# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Aredia 30mg powder and solvent for concentrate for solution for infusion.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 30 mg vial contains lyophilised pamidronate disodium pentahydrate equivalent to 30 mg pamidronate disodium anhydrous.

A 10 ml ampoule of water for injections is supplied with each vial. When reconstituted, the concentration is 3mg/ml. Further dilution is required.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion (Powder and solvent for sterile concentrate)

White, lyophilized mass.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the treatment of tumour-induced osteolysis with or without tumour-induced hypercalcaemia.

For the treatment of Paget's disease of bone.

### 4.2 Posology and method of administration

***Directions for use:***

For intravenous infusion

Aredia must never be given as a bolus injection (see section 4.4 Special warnings and precautions for use).

Aredia should always be diluted before use and administered as a slow intravenous infusion.

***Preparation of Infusion:***

This is a two step procedure:

1. Using aseptic technique, Aredia dry powder 30mg should be dissolved in 10 ml of Water for Injections Ph.Eur. It is important that the dry substance is completely dissolved before proceeding to step 2.
2. The reconstituted solution is withdrawn for dilution. Reconstituted solution of Aredia from powder in vials should be diluted in a calcium-free infusion solution (0.9% sodium chloride or 5% glucose). Aredia must not be mixed with calcium or other divalent cation-containing solutions such as Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs. The infusion rate should not exceed 60mg in 1 hour (1mg/min) and the concentration of Aredia in the infusion solution should not exceed 90mg/250ml. A dose of 90mg should normally be administered as a 2-hour infusion in 250ml infusion solution. However, in patients with multiple myeloma and in patients with tumour-induced hypercalcaemia, it is recommended not to exceed 90mg in 500ml over 4 hours.

In order to minimise local reactions at the infusion site; the cannula should be carefully inserted into a relatively large vein.

***Adults and the Elderly:***

Predominantly lytic bone metastases and multiple myeloma

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

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

**Tumour-Induced Osteolysis**

The recommended dose is 30mg once a week for four consecutive weeks and then once every two weeks, for six months, or until there is evidence of disease progression in the bone, when patient management should be reassessed.

If patients progress to clinically significant hypercalcaemia, the following regime should be adopted.

**Tumour-Induced Hypercalcaemia**

Patients must be adequately rehydrated prior to and during administration of Aredia. The total dose of Aredia to be used for a treatment course depends on the patient's initial serum calcium levels.

The following guidelines are derived from clinical data on uncorrected calcium values. However, doses within the ranges given are also applicable for calcium values corrected for serum protein or albumin in rehydrated patients:

Table 1 Recommended doses according to serum calcium levels

| **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 |

A dose of 30 to 60mg has been found to be appropriate for the majority of patients.The total dose of Aredia may be administered either in a single infusion or in multiple infusions over 2 to 4 consecutive days. The maximum dose per treatment course of Aredia is 90 mg for both initial and repeat courses. Patient experience indicates that doses above 90mg bring no increased clinical benefit. A significant decrease in serum calcium is generally observed 24 to 48 hours after administration of Aredia 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 Aredia may become less effective as the number of treatments increases.

**Paget's Disease of Bone**

Treatment should be made under the supervision of a hospital based specialist. The recommended total dose of Aredia for a treatment course is 180 to 210mg. This can be administered either in 6 unit doses of 30mg once a week (total dose 180mg) or in 3 unit doses of 60mg every other week. If unit doses of 60mg are used, it is recommended to start the treatment with an initial dose of 30mg (total dose 210mg).

Experience to date suggests that any mild or transient unwanted effects (See side 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 (total dose 210mg).

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

Renal impairment:

Aredia 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.

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

For patients with normal baseline creatinine, increase of 0.5 mg/dL.

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

A pharmacokinetic study conducted in patients with cancer and normal or impaired renal function indicates that the dose adjustment is not necessary in mild (creatinine clearance 61 -to 90 mL/min) to moderate renal impairment (creatinine clearance 30 -to 60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4h (approximately 20 -to 22 mg/h).

Hepatic Impairment:

A pharmacokinetic study indicates that no dose adjustment is necessary in patients with mild to moderate abnormal hepatic function ( see section 5.2.- Pharmacokinetic properties – Hepatic impairment). Aredia has not been studied in patients with severe hepatic impairment (see section 4.4 Special warnings and precautions for use). Therefore, caution should be exercised when Aredia is given to patients with severe hepatic impairment.

**Pediatrics**

There are limited data on efficacy and safety of Aredia in pediatric patients. Therefore, Aredia is not recommended for the use in children.

## 4.3 Contraindications

Aredia is contraindicated

- in patients with known hypersensitivity to pamidronate disodium or other bisphosphonates, or to any of the excipients of Aredia.

## 4.4 Special warnings and precautions for use

**General:**

Aredia must never be given as a bolus injection since local reactions and thrombophlebitis may occur. Aredia 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 Aredia to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

Standard hypercalcaemia-related metabolic parameters including serum calcium, phosphate, magnesium and potassium should be monitored following initiation of therapy with Aredia. Patients who have undergone thyroid surgery may be particularly susceptible to develop 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). Therefore, overhydration should be avoided especially in patients at risk of cardiac failure. Fever (influenza like symptoms) may also contribute to this deterioration. Patients with anaemia, leukopenia or thrombocytopenia should have regular hematology assessments.

**Special population**

**Renal Impairment:**

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

Aredia is excreted intact primarily via the kidney (see 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 Aredia 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 Aredia.

Patients receiving frequent infusions of Aredia over a prolonged period of time, especially those with pre-existing renal disease or a predisposition to renal impairment (e.g. patients with multiple myeloma and/or tumour induced hypercalcaemia) should have evaluations of standard laboratory and clinical parameters of renal function prior to each dose of Aredia.

Patients treated with Aredia for bone metastases should have the dose withheld if renal function has deteriorated (see section 4.2. Posology and method of administration).

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

Aredia should not be given with other bisphosphonates because their combined effects have not been investigated.

There is a possibility of precipitating convulsions in some patients due to the electrolyte changes associated with tumour-induced hypercalcaemia and its effective treatment.

Hepatic Impairment:

As there are no clinical data available in patients with severe hepatic impairment, no specific recommendations can be given for this patient population but caution should be exercised when Aredia is given to these patients (see section 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 deficiency and patients with Paget's disease of the bone should take oral calcium and vitamin D supplementation in order to minimise the risk of hypocalcaemia.

Osteonecrosis of the Jaw:

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

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)

Patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

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 judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**Atypical fractures of the femur**

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in Aredia-treated patients, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of Aredia therapy in patients

suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. Reports of atypical femoral fracture have been received in patients treated with Aredia; however causality with Aredia therapy has not been established.

During Aredia treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Musculoskeletal Pain:

In post-marketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates including Aredia. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief 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

Aredia displays little potential for drug-drug interactions (see section 5.2 Pharmacokinetics). Aredia has been administered concomitantly with commonly used anti-cancer agents without interactions occurring.

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

**Observed interactions to be considered**

Aredia 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.

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

**Anticipated interactions to be considered**

Caution is warranted when Aredia is used with other potentially nephrotoxic drugs.

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

## 4.6 Fertility, pregnancy and lactation

**Women of child-bearing potential and contraceptive measures**

Women of child-bearing potential must use highly effective contraception during treatment.

**Pregnancy**

There are no adequate data for the use of Aredia in pregnant women. There is no unequivocal evidence for teratogenicity in animal studies (see section 5.3 Preclinical safety data). Pamidronate may pose a risk to the foetus/newborn child through its pharmacological action on calcium homeostasis. When administered during the whole period of gestation in animals, pamidronate can cause bone mineralization disorder especially of long bones resulting in angular distortion.

The potential risk for humans is unknown. Therefore, Aredia should not be given to pregnant women except in cases of life-threatening hypercalcaemia.

**Breast-feeding**

Very limited experience indicates maternal milk levels of pamidronate under the limit of detection. Moreover the oral bioavailability is poor so the total absorption of pamidronate by a breast-fed infant is not likely (see section 5.2 Clinical pharmacology/Pharmacokinetics). However due to extremely limited experience and the potential of pamidronate to have an important impact on bone mineralization breast-feeding during the therapy should be avoided.

**Fertility**

There are no data available.

## 4.7 Effects on ability to drive and use machines

Patients should be warned that somnolence and/or dizziness may occur following Aredia 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

### Summary of the safety profile

Adverse reactions to Aredia are usually mild and transient. The most common adverse reactions are asymptomatic hypocalcaemia and fever **(**an increase in body temperature of 1 to 2°C), typically occurring within the first 48 hours of infusion. Fever usually resolves spontaneously and does not require treatment.

### Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 2) are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

*Table 2*

| | |
|---|---|
| *Infections and Infestations* | |
| Very rare | Reactivation of Herpes simplex, reactivation of Herpes zoster. |
| *Blood and lymphatic systems disorders* | |
| Common: | Anaemia, thrombocytopenia, lymphocytopenia, leukopenia. |
| *Immune system disorders* | |
| Uncommon: | Allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke's (angioneurotic) oedema. |
| Very rare: | Anaphylactic shock |
| *Metabolism and Nutritional disorders* | |
| Very common: | Hypocalcaemia, hypophosphataemia |
| Common: | Hypokalaemia, hypomagnesaemia |
| Very rare: | Hyperkalaemia, hypernatraemia |
| *Nervous system disorders* | |
| Common: | Symptomatic hypocalcemia (tetany paresthesia), headache, insomnia, somnolence. |
| Uncommon: | Seizures, lethargy, agitation, dizziness. |
| Very rare: | Confusion, visual hallucinations. |

*Eye disorders*

| | |
|---|---|
| Common: | Conjunctivitis. |
| Uncommon: | Uveitis (iritis, iridocyclitis). |
| Very rare: | Scleritis, episcleritis, xanthopsia. |
| Not known: | Orbital inflammation |

*Cardiac disorders*

| | |
|---|---|
| Common: | Atrial fibrillation |
| Very rare: | Left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload. |

Vascular disorders

| | |
|---|---|
| Common: | Hypertension |
| Uncommon: | Hypotension |

*Respiratory, thoracic and mediastinal disorders*

| | |
|---|---|
| Very rare: | Acute respiratory distress syndrome, interstitial lung disease |

*Gastrointestinal disorders*

| | |
|---|---|
| Common: | Nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation, gastritis. |
| Uncommon: | Dyspepsia. |

*Skin and subcutaneous disorders*

| | |
|---|---|
| Common: | Rash. |
| Uncommon: | Pruritus. |

*Musculoskeletal and connective tissue disorders*

| | |
|---|---|
| Common: | Transient bone pain, arthralgia, myalgia, generalised pain. |
| Uncommon: | Muscle cramps, osteonecrosis. |

*Renal and urinary disorders*

| | |
|---|---|
| Uncommon: | Acute renal failure. |
| Rare: | Focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome |
| Very rare: | Deterioration of pre-existing renal disease, haematuria, renal tubular disorder, tubulointerstitial nephritis, glomeruloephropathy. |

*General disorders and administration site conditions*

| | |
|---|---|
| Very Common: | Fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue, |

| | |
|---|---|
| and flushes. | |
| Common: | Reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis). |
| *Investigations* | |
| Common: | Increase in serum creatinine. |
| Uncommon: | Abnormal liver function tests, increase in serum urea. |

**Adverse drug reactions from spontaneous reports and literature cases (frequency not known)**

The following adverse reactions have been reported during post-approval use of Aredia. 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 (which is therefore categorized as not known) or establish a causal relationship to drug exposure.

**Eye disorders**: orbital inflammation.

**Respiratory, thoracic and mediastinal disorders**: adult respiratory distress syndrome (ARDS), interstitial lung disease (ILD).

**Musculoskeletal and connective tissue disorders:** severe and occasionally incapacitating bone, joint, and/or muscle pain, osteonecrosis of the jaw (ONJ). Cases of atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonates (class adverse reaction), including Aredia.

**Renal and urinary disorders**: renal tubular disorders (RTD), tubulointerstitial nephritis, and glomerulonephropathies.

**Description of selected ADRs (class label)**

*Atrial fibrillation*: 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%). Isolated instances of higher incidence of atrial fibrillation have also been reported in a few studies with other bisphosphonates. The mechanism of this increased incidence of atrial fibrillation in isolated studies with some bisphosphonates, including Aredia, is unknown.

*Osteonecrosis of the jaw*: Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with bisphosphonates, including Aredia. Many of these patients had signs of local infection including osteomyelitis and the majority of the reports refers to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anemia, 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 Warnings and precautions). Data suggest a greater frequency of reports of ONJ based on tumor 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

Pharmacotherapeutic group ATC:
Inhibitor of bone resorption (ATC code: M05B A03)

Pamidronate disodium, the active substance of Aredia, 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 at least in part be due to binding of the drug to the bone mineral.

Pamidronate suppresses the accession of the osteoclast precursors onto the bone and their subsequent transformation into mature resorbing osteoclasts. 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 in animals have demonstrated that Aredia 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 Aredia on tumour-induced osteolysis, and specifically on tumour-induced hypercalcaemia, are characterised by a decrease in serum calcium and, secondarily by decrease 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, Aredia improves GFR and lowers elevated serum creatinine levels in most patients.

## 5.2 Pharmacokinetic properties

***General characteristics***

Pamidronate has a strong affinity for calcified tissues, and total elimination of pamidronate from the body is not observed within the time frame of experimental studies. Calcified tissues are therefore regarded as site of “apparent elimination”.

***Absorption***

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

***Distribution***

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

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

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

**Biotransformation/metabolism**

Hepatic and metabolic clearances of pamidronate are minor. Thus, Aredia displays little potential for drug-drug interactions both at the metabolic level and at the level of protein binding (see above).

***Elimination***

Pamidronate does not appear to be eliminated by biotransformation. After an intravenous infusion, about 20 –to 55 % of the dose is recovered in the urine within 72 hours as unchanged pamidronate.

Within the time frame of experimental studies the remaining fraction of the dose is retained in the body. The percentage of the dose retained in the body is independent of both the dose (range 15 –to 180 mg) and the infusion rate

(range 1.25 –to 60 mg/hour). The elimination of pamidronate in the urine is biexponential, with apparent half-lives of about 1.6 and 27 hours.

The apparent total plasma clearance is about 180ml/min and the apparent renal clearance is about 54 mL/min, and there is a tendency for the renal clearance to correlate with creatinine clearance.

**Special populations**

**Hepatic impairment**

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=9). Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean Area Under the Curve (AUC 39,7%) and Maximum Concentration (Cmax 28,6%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 –to 36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function (see 4.2. Posology and method of administration).

**Renal impairment:**

A pharmacokinetic study conducted in patients with cancer showed no differences in plasma AUC of pamidronate between patients with normal renal function and patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC of pamidronate was approximately 3 times higher than in patients with normal renal function (creatinine clearance >90 mL/min).

**Geriatrics**

No specific data are available in this population.

**Pediatrics**

No specific data are available in this population.

**Clinical studies**

Clinical trials in patients with predominantly lytic bone metastases or multiple myeloma showed that Aredia prevented or delayed skeletal-related events (hypercalcemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain. When used in combination with standard anticancer treatment, Aredia led to a delay in progression of bone metastases. In addition, osteolytic bone metastases which have proved refractory to cytotoxic and hormonal therapy may show radiological evidence of disease stabilization or sclerosis.

Paget's disease of bone, which is characterized by local areas of increased bone resorption and formation with qualitative changes in bone remodeling, responds well to treatment with Aredia. 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.

## 5.3 Preclinical safety data

**Acute toxicity**

The toxicity of pamidronate is characterised by direct (cytotoxic) effects on organs with a copious blood supply, particularly the kidneys following i.v. exposure.

**Reproduction toxicity**

Bolus intravenous studies conducted in rats and rabbits determined that pamidronate produces maternal toxicity and embryo/fetal effects when given during organogenesis at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion. As it has been shown that pamidronate can cross the placenta in rats and has produced marked maternal and nonteratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back

into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are very limited data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

A study in lactating rats has shown that pamidronate will pass into the milk.

**Mutagenicity and carcinogenic potential**

The compound is not mutagenic and does not appear to have carcinogenic potential.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Vials
Mannitol
Phosphoric acid

Ampoules
Water for Injections

### 6.2 Incompatibilities

Aredia must not be admixed with calcium or other divalent cation-containing infusion solutions, e.g. Ringers, Hartmann's solution.

### 6.3 Shelf life

3 years.
Use diluted solutions immediately and discard any solution remaining after use.

### 6.4 Special precautions for storage

Do not store above $30^0$C.

### 6.5 Nature and contents of container

Clear, colourless glass Type III (Ph.Eur.) 10 ml vial with bromobutyl rubber closure, packaged in a cardboard carton. A clear, colourless Type I glass ampoule containing solvent for reconstitution.

Pack contains 2 Aredia Dry Powder 30 mg vials and 2 ampoules of Water for Injections.

### 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Powder in vials should be first dissolved in Water for Injection, i.e. 30mg in 10 mL. The sterile Water for Injection is available in ampoules which are supplied together with vials. The appearance of the reconstituted solution is clear and should be free from any undissolved particles.

The pH of the reconstituted solution is 6.0 – 7.0. The reconstituted solution should be further diluted with calcium free infusion solution (0.9% sodium chloride or 5% glucose) before administration. It is important that the powder be completely dissolved before the reconstituted solution is withdrawn for dilution.

Discard any solution remaining after use.

## 7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park
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Surrey GU16 5SG
England.

## 8 MARKETING AUTHORISATION NUMBER

PA 0013/090/002

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

Date of first authorisation: 11 November 1993

Date of last renewal: 11 November 2008

## 10 DATE OF REVISION OF THE TEXT

June 2014