, throat, mouth, tongue or throat (which may cause difficulty in swallowing or breathing), and you may feel that you are getting faint

These are very serious side effects. You may need urgent medical attention. All of these very serious side effects are rare.

The most common effects not listed above are listed below (not serious). Many occur at the start of treatment and may last for 24 hours.

Some patients notice an increase in pain pain within a week after starting treatment. This usually improves after a few days. If it does not, tell your doctor.

Other side effects:

Tell your doctor if you experience any of the following during or soon after starting treatment:

- changes in your mood or behaviour (including lack of concentration, irritability, mood swings, or depression)
- changes in your appetite, energy level, or well-being
- changes in your vision, including temporary vision loss or changes to colour vision
- changes in your ability to concentrate
- changes in your self-esteem or feelings of well-being
- changes in your memory or concentration

If any of the side effects listed above worry you or become severe, please tell your doctor or pharmacist.

5. HOW TO REPORT SIDE EFFECTS

If you get any side effects, talk to your doctor or pharmacist. If you have a problem with side effects, they can sometimes recommend a medication that is less likely to cause the side effects you are experiencing.

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LABELLING

Pamidronate Disodium 3mg/ml Concentrate for solution for infusion:

Following dilution, 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 not normally be longer than 24 hours at 2°C - 8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions. Discard any unused solution immediately after use.

Store in the original package in order to protect from light. Store below 25°C. Read the package leaflet before use. Waste material may be disposed of by incineration.

Pamidronate Disodium 3 mg/ml Concentrate for solution for infusion

Pamidronate disodium

Contains 3 mg Pamidronate disodium in 1 ml of solution. Also contains mannitol, phosphoric acid and water for injections. Concentrate for solution for infusion. 30 mg in 10 ml

Keep out of the reach and sight of children.

For intravenous use only.

Must be diluted before use.

Each vial contains 3.97 mg/ml of pamidronate disodium pentahydrate, which is equivalent to 3 mg/ml of pamidronate disodium anhydrous.

Store below 25°C. Store in the original package in order to protect from light. Diluted solution must be used immediately or within 24 hours if stored at 2°C - 8°C. Also contains mannitol, phosphoric acid and water for injections.
Pamidronate Disodium 6mg/ml Concentrate for solution for infusion:

Following dilution, 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 not normally be longer than 24 hours at 2°C to 8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions. Discard any unused solution immediately after use.
Store in the original package in order to protect from light.
Store below 25°C. Read the package leaflet before use.
Waste material may be disposed of by incineration.

Pamidronate Disodium
6 mg/ml Concentrate for solution for infusion
Pamidronate disodium

Each vial contains 7.09mg/ml of pamidronate disodium pentahydrate, which is equivalent to 6mg/ml of pamidronate disodium anhydrous

For intravenous use only. Must be diluted before use.

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APC Pharmaceuticals & Chemicals (Europe) Ltd., Suite 501, Park House, 111 Oldsbridge Road, Eding, London, W3 9LE.

Over Printing Area

PAMIDRONATE DISODIUM 6 mg/ml Concentrate for solution for infusion
Pamidronate disodium

Must be diluted before use.
Read the package leaflet before use.

Each vial contains 7.09mg/ml of pamidronate disodium pentahydrate, which is equivalent to 6mg/ml of pamidronate disodium anhydrous
Store below 25°C. Store in the original package in order to protect from light.
Diluted solution must be used immediately or within 24 hours if stored at 2°C to 8°C.
Also contains mannitol, phosphoric acid and water for injections.
Pamidronate Disodium 9mg/ml Concentrate for solution for infusion:

Following dilution, 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 not normally be longer than 24 hours at 2°C - 8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.
Discard any unused solution immediately after use.
Store in the original package in order to protect from light.
Store below 25°C. Read the package leaflet before use.
Waste material may be disposed of by incineration.

Pamidronate Disodium 9mg/ml Concentrate for solution for infusion
Pamidronate disodium
Contains 9mg Pamidronate disodium in 1ml of solution.
Also contains mannitol, phosphoric acid and water for injections.
Concentrate for solution for infusion. 90mg in 10ml
Keep out of the reach and sight of children.

Pamidronate Disodium 9mg/ml Concentrate for solution for infusion
Pamidronate disodium
Each vial contains 11.9mg/ml of pamidronate disodium pentahydrate, which is equivalent to 9mg/ml of pamidronate disodium anhydrous
For intravenous use only.
Must be diluted before use.

PL Holder:
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland.
Marketed and Distributed By:
APC Pharmaceuticals &
Chemicals (Europe) Ltd,
Suite 505, Park House,
113 Unbridge Road,
Ealing, London, W5 3LB.

PAMIDRONATE DISODIUM 9 mg/ ml
Concentrate for solution for infusion
Pamidronate disodium
Must be diluted before use.
Read the package leaflet before use.
Each vial contains 11.9mg/ml of pamidronate disodium pentahydrate,
which is equivalent to 9mg/ml of pamidronate disodium anhydrous
Store below 25°C. Store in the original package in order to protect from light.
Diluted solution must be used immediately or within 24 hours if stored at 2°C - 8°C.
Also contains mannitol, phosphoric acid and water for injections.

90 mg in 10 ml
For intravenous use only.
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