

**Pamidronate Disodium 3mg/ml Concentrate for Solution  
for Infusion**  
**Pamidronate Disodium 6mg/ml Concentrate for Solution  
for Infusion**  
**Pamidronate Disodium 9mg/ml Concentrate for Solution  
for Infusion**

**PL 11311/0217**  
**PL 11311/0218**  
**PL 11311/0219**  
**PL 11311/0220**

**UKPAR**

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**PL 11311/0217**

**PL 11311/0218**

**PL 11311/0219**

**PL 11311/0220**

### **LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for Solution for Infusion (Product Licence numbers: PL 11311/0217-0220) on 21 September 2011.

Pamidronate disodium belongs to a group of medicines known as bisphosphonates, which work by reducing the amount of calcium in the blood. A high blood calcium level (hypercalcaemia) occurs in a number of conditions, including some types of cancer associated with bone pain. Pamidronate disodium is also used to treat Paget's disease, a disease which results in a change in bone structure. Pamidronate disodium is absorbed into bones and helps to reduce the release of calcium into the blood. In some patients with cancer, pamidronate disodium is also used to treat bone disease and to relieve bone pain.

No clinically significant safety concerns were raised in relation to the Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for Solution for Infusion applications and it was therefore judged that the benefits of using these products outweigh the risks and Marketing Authorisations have been granted.

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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted Marketing Authorisations for the medicinal products Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for Solution for Infusion (PL 11311/0217-0220) to Tillomed Laboratories Ltd on 21 September 2011. These medicines are only available on prescription.

Pamidronate Disodium Concentrate for Solution for Infusion is used in the treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer and multiple myeloma
- Paget's disease of bone

These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for Solution for Infusion are generic versions of Aredia Dry Powder 15 mg and 30 mg, which were licensed on 22 October 1992 and Aredia Dry Powder 60 mg and 90 mg, which were licensed on 9 September 1993. Pamidronate Disodium 3mg/ml Concentrate for Solution for Infusion is available in either a 5 ml (PL 11311/0217) or 10 ml (PL 11311/0218) vial. Therefore, PL 11311/0217 is a generic version of Aredia Dry Powder 15 mg and PL 11311/0218 is a generic version of Aredia Dry Powder 30 mg.

Aredia Dry Powder 15 mg, 30 mg, 60 mg and 90 mg (PL 00101/0518-0521) are currently licensed to Novartis Pharmaceuticals UK Ltd and have the same qualitative and quantitative (amount of drug substance per container) composition as Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for Solution following reconstitution (15 mg in 5 mL, and 30 mg, 60 mg and 90 mg in 10 mL). The reference products have been authorised in the EEA for over 10 years and the legal basis of these applications is therefore acceptable.

Assurance has been provided that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

No new preclinical studies were conducted, which is acceptable given that the applications are for generic versions of originator products that have been licensed for over 10 years.

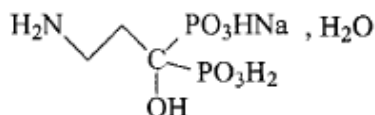
No new clinical studies were conducted, which is acceptable given that the applications are for generic versions of originator products that have been licensed for over 10 years.

## PHARMACEUTICAL ASSESSMENT

### **DRUG SUBSTANCE: PAMIDRONATE DISODIUM**

**USAN:** Pamidronate monosodium  
**Chemical name:** Sodium (3-amino-1-hydroxypropylidene) bisphosphonate monohydrate

**Structure:**



**Molecular formula:** C<sub>3</sub> H<sub>10</sub> N O<sub>7</sub> NaP<sub>2</sub>, H<sub>2</sub>O

**Molecular weight:** 275.07

**Physical form:** A white or almost white crystalline powder. Non-chiral

#### **Manufacture**

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

#### **Control**

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

#### **Container closure system**

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

#### **Stability**

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

## **DRUG PRODUCTS: PAMIDRONATE DISODIUM 3MG/ML, 6MG/ML AND 9MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION**

### **Description and composition**

Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for Solution for Infusion are clear, colourless solutions containing pamidronate disodium and the pharmaceutical excipients mannitol, sodium hydroxide, phosphoric acid (for pH adjustment) and water for injection. All excipients comply with the specifications in their respective Ph Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

### **Pharmaceutical development**

The objective of the pharmaceutical development programme was to formulate robust, stable, concentrates for solution for infusion equivalent to the reference products, Aredia Dry Powder 15 mg, 30 mg, 60 mg and 90 mg and exhibiting the same bioavailability following reconstitution, in order to comply with the regulations pertaining to generic medicinal product applications.

Suitable pharmaceutical development data have been provided for these applications. The physico-chemical properties of the drug products have been compared with those of the originator products. These data demonstrate that the proposed products can be considered generic versions of Aredia Dry Powder 15 mg, 30 mg, 60 mg and 90 mg.

### **Manufacture**

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

### **Finished product specification**

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

### **Container closure system**

The products are stored in 5 ml (PL 11311/0217) or 10 ml (PL 11311/0218-0220) vials made of clear, colourless glass (Type I glass, Ph Eur). The vial closures are made from chlorobutyl rubber, with a PTFE coated surface. The vials are then sealed with tamper proof aluminium caps and packaged in a carton. The products may be available in packs of 1, 2, 4, 5, 6 or 10 vials, although not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months has been set for the products, which is acceptable.

**Expert report**

A satisfactory expert report is provided from an appropriately qualified author.

**Product literature**

The SmPCs, PIL and labels are pharmaceutically acceptable.

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. 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.

**Conclusion**

There are no objections to the approval of these products from a quality viewpoint.

## **PRECLINICAL ASSESSMENT**

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

The applicant's preclinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

Suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a preclinical viewpoint.

## CLINICAL ASSESSMENT

### **Indications**

The claimed indications are identical to those of the reference products and are acceptable.

### **Dose and dose schedule**

These are in line with the reference products and are therefore appropriate.

### **Pharmacology**

No new clinical pharmacology data were submitted. The clinical pharmacology of the drug substance has been well documented over the years of use of the substance.

In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), point 5.1.6, a bioequivalence study is not requested if the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently licensed reference product.

### **Efficacy**

No new data on the efficacy of these products have been submitted and none are required for this type of application. The documented clinical efficacy of the drug substance remains satisfactory for the claimed indications and the proposed dosages.

### **Safety**

No new or unexpected safety issues were raised for these applications. The recorded safety profile of the drug substance remains satisfactory when used for the claimed indications and at the recommended dosages.

### **Product literature**

The SmPCs, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator products.

### **Pharmacovigilance system**

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.

### **Risk Management Plan (RMP)**

The applicant has not submitted an RMP, nor is one needed for an application of this kind.

### **Clinical expert report**

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

### **Conclusion**

The grant of a Marketing Authorisation is recommended.

## **OVERALL CONCLUSION AND BENEFIT/ RISK ASSESSMENT**

### **QUALITY**

The important quality characteristics of Pamidronate Disodium 3mg/ml, 6mg/ml and 9mg/ml Concentrate for 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.

### **PRE-CLINICAL**

No new pre-clinical data were submitted and none are required for applications of this type.

### **EFFICACY**

The efficacy of pamidronate disodium is well established. No new efficacy data are needed for applications of this type.

### **SAFETY**

No new or unexpected safety concerns arise from these applications.

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

### **BENEFIT/RISK ASSESSMENT**

The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. Extensive clinical experience with pamidronate disodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be acceptable for these products and Marketing Authorisations may be granted.

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**STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation applications on 9 August 2002
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 7 December 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 8 August 2007
4	The applicant responded to the MHRA's request, providing further information on the quality dossier on 18 October 2007
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 15 May 2008
6	The applicant responded to the MHRA's request, providing further information on the quality dossier on 19 September 2008
7	Following assessment of the response the MHRA requested further information relating to the quality dossier on 19 January 2009
8	The applicant responded to the MHRA's request, providing further information on the quality dossier on 24 September 2009
9	Following assessment of the response the MHRA requested further information relating to the quality dossier on 11 November 2010
10	The applicant responded to the MHRA's request, providing further information on the quality dossier on 3 February 2011
11	The application was determined on 21 September 2011

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Pamidronate Disodium 3mg/ml Concentrate for Solution for Infusion

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml of concentrate for solution for infusion contains 3mg pamidronate disodium.

1 vial of 5ml of sterile concentrate contains 15mg of pamidronate disodium.

For excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

The concentrate is a clear and colourless solution, free from visible particles.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia.
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer and 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 Special warnings and special precautions for use"). The concentrate must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to Section "6.6 Instructions for use and handling". The infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of pamidronate disodium in the infusion solution should not exceed 60mg/250ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20mg/hour (see also "Patients with renal impairment"). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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

*Tumour-induced hypercalcaemia:*

Patient must be adequately 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 protein or albumin in rehydrated patients.

Initial serum calcium (mmol/L)	(mg %)	Recommended total dose (mg)
up to 3.0	up to 12.0	15 – 30
3.0 - 3.5	12.0 - 14.0	30 – 60
3.5 - 4.0	14.0 - 16.0	60 – 90
> 4.0	> 16.0	90

The total dose of 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 90mg for both initial and repeated 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 treatment increases.

*Osteolytic lesions and bone pain in bone metastases associated with breast cancer:* The recommended dose is 90mg every 4 weeks. This dose may also be administered at 3 weekly intervals to coincide with chemotherapy if desired.

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

*Paget's disease of Bone:*

The recommended treatment course consists of a total dose of 180mg administered in unit doses of either 30mg once a week for 6 consecutive weeks, or 60mg every other week over 6 weeks. Experience to date suggests that any mild and transient unwanted effects (see Section “4.8 Undesirable Effects”) tend to occur after the first dose. For this reason if unit doses of 60mg are used it is recommended that treatment be started with an initial dose of 30mg followed by 60mg every other week (i.e. total dose 210mg). Each dose of 30 or 60mg should be diluted in 125 or 250 ml 0.9% w/v sodium chloride solution respectively, and the infusion rate should not exceed 60mg/hour (1mg/min). This regimen or increased dose levels according to disease severity, up to a maximum total dose of 360mg (in divided doses of

60mg) can be repeated every 6 months until remission of disease is achieved, and if relapse occurs.

*Patients with renal impairment:*

Until further experience is gained a maximum infusion rate of 20mg/hour is recommended in renal impaired patients.

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).

*Patients with hepatic impairment:*

Although patients with hepatic impairment exhibited higher mean AUC and C<sub>max</sub> 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.

Pamidronate disodium should be administered to this patient population with caution.

*Children:*

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

### **4.3 Contraindications**

Known hypersensitivity to pamidronate disodium or to other Bisphosphonates, or to any of the excipients of Pamidronate disodium.

in pregnancy (see also section 4.6)

in breast feeding women (see also section 4.6)

#### **4.4 Special warnings and precautions for use**

##### **General**

Pamidronate disodium 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 disodium to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

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

Standard hypocalcaemia-related metabolic parameters including serum electrolyte, calcium and phosphate should be monitored following initiation of therapy with Pamidronate disodium . 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.

Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects.

##### **Renal Insufficiency**

Bisphosphonates, including Pamidronate disodium , 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 disodium . Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate disodium in patients with multiple myeloma.

Pamidronate disodium 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 disodium 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 disodium.

Patients treated with Pamidronate disodium 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 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. (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 disodium should not be given with other bisphosphonates because their combined effects have not been investigated.

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

### **Hepatic Insufficiency**

As there are no clinical data available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population (see 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 (ONJ) has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate disodium. Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

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 (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 should not be co-administered with other bisphosphonates because their combined effects have not been investigated.

Pamidronate disodium has been administered concomitantly with commonly used anticancer agents without interactions occurring.

Pamidronate disodium has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.

Caution is warranted when Pamidronate disodium is used with other potentially nephrotoxic drugs.

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

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

#### **4.6 Fertility, pregnancy and lactation**

##### *Pregnancy:*

Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. In rats, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels. In pregnant rats, pamidronate disodium has been shown to cross the placental barrier and accumulate in foetal bone in a manner similar to that observed in adult animals.

There is insufficient clinical experience to support the use of pamidronate disodium in pregnant women. Therefore, pamidronate disodium should not be

administered during pregnancy except in cases of life-threatening hypercalcaemia.

*Lactation:*

It is not known whether pamidronate disodium is excreted in human milk. A study in lactating rats has shown that pamidronate disodium will pass into the milk. Mothers treated with pamidronate disodium should therefore not breast-feed their infants.

**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**

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.

The frequency is defined using the following conventions:

Very common (>1/10)

Common (>1/100, <1/10)

Uncommon (>1/1,000 <1/100)

Rare (>1/10,000, <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Infections and infestations					Reactivation of herpes simplex and herpes zoster
Blood and the lymphatic system disorders		Lymphocytopenia Thrombocytopenia, Anaemia			Leukopenia

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Immune system disorders			Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoe, Quincke's (angioneurotic oedema)		Anaphylactic shock
Metabolism and nutrition disorders		Asymptomatic hypocalcaemia Anorexia			
Psychiatric disorders					Visual hallucinations Confusion
Nervous system disorders		Symptomatic hypocalcaemia (paraesthesia, tetany), Headache, Insomnia, Somnolence	Agitation Dizziness Seizures, lethargy		
Eye disorders		Conjunctivitis	Uveitis (iritis, iridocyclitis)		Scleritis Episcleritis Xanthopsia
Cardio-Vascular disorders		Hypertension	Hypotension		left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.
Gastro-intestinal disorders		Nausea Vomiting Abdominal pain Diarrhoea Constipation Gastritis	Dyspepsia		

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Skin and subcutaneous tissue disorders		Rash	Pruritus		
Musculo-skeletal, connective tissue and bone disorders		Transient bone pain Arthralgia Myalgia Generalised pain	Muscle cramps		
Renal and urinary disorders			Acute renal failure	focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome	Haematuria deterioration of pre-existing renal disease
General disorders and administration site conditions		Fever and influenza-like symptoms, sometimes accompanied by malaise, rigor, fatigue and flushes Reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis.			
Investigations	hypocalcaemia, hypophosphataemia	Hypomagnesaemia, hypokalaemia, increase in serum creatinine	abnormal liver function tests, increase in serum urea		hyperkalaemia, hypernatraemia

Many of the adverse drug reactions may have been related to the underlying disease.

When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Previously, it has been observed in a clinical trial,

investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased risk of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism behind the increased incidence of atrial fibrillation in association with zoledronic acid and pamidronate treatment is unknown.

#### **Postmarketing experience:**

The following adverse reactions have been reported during post-approval use of pamidronate disodium. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including pamidronate disodium (uncommon). 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 precautions for use). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

#### **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**

ATC code: M05B A03

The active substance 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 disodium suppresses the accession of osteoclast precursors onto the bone. However, the local and direct antiresorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*.

Experimental studies have demonstrated that pamidronate disodium 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 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**

Pamidronate disodium has a strong affinity for calcified tissues, and total elimination of pamidronate disodium 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 disodium 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 disodium concentrations of about 10 nmol/ml are achieved after an intravenous infusion of 60mg given over 1 hour and the apparent plasma clearance is about 180 ml/min.

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 disodium in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

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

*Elimination.* Pamidronate disodium does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20-55 % of the dose is recovered in the urine within 72 hours as unchanged pamidronate disodium. 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 1.25-60mg/h). From the urinary elimination of pamidronate disodium, two decay phases, with apparent half-life of about 1.6 and 27 hours, can be observed. 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 disodium is insignificant.

*Hepatic Impairment:*

Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate disodium. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above). No changes in dosing are recommended for patients with mild to moderate hepatic dysfunction.

*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 disodium 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, sodium hydroxide, phosphoric acid (for pH adjustment), water for injection.

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

36 months

### **6.4 Special precautions for storage**

Chemical and physical in-use stability in glucose 50mg/ml has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

### **6.5 Nature and contents of container**

5ml vials made of clear, colourless glass (Type I glass, Ph.Eur.). The vial closures are made from chlorobutyl rubber, with a PTFE coated surface. The vials are then sealed with tamper proof aluminium caps, and packaged in a carton.

Pack sizes:

1, 2, 4, 5, 6 and 10 vials

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

The concentrate should be further diluted with a calcium-free infusion solution (0.9% w/v Sodium Chloride Intravenous Infusion is recommended) before administration. Do not use if particles are present. Any portion of the contents remaining after use should be discarded.

## **7 MARKETING AUTHORISATION HOLDER**

Tillomed Laboratories Ltd.  
3 Howard Road, Eaton Socon  
St. Neots, Cambridgeshire PE19 3ET  
United Kingdom

- 8**     **MARKETING AUTHORISATION NUMBER(S)**  
PL 11311/0217
- 9**     **DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**  
21/09/2011
- 10**    **DATE OF REVISION OF THE TEXT**  
21/09/2011

## **1 NAME OF THE MEDICINAL PRODUCT**

Pamidronate Disodium 3mg/ml Concentrate for Solution for Infusion

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

*30mg pamidronate disodium :*

Each ml of concentrate for solution for infusion contains 3mg pamidronate disodium.

1 vial of 10ml of sterile concentrate contains 30mg of pamidronate disodium.

For excipients, see section 6.1

## **3 PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

The concentrate is a clear and colourless solution, free from visible particles.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia.
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer and 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 Special warnings and special precautions for use"). The concentrate must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to Section "6.6 Instructions for use and handling". The infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of pamidronate disodium in the infusion solution should not exceed 60mg/250ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20mg/hour (see also "Patients with renal impairment"). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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

*Tumour-induced hypercalcaemia:*

Patient must be adequately 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 protein or albumin in rehydrated patients.

Initial serum calcium		Recommended total
(mmol/L)	(mg %)	dose (mg)
up to 3.0	up to 12.0	15 – 30
3.0 - 3.5	12.0 - 14.0	30 – 60
3.5 - 4.0	14.0 - 16.0	60 – 90
> 4.0	> 16.0	90

The total dose of 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 90mg for both initial and repeated 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 treatment increases.

*Osteolytic lesions and bone pain in bone metastases associated with breast cancer:* The recommended dose is 90mg every 4 weeks. This dose may also be administered at 3 weekly intervals to coincide with chemotherapy if desired.

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

*Paget's disease of Bone:*

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

*Patients with renal impairment:*

Until further experience is gained a maximum infusion rate of 20mg/hour is recommended in renal impaired patients.

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).

#### *Patients with hepatic impairment:*

Although patients with hepatic impairment exhibited higher mean AUC and C<sub>max</sub> 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. Pamidronate disodium should be administered to this patient population with caution.

#### *Children:*

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

### **4.3 Contraindications**

Known hypersensitivity to pamidronate disodium or to other Bisphosphonates, or to any of the excipients of Pamidronate disodium.

in pregnancy (see also section 4.6)

in breast feeding women (see also section 4.6)

## 4.4 Special warnings and precautions for use

### General

Pamidronate disodium 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 disodium to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

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

Standard hypocalcaemia-related metabolic parameters including serum electrolyte, calcium and phosphate should be monitored following initiation of therapy with Pamidronate disodium. 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.

Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects.

### Renal Insufficiency

Bisphosphonates, including Pamidronate disodium, 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 disodium. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate disodium in patients with multiple myeloma.

Pamidronate disodium 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 disodium 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 disodium.

Patients treated with Pamidronate disodium 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 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. (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 disodium should not be given with other bisphosphonates because their combined effects have not been investigated.

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

### **Hepatic Insufficiency**

As there are no clinical data available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population (see 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) should take oral supplements of both during pamidronate disodium therapy to minimise the potential risk of hypocalcaemia.

### **Osteonecrosis of the jaw**

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate disodium . Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

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 (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 should not be co-administered with other bisphosphonates because their combined effects have not been investigated.

Pamidronate disodium has been administered concomitantly with commonly used anticancer agents without interactions occurring.

Pamidronate disodium has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.

Caution is warranted when Pamidronate disodium is used with other potentially nephrotoxic drugs.

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

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

#### **4.6 Pregnancy and lactation**

##### *Pregnancy:*

Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. In rats, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels. In pregnant rats, pamidronate disodium has been shown to cross the placental barrier and accumulate in foetal bone in a manner similar to that observed in adult animals.

There is insufficient clinical experience to support the use of pamidronate disodium in pregnant women. Therefore, pamidronate disodium should not be administered during pregnancy except in cases of life-threatening hypercalcaemia.

##### *Lactation:*

It is not known whether pamidronate disodium is excreted in human milk. A study in lactating rats has shown that pamidronate disodium will pass into the milk. Mothers treated with pamidronate disodium should therefore not breast-feed their infants.

#### 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

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.

The frequency is defined using the following conventions:

Very common (>1/10)

Common (>1/100, <1/10)

Uncommon (>1/1,000 <1/100)

Rare (>1/10,000, <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Infections and infestations					Reactivation of herpes simplex and herpes zoster
Blood and the lymphatic system disorders		Lymphocytopenia Thrombocytopenia, Anaemia			Leukopenia
Immune system disorders			Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoe, Quincke's (angioneurotic oedema)		Anaphylactic shock
Metabolism and nutrition disorders		Asymptomatic hypocalcaemia Anorexia			

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Psychiatric disorders					Visual hallucinations Confusion
Nervous system disorders		Symptomatic hypocalcaemia (paraesthesia, tetany), Headache, Insomnia, Somnolence	Agitation Dizziness Seizures, lethargy		
Eye disorders		Conjunctivitis	Uveitis (iritis, iridocyclitis)		Scleritis Episcleritis Xanthopsia
Cardio-Vascular disorders		Hypertension	Hypotension		left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.
Gastro-intestinal disorders		Nausea Vomiting Abdominal pain Diarrhoea Constipation Gastritis	Dyspepsia		
Skin and subcutaneous tissue disorders		Rash	Pruritus		
Musculo-skeletal, connective tissue and bone disorders		Transient bone pain Arthralgia Myalgia Generalised pain	Muscle cramps		

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Renal and urinary disorders			Acute renal failure	focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome	Haematuria deterioration of pre-existing renal disease
General disorders and administration site conditions		Fever and influenza-like symptoms, sometimes accompanied by malaise, rigor, fatigue and flushes Reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis.			
Investigations	hypocalcaemia, hypophosphataemia	Hypomagnesaemia, hypokalaemia, increase in serum creatinine	abnormal liver function tests, increase in serum urea		hyperkalaemia, hypernatraemia

Many of the adverse drug reactions may have been related to the underlying disease.

When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Previously, it has been observed in a clinical trial, investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased risk of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism behind the increased incidence of atrial fibrillation in association with zoledronic acid and pamidronate treatment is unknown.

#### **Postmarketing experience:**

The following adverse reactions have been reported during post-approval use of pamidronate disodium. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to

reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including pamidronate disodium (uncommon). 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 precautions for use). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

#### **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**

ATC code: M05B A03

The active substance 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 disodium suppresses the accession of osteoclast precursors onto the bone. However, the local and direct antiresorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*.

Experimental studies have demonstrated that pamidronate disodium 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 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**

Pamidronate disodium has a strong affinity for calcified tissues, and total elimination of pamidronate disodium 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 disodium 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 disodium concentrations of about 10 nmol/ml are achieved after an intravenous infusion of 60mg given over 1 hour and the apparent plasma clearance is about 180 ml/min.

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 disodium in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

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

*Elimination.* Pamidronate disodium does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20-55 % of the dose is recovered in the urine within 72 hours as unchanged pamidronate disodium. 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 1.25-60mg/h). From the urinary elimination of pamidronate disodium, two decay phases, with apparent half-life of about 1.6 and 27 hours, can be

observed. 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 disodium is insignificant.

*Hepatic Impairment:*

Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate disodium. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above). No changes in dosing are recommended for patients with mild to moderate hepatic dysfunction.

*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 disodium 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, sodium hydroxide, phosphoric acid (for pH adjustment), water for injection.

### **6.2 Incompatibilities**

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

**6.3 Shelf life**  
36 months

**6.4 Special precautions for storage**  
Chemical and physical in-use stability in glucose 50mg/ml has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**6.5 Nature and contents of container**  
10ml vials made of clear, colourless glass (Type I glass, Ph.Eur.).  
The vial closures are made from chlorobutyl rubber, with a PTFE coated surface. The vials are then sealed with tamper proof aluminium caps, and packaged in a carton.

Pack sizes:  
1, 2, 4, 5, 6 and 10 vials

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**  
The concentrate should be further diluted with a calcium-free infusion solution (0.9% w/v Sodium Chloride Intravenous Infusion is recommended) before administration. Do not use if particles are present. Any portion of the contents remaining after use should be discarded.

**7 MARKETING AUTHORISATION HOLDER**

Tillomed Laboratories Ltd  
3 Howard Road  
Eaton Socon, St. Neots  
Cambs PE 19 8 ET  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**  
PL 11311/0218

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
21/09/2011

**10 DATE OF REVISION OF THE TEXT**

21/09/2011

## **1 NAME OF THE MEDICINAL PRODUCT**

Pamidronate Disodium 6mg/ml Concentrate for Solution for Infusion

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

*60mg pamidronate disodium :*

Each ml of concentrate for solution for infusion contains 6mg pamidronate disodium.

1 vial of 10ml of sterile concentrate contains 60mg of pamidronate disodium.

For excipients, see section 6.1

## **3 PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

The concentrate is a clear and colourless solution, free from visible particles.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia.
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer and 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 Special warnings and special precautions for use"). The concentrate must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to Section "6.6 Instructions for use and handling". The infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of pamidronate disodium in the infusion solution should not exceed 60mg/250ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20mg/hour (see also "Patients with renal impairment"). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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

*Tumour-induced hypercalcaemia:*

Patient must be adequately 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 protein or albumin in rehydrated patients.

Initial serum calcium		Recommended total dose (mg)
(mmol/L)	(mg %)	
up to 3.0	up to 12.0	15 – 30
3.0 - 3.5	12.0 - 14.0	30 – 60
3.5 - 4.0	14.0 - 16.0	60 – 90
> 4.0	> 16.0	90

The total dose of 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 90mg for both initial and repeated 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 treatment increases.

*Osteolytic lesions and bone pain in bone metastases associated with breast cancer:* The recommended dose is 90mg every 4 weeks. This dose may also be administered at 3 weekly intervals to coincide with chemotherapy if desired.

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

*Paget's disease of Bone:*

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

*Patients with renal impairment:*

Until further experience is gained a maximum infusion rate of 20mg/hour is recommended in renal impaired patients.

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).

*Patients with 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. Pamidronate disodium should be administered to this patient population with caution.

*Children:*

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

#### **4.3 Contraindications**

Known hypersensitivity to pamidronate disodium or to other Bisphosphonates, or to any of the excipients of Pamidronate disodium.

in pregnancy (see also section 4.6)

in breast feeding women (see also section 4.6)

## 4.4 Special warnings and precautions for use

### General

Pamidronate disodium 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 disodium to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

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

Standard hypocalcaemia-related metabolic parameters including serum electrolyte, calcium and phosphate should be monitored following initiation of therapy with Pamidronate disodium. 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.

Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects.

### Renal Insufficiency

Bisphosphonates, including Pamidronate disodium, 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 disodium. Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate disodium in patients with multiple myeloma.

Pamidronate disodium 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 disodium 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 disodium.

Patients treated with Pamidronate disodium 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 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. (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 disodium should not be given with other bisphosphonates because their combined effects have not been investigated.

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

### **Hepatic Insufficiency**

As there are no clinical data available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population (see 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) should take oral supplements of both during pamidronate disodium therapy to minimise the potential risk of hypocalcaemia.

### **Osteonecrosis of the jaw**

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate disodium . Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

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 (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 should not be co-administered with other bisphosphonates because their combined effects have not been investigated.

Pamidronate disodium has been administered concomitantly with commonly used anticancer agents without interactions occurring.

Pamidronate disodium has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.

Caution is warranted when Pamidronate disodium is used with other potentially nephrotoxic drugs.

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

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

#### **4.6 Pregnancy and lactation**

##### *Pregnancy:*

Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. In rats, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels. In pregnant rats, pamidronate disodium has been shown to cross the placental barrier and accumulate in foetal bone in a manner similar to that observed in adult animals.

There is insufficient clinical experience to support the use of pamidronate disodium in pregnant women. Therefore, pamidronate disodium should not be administered during pregnancy except in cases of life-threatening hypercalcaemia.

##### *Lactation:*

It is not known whether pamidronate disodium is excreted in human milk. A study in lactating rats has shown that pamidronate disodium will pass into the milk. Mothers treated with pamidronate disodium should therefore not breast-feed their infants.

#### 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

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.

The frequency is defined using the following conventions:

Very common (>1/10)

Common (>1/100, <1/10)

Uncommon (>1/1,000 <1/100)

Rare (>1/10,000, <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Infections and infestations					Reactivation of herpes simplex and herpes zoster
Blood and the lymphatic system disorders		Lymphocytopenia Thrombocytopenia, Anaemia			Leukopenia
Immune system disorders			Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoe, Quincke's (angioneurotic oedema)		Anaphylactic shock
Metabolism and nutrition disorders		Asymptomatic hypocalcaemia Anorexia			

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Psychiatric disorders					Visual hallucinations Confusion
Nervous system disorders		Symptomatic hypocalcaemia (paraesthesia, tetany), Headache, Insomnia, Somnolence	Agitation Dizziness Seizures, lethargy		
Eye disorders		Conjunctivitis	Uveitis (iritis, iridocyclitis)		Scleritis Episcleritis Xanthopsia
Cardio-Vascular disorders		Hypertension	Hypotension		left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.
Gastro-intestinal disorders		Nausea Vomiting Abdominal pain Diarrhoea Constipation Gastritis	Dyspepsia		
Skin and subcutaneous tissue disorders		Rash	Pruritus		
Musculo-skeletal, connective tissue and bone disorders		Transient bone pain Arthralgia Myalgia Generalised pain	Muscle cramps		

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Renal and urinary disorders			Acute renal failure	focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome	Haematuria deterioration of pre-existing renal disease
General disorders and administration site conditions		Fever and influenza-like symptoms, sometimes accompanied by malaise, rigor, fatigue and flushes Reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis.			
Investigations	hypocalcaemia, hypophosphataemia	Hypomagnesaemia, hypokalaemia, increase in serum creatinine	abnormal liver function tests, increase in serum urea		hyperkalaemia, hypernatraemia

Many of the adverse drug reactions may have been related to the underlying disease.

When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Previously, it has been observed in a clinical trial, investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased risk of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism behind the increased incidence of atrial fibrillation in association with zoledronic acid and pamidronate treatment is unknown.

**Postmarketing experience:**

The following adverse reactions have been reported during post-approval use of pamidronate disodium. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to

reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including pamidronate disodium (uncommon). 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 precautions for use). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

#### **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**

ATC code: M05B A03

The active substance 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 disodium suppresses the accession of osteoclast precursors onto the bone. However, the local and direct antiresorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*.

Experimental studies have demonstrated that pamidronate disodium 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 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**

Pamidronate disodium has a strong affinity for calcified tissues, and total elimination of pamidronate disodium 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 disodium 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 disodium concentrations of about 10 nmol/ml are achieved after an intravenous infusion of 60mg given over 1 hour and the apparent plasma clearance is about 180 ml/min.

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 disodium in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

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

*Elimination.* Pamidronate disodium does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20-55 % of the dose is recovered in the urine within 72 hours as unchanged pamidronate disodium. 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 1.25-60mg/h). From the urinary elimination of pamidronate disodium, two decay phases, with apparent half-life of about 1.6 and 27 hours, can be

observed. 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 disodium is insignificant.

*Hepatic Impairment:*

Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate disodium. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above). No changes in dosing are recommended for patients with mild to moderate hepatic dysfunction.

*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 disodium 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, sodium hydroxide, phosphoric acid (for pH adjustment), water for injection.

### **6.2 Incompatibilities**

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

**6.3 Shelf life**  
36 months

**6.4 Special precautions for storage**  
Chemical and physical in-use stability in glucose 50mg/ml has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**6.5 Nature and contents of container**  
10ml vials made of clear, colourless glass (Type I glass, Ph.Eur.).  
The vial closures are made from chlorobutyl rubber, with a PTFE coated surface. The vials are then sealed with tamper proof aluminium caps, and packaged in a carton.

Pack sizes:  
1, 2, 4, 5, 6 and 10 vials

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**  
The concentrate should be further diluted with a calcium-free infusion solution (0.9% w/v Sodium Chloride Intravenous Infusion is recommended) before administration. Do not use if particles are present. Any portion of the contents remaining after use should be discarded.

**7 MARKETING AUTHORISATION HOLDER**

Tillomed Laboratories Ltd  
3 Howard Road  
Eaton Socon, St. Neots  
Cambs PE 19 8 ET  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**  
PL 11311/0219

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
21/09/2011

**10 DATE OF REVISION OF THE TEXT**

21/09/2011

## **1 NAME OF THE MEDICINAL PRODUCT**

Pamidronate Disodium 9mg/ml Concentrate for Solution for Infusion

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

*15mg pamidronate disodium :*

Each ml of concentrate for solution for infusion contains 9mg pamidronate disodium.

1 vial of 10ml of sterile concentrate contains 90mg of pamidronate disodium.

For excipients, see section 6.1

## **3 PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

The concentrate is a clear and colourless solution, free from visible particles.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of conditions associated with increased osteoclast activity:

- Tumour-induced hypercalcaemia.
- Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer and 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 Special warnings and special precautions for use"). The concentrate must be diluted before use (see below) and must be infused slowly.

For information concerning compatibility with infusion solutions, refer to Section "6.6 Instructions for use and handling". The infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of pamidronate disodium in the infusion solution should not exceed 60mg/250ml. In patients with established or suspected renal impairment (e.g. those with tumour-induced hypercalcaemia or multiple myeloma) it is recommended that the infusion rate does not exceed 20mg/hour (see also "Patients with renal impairment"). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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

*Tumour-induced hypercalcaemia:*

Patient must be adequately 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 protein or albumin in rehydrated patients.

Initial serum calcium		Recommended total
(mmol/L)	(mg %)	dose (mg)
up to 3.0	up to 12.0	15 – 30
3.0 - 3.5	12.0 - 14.0	30 – 60
3.5 - 4.0	14.0 - 16.0	60 – 90
> 4.0	> 16.0	90

The total dose of 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 90mg for both initial and repeated 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 treatment increases.

*Osteolytic lesions and bone pain in bone metastases associated with breast cancer:* The recommended dose is 90mg every 4 weeks. This dose may also be administered at 3 weekly intervals to coincide with chemotherapy if desired.

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

*Paget's disease of Bone:*

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

*Patients with renal impairment:*

Until further experience is gained a maximum infusion rate of 20mg/hour is recommended in renal impaired patients.

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).

*Patients with 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. Pamidronate disodium should be administered to this patient population with caution.

*Children:*

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

#### **4.3 Contraindications**

Known hypersensitivity to pamidronate disodium or to other Bisphosphonates, or to any of the excipients of Pamidronate disodium.

in pregnancy (see also section 4.6)

in breast feeding women (see also section 4.6)

## 4.4 Special warnings and precautions for use

### General

Pamidronate disodium 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 disodium to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

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

Standard hypocalcaemia-related metabolic parameters including serum electrolyte, calcium and phosphate should be monitored following initiation of therapy with Pamidronate disodium . 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.

Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects.

### Renal Insufficiency

Bisphosphonates, including Pamidronate disodium , 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 disodium . Deterioration of renal function (including renal failure) has also been reported following long-term treatment with Pamidronate disodium in patients with multiple myeloma.

Pamidronate disodium 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 disodium 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 disodium.

Patients treated with Pamidronate disodium 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 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. (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 disodium should not be given with other bisphosphonates because their combined effects have not been investigated.

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

### **Hepatic Insufficiency**

As there are no clinical data available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population (see 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 (ONJ) has been reported predominantly in cancer patients treated with bisphosphonates, including Pamidronate disodium . Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

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 (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 should not be co-administered with other bisphosphonates because their combined effects have not been investigated.

Pamidronate disodium has been administered concomitantly with commonly used anticancer agents without interactions occurring.

Pamidronate disodium has been used in combination with calcitonin in patients with severe hypercalcaemia, resulting in a synergistic effect producing a more rapid fall in serum calcium.

Caution is warranted when Pamidronate disodium is used with other potentially nephrotoxic drugs.

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

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

#### **4.6 Pregnancy and lactation**

##### *Pregnancy:*

Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Dystocia was observed in the rats. In rats, prolonged parturition and reduced survival rate of pups were probably caused by a decrease in maternal serum calcium levels. In pregnant rats, pamidronate disodium has been shown to cross the placental barrier and accumulate in foetal bone in a manner similar to that observed in adult animals.

There is insufficient clinical experience to support the use of pamidronate disodium in pregnant women. Therefore, pamidronate disodium should not be administered during pregnancy except in cases of life-threatening hypercalcaemia.

##### *Lactation:*

It is not known whether pamidronate disodium is excreted in human milk. A study in lactating rats has shown that pamidronate disodium will pass into the milk. Mothers treated with pamidronate disodium should therefore not breast-feed their infants.

#### 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

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.

The frequency is defined using the following conventions:

Very common (>1/10)

Common (>1/100, <1/10)

Uncommon (>1/1,000 <1/100)

Rare (>1/10,000, <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Infections and infestations					Reactivation of herpes simplex and herpes zoster
Blood and the lymphatic system disorders		Lymphocytopenia Thrombocytopenia, Anaemia			Leukopenia
Immune system disorders			Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoe, Quincke's (angioneurotic oedema)		Anaphylactic shock
Metabolism and nutrition disorders		Asymptomatic hypocalcaemia Anorexia			

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Psychiatric disorders					Visual hallucinations Confusion
Nervous system disorders		Symptomatic hypocalcaemia (paraesthesia, tetany), Headache, Insomnia, Somnolence	Agitation Dizziness Seizures, lethargy		
Eye disorders		Conjunctivitis	Uveitis (iritis, iridocyclitis)		Scleritis Episcleritis Xanthopsia
Cardio-Vascular disorders		Hypertension	Hypotension		left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload.
Gastro-intestinal disorders		Nausea Vomiting Abdominal pain Diarrhoea Constipation Gastritis	Dyspepsia		
Skin and subcutaneous tissue disorders		Rash	Pruritus		
Musculo-skeletal, connective tissue and bone disorders		Transient bone pain Arthralgia Myalgia Generalised pain	Muscle cramps		

	VERY COMMON (>1/10)	COMMON (>1/100, <1/10)	UNCOMMON (>1/1000, <1/100)	RARE (>1/10,000, <1/1000)	VERY RARE (<1/10,000)
Renal and urinary disorders			Acute renal failure	focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome	Haematuria deterioration of pre-existing renal disease
General disorders and administration site conditions		Fever and influenza-like symptoms, sometimes accompanied by malaise, rigor, fatigue and flushes Reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis.			
Investigations	hypocalcaemia, hypophosphataemia	Hypomagnesaemia, hypokalaemia, increase in serum creatinine	abnormal liver function tests, increase in serum urea		hyperkalaemia, hypernatraemia

Many of the adverse drug reactions may have been related to the underlying disease.

When the effects of zoledronic acid (4 mg) and pamidronate (90 mg) were compared in one clinical trial, the number of atrial fibrillation adverse events was higher in the pamidronate group (12/556, 2.2%) than in the zoledronic acid group (3/563, 0.5%). Previously, it has been observed in a clinical trial, investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased risk of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism behind the increased incidence of atrial fibrillation in association with zoledronic acid and pamidronate treatment is unknown.

#### **Postmarketing experience:**

The following adverse reactions have been reported during post-approval use of pamidronate disodium. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to

reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates including pamidronate disodium (uncommon). 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 precautions for use). Data suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

#### **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**

ATC code: M05B A03

The active substance 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 disodium suppresses the accession of osteoclast precursors onto the bone. However, the local and direct antiresorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*.

Experimental studies have demonstrated that pamidronate disodium 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 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**

Pamidronate disodium has a strong affinity for calcified tissues, and total elimination of pamidronate disodium 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 disodium 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 disodium concentrations of about 10 nmol/ml are achieved after an intravenous infusion of 60mg given over 1 hour and the apparent plasma clearance is about 180 ml/min.

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 disodium in bone is not capacity-limited, and is dependent solely on the total cumulative dose administered.

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

*Elimination.* Pamidronate disodium does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20-55 % of the dose is recovered in the urine within 72 hours as unchanged pamidronate disodium. 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 1.25-60mg/h). From the urinary elimination of pamidronate disodium, two decay phases, with apparent half-life of about 1.6 and 27 hours, can be

observed. 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 disodium is insignificant.

*Hepatic Impairment:*

Impairment of liver function is therefore not expected to influence the pharmacokinetics of pamidronate disodium. Pamidronate disodium thus displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above). No changes in dosing are recommended for patients with mild to moderate hepatic dysfunction.

*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 disodium 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, sodium hydroxide, phosphoric acid (for pH adjustment), water for injection.

### **6.2 Incompatibilities**

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

**6.3 Shelf life**  
36 months

**6.4 Special precautions for storage**  
Chemical and physical in-use stability in glucose 50mg/ml has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**6.5 Nature and contents of container**  
10ml vials made of clear, colourless glass (Type I glass, Ph.Eur.).  
The vial closures are made from chlorobutyl rubber, with a PTFE coated surface. The vials are then sealed with tamper proof aluminium caps, and packaged in a carton.

Pack sizes:  
1, 2, 4, 5, 6 and 10 vials

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**  
The concentrate should be further diluted with a calcium-free infusion solution (0.9% w/v Sodium Chloride Intravenous Infusion is recommended) before administration. Do not use if particles are present. Any portion of the contents remaining after use should be discarded.

**7 MARKETING AUTHORISATION HOLDER**

Tillomed Laboratories Ltd  
3 Howard Road  
Eaton Socon, St. Neots  
Cambs PE19 8ET  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 11311/0220

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/09/2011

**10**    **DATE OF REVISION OF THE TEXT**  
21/09/2011

## **PATIENT INFORMATION LEAFLET**

A Change of Ownership transfer of these Marketing Authorisations from Tillomed Laboratories Ltd to Sandoz Ltd is planned. It has been agreed that the Product Leaflet may refer to Sandoz Ltd as the product will not be marketed by Tillomed Laboratories Ltd prior to the Change of Ownership.

**Pamidronate Disodium 3 mg/ml  
Concentrate for Solution for Infusion  
Pamidronate Disodium 6 mg/ml  
Concentrate for Solution for Infusion  
Pamidronate Disodium 9 mg/ml  
Concentrate for Solution for Infusion**

**Read all of this leaflet carefully before you start to take this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

1. What Pamidronate Disodium is and what it is used for
2. Before you use Pamidronate Disodium
3. How to use Pamidronate Disodium
4. Possible side effects
5. How to store Pamidronate Disodium
6. Further information



## 1 What Pamidronate Disodium is and what it is used for

Pamidronate Disodium belongs to a group of medicines called bisphosphonates, which work by reducing the amount of calcium in the blood.

Pamidronate Disodium is used to help reduce the amount of calcium in the blood. High blood calcium levels (hypercalcaemia) occur in a number of conditions, including some types of cancer associated with bone pain.

Often, hypercalcaemia is caused by the release of calcium from bones.

Pamidronate Disodium is also used in Paget's disease, a disease which results in a change in bone structure (deformities). Pamidronate Disodium is absorbed into bones and helps to reduce the release of calcium into the blood.

In some patients with cancer, Pamidronate Disodium is also used to treat bone disease and to help relieve bone pain.

## 2 Before you use Pamidronate Disodium

**Do not use Pamidronate Disodium**

- if you are allergic (hypersensitive) to pamidronate disodium or to any of the other ingredients of this medicine (listed in section 6 'Further information')
- if you are pregnant or breast-feeding.

**Take special care with Pamidronate Disodium**

- if you have a history of kidney disease
- if you have a history of heart disease
- if you have undergone thyroid surgery
- if you have a fever e.g. flu or something similar
- if you have severe liver problems
- if you are at risk of having calcium or vitamin D deficiency
- if you have problems with your teeth or jaw.

If any of the above apply to you, tell your doctor before starting treatment with Pamidronate Disodium.

**Taking other medicines**

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Certain other medicines may influence the effect of Pamidronate Disodium, or their effect may be influenced by Pamidronate Disodium.

- You **should not take** other bisphosphonates, whilst being treated with Pamidronate Disodium.

You should tell your doctor if you are taking the following:

- Other medicines for high calcium levels, such as calcitonin
- Other medicines which may affect the kidneys (your doctor or nurse will know which drugs these are)
- Thalidomide, used to treat some cancers.

**Pregnancy and breast-feeding****Pregnancy**

If you are pregnant or think you may be pregnant you **must not use** Pamidronate Disodium. Your doctor will only advise you to take this medicine during pregnancy if your life is at risk from high blood calcium levels (hypercalcaemia).

**Breast-feeding**

You **must not** breast-feed your baby if you are being treated with Pamidronate Disodium. Ask your doctor for advice before taking any medicine.

**Driving and using machines**

Pamidronate Disodium may, in rare cases, cause drowsiness and/or dizziness. If affected you should not drive or operate dangerous machinery.

## 3 How to use Pamidronate Disodium

Pamidronate Disodium should only be given under the supervision of a physician. Your doctor will decide on a suitable dose depending on your condition.

Pamidronate Disodium is diluted and then given by slow injection into a vein (intravenous infusion).

The infusion will last from one to several hours depending on the dose. Your doctor will decide how many infusions you need and how often they will be given.

Dosage guidelines are as follows:

**Hypercalcaemia:**

15 - 90 mg given as a single or several infusions.

**Bone diseases and bone pain:**

90 mg every 4 weeks. In some patients the dose may be given every 3 weeks at the same time as chemotherapy.

**Paget's disease:**

30 mg once a week for 6 weeks, or 60 mg every other week over 6 weeks.

When doses of 60 mg are given your doctor may give you a test dose of 30 mg to see how you respond to the treatment.

**Children:**

This medicine is not recommended for children and should only be used in adult patients.

*Continued on the next page >>*



The following information is intended for medical or healthcare professionals only: SZ00000LT000

#### Instructions for use

Do not use if particles are present.

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

The concentrate must be further diluted with a calcium-free infusion solution before administration.

The reconstituted solution is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The reconstituted solution must not be mixed with calcium-containing solution such as Ringer's solution.

#### Incompatibilities

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

#### Special precautions for storage

##### Storage after dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

#### Posology and method of administration

Pamidronate disodium must never be given as a bolus injection (See SmPC Section 4.4). The concentrate must be diluted before use (see below) and must be infused slowly.

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 "Patients with renal impairment"). In order to minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein.

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

#### 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 protein or albumin in rehydrated patients.

Initial serum calcium		Recommended total dose (mg)
(mmol/l)	(mg %)	
up to 3.0	up to 12.0	15 – 30
3.0 - 3.5	12.0 - 14.0	30 – 60
3.5 - 4.0	14.0 - 16.0	60 – 90
> 4.0	> 16.0	90

The total dose of 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 repeated courses.

*Continued on the next page >>*

## 4 Possible side effects

Like all medicines, Pamidronate Disodium can cause side effects.

### Side effects can be serious

Tell your doctor **straight away** if you notice the following, as they may be signs of an allergic reaction:

- Difficulty in breathing or wheezing and dizziness
- Swelling of the face and throat.

Tell your doctor **straight away** if you notice the following:

- Fluid retention, feeling sick or tiredness as these may be symptoms of a change in kidney function known as glomerulosclerosis
- Pain, swelling, or gum infections, loosening of teeth, numbness or a feeling of heaviness in the jaw, as these may be signs of a bone problem known as osteonecrosis.

The frequency of having osteonecrosis is not known but reported cases have predominantly been in cancer patients and have affected the jaw.

The side effects listed below have also been reported.

### Common (Up to 1 in 10 people have experienced):

- Pain, redness or swelling at the infusion site
- Skin rash or unexplained bruising/increased bleeding
- Joint or muscle pain
- Nausea, vomiting, loss of appetite, stomach pain, gastritis, constipation or diarrhoea
- Headache, sleeplessness, tiredness
- Conjunctivitis
- Tingling in hands and feet and muscle spasms (symptoms of low level of calcium)
- High blood pressure
- Low level of white blood cells (leucopenia) or red blood cells (anaemia)
- Changes in blood test results (including low potassium, low phosphate, low magnesium and raised serum creatinine levels or, very rarely, raised potassium or sodium levels).

### Uncommon (Up to 1 in 100 people have experienced):

- Muscle cramps
- Dizziness, lethargy, feeling agitated, seizures
- Problems with vision, painful red eyes
- Low blood pressure
- Itching, indigestion
- Deterioration of kidney function (e.g. unexpected change in the amount of urine produced and/or its appearance), abnormal liver function tests or increases in serum urea
- Problems with teeth or jaw.

### Rare (Up to 1 in 1,000 people have experienced):

A change in kidney function known as glomerulosclerosis, some of the symptoms of this condition may be, fluid retention, nausea and fatigue. Tell your doctor if you suspect that you might have these symptoms.

### Very Rare (Up to 1 in 10,000 people have experienced):

- Cardiac effects which may include a difficulty in breathing and fluid retention
- Worsening of an existing kidney problem e.g. blood in urine
- A flare-up of cold sores or shingles
- Confusion or visual hallucinations (seeing things that are not there).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist.

## 5 How to store Pamidronate Disodium

Keep Pamidronate Disodium out of the reach and sight of children.

Do not use Pamidronate Disodium after the expiry date on the carton.

Prepared product should be used immediately. If this is not possible it can be stored for up to 24 hours at 2-8°C before use.

If your doctor tells you to stop taking Pamidronate Disodium and you have been keeping some at home, please take any unused vials back to your pharmacist to be destroyed. Do not throw them away with your normal household water or waste. This will help to protect the environment.

## 6 Further information

### What Pamidronate Disodium contains

The active substance is: pamidronate disodium 15 mg, 30 mg, 60 mg or 90 mg.

Each ml of concentrate for solution for infusion contains either 3 mg, 6 mg or 9 mg pamidronate disodium.

1 vial of 5 ml of sterile concentrate contains 15 mg of pamidronate disodium.

1 vial of 10 ml of sterile concentrate contains either 30 mg, 60 mg or 90 mg of pamidronate disodium.

### The other ingredients are:

mannitol, sodium hydroxide, phosphoric acid, water for injection.

### What Pamidronate Disodium looks like and contents of the pack

Pamidronate Disodium is a clear and colourless solution and comes in clear, colourless glass vials.

Pamidronate Disodium 3 mg, 6 mg and 9 mg comes in packs of 1, 2, 4, 5, 6, and 10 vials.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

#### Marketing Authorisation

Sandoz Ltd.,  
Frimley Business Park,  
Frimley, Camberley, Surrey, GU16 7SR, UK.

#### Manufacturer

Lek Pharmaceuticals d.d.,  
Verovskova 57,  
1526 Ljubljana,  
Slovenia.

or

Salutas Pharma GmbH,  
Otto-von-Guericke-Allee 1,  
D-39179 Barleben,  
Germany.

This leaflet was last approved in 07/2011 (to be amended after approval).

SZ00000LT000



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 treatment increases.

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.

Osteolytic lesions and bone pain in multiple myeloma

The recommended dose is 90 mg every 4 weeks.

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 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 one week in advance (i.e. total dose 210 mg). This regimen or increased dose levels according to disease severity, up to a maximum total dose of 360 mg (omitting the initial 30 mg dose) can be repeated every 6 months until remission of disease is achieved, and if relapse occurs.

Patients with 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 SmPC Section 4.4 and 5.2).

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 0.5 mg/dl.  
For patients with abnormal baseline creatinine, increase of 1.0 mg/dl.

A pharmacokinetic study conducted in patients with cancer and normal or impaired renal function indicates that the dose adjustment is not necessary in mild (creatinine clearance 61-90 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).

Patients with 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 SmPC section 5.2). Clinical data in patients with severe hepatic impairment is not available (see SmPC Section 4.4). Pamidronate should be administered to this patient population with caution.

Children

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

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## LABELLING

A Change of Ownership transfer of these Marketing Authorisations from Tillomed Laboratories Ltd to Sandoz Ltd is planned. It has been agreed that the product labelling may refer to Sandoz Ltd as the product will not be marketed by Tillomed Laboratories Ltd prior to the Change of Ownership.

**PL 11311/0217**

### **Label:**

**For intravenous use only.**  
**Dilute prior to use.**  
Read the package leaflet before use.  
Each ml of concentrate for solution for infusion contains 3 mg pamidronate disodium.  
1 vial of 5 ml of sterile concentrate contains 15 mg of disodium pamidronate.

PL 04416/0894 POM

Sandoz Ltd,  
Frimley Business Park, Frimley,  
Camberley, Surrey, GU16 7SR. SZ000001B000

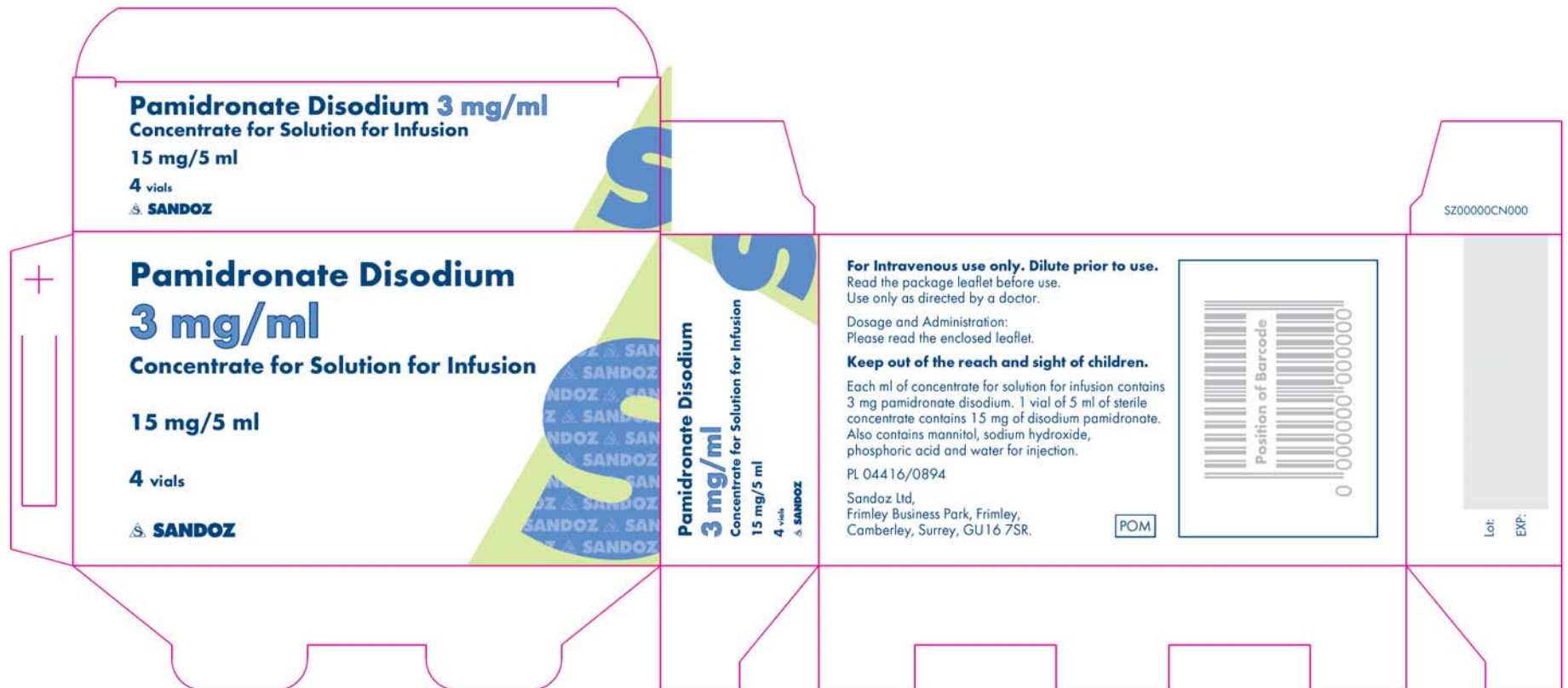
**Pamidronate Disodium**  
**3 mg/ml**  
**Concentrate for Solution**  
**for Infusion**

**15 mg/5 ml**

**SANDOZ**

Batch: \_\_\_\_\_  
EXP: \_\_\_\_\_

**Carton:**



PL 11311/0218

**Label:**

**For intravenous use only.  
Dilute prior to use.**  
Read the package leaflet before use.  
Each ml of concentrate for solution for infusion contains 3 mg pamidronate disodium.  
1 vial of 10 ml of sterile concentrate contains 30 mg of disodium pamidronate.

PL 04416/0895 POM

Sandoz Ltd,  
Frimley Business Park, Frimley,  
Camberley, Surrey, GU16 7SR. SZ000001B000

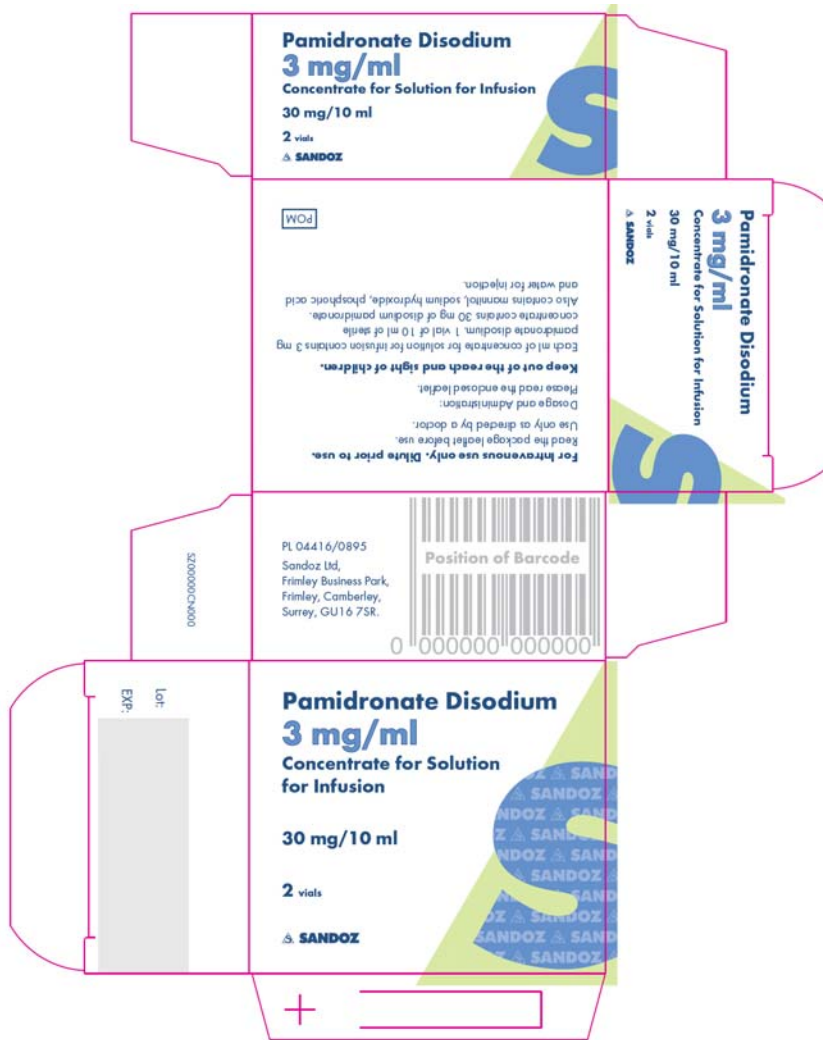
**Pamidronate Disodium**  
**3 mg/ml**  
**Concentrate for Solution**  
**for Infusion**

**30 mg/10 ml**

**SANDOZ**

Batch: \_\_\_\_\_  
EXP: \_\_\_\_\_

**Carton:**



PL 11311/0219

Label:


**For intravenous use only.**  
**Dilute prior to use.**  
Read the package leaflet before use.  
Each ml of concentrate for solution for infusion contains 6 mg pamidronate disodium.  
1 vial of 10 ml of sterile concentrate contains 60 mg of disodium pamidronate.

PL 04416/0896 POM

Sandoz Ltd,  
Frimley Business Park, Frimley,  
Camberley, Surrey, GU16 7SR. SZ000001B000

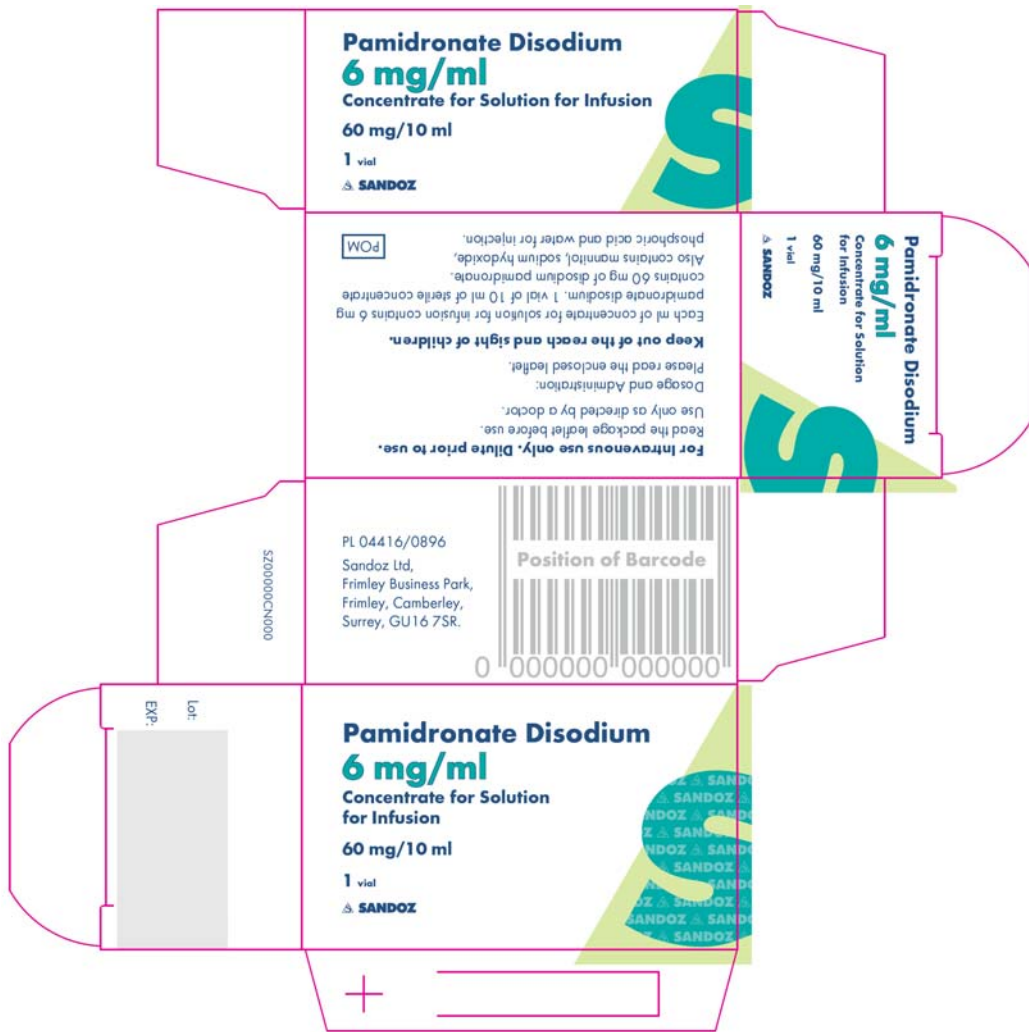
**Pamidronate Disodium**  
**6 mg/ml**  
**Concentrate for Solution**  
**for Infusion**

**60 mg/10 ml**

 **SANDOZ**

Batch: \_\_\_\_\_  
EXP: \_\_\_\_\_

**Carton:**



PL 11311/0220

**Label:**

**For intravenous use only.**  
**Dilute prior to use.**  
Read the package leaflet before use.  
Each ml of concentrate for solution for infusion contains 9 mg pamidronate disodium.  
1 vial of 10 ml of sterile concentrate contains 90 mg of disodium pamidronate.

PL 04416/0897

**POM**

Sandoz Ltd,  
Frimley Business Park, Frimley,  
Camberley, Surrey, GU16 7SR.

SZ00000LB000

**Pamidronate Disodium**  
**9 mg/ml**  
**Concentrate for Solution**  
**for Infusion**

**90 mg/10 ml**

**SANDOZ**

Batch:  
EXP:

