

INFORMATION FOR THE MEDICAL PROFESSIONALS

1 NAME OF THE MEDICINAL PRODUCT

Aredia 90mg

Powder and solvent for concentrate for solution for infusion

Aredia 30mg

Powder and solvent for concentrate for solution for infusion

Pamidronate disodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 30mg or 90mg vial contains lyophilised pamidronate disodium pentahydrate equivalent to 30mg or 90mg of pamidronate disodium anhydrous.

A 10ml ampoule of water for injections is supplied with each vial. When reconstituted, the concentration is 3mg/ml or 9mg/ml. Further dilution is required.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.

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 or 90mg should be dissolved in 10ml 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 The reconstituted solution is withdrawn for dilution.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 30-60mg 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 90mg for both initial and repeat courses. Patients 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 < 30mL/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 61-90 mL/min) to moderate renal impairment (creatinine clearance 30-60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4h (approximately 20-22 mg/h).

Hepatic Impairment

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 or to other bisphosphonates, or to any of the excipients of Aredia

4.4 Special warnings and precautions for use

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.

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).

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 electrolyte changes associated with tumour-induced hypercalcaemia and its effective treatment.

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

Hepatic Impairment:

As there are no clinical data available in patients with severe hepatic impairment, no specific recommendations can be given for this patient 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).

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

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 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 Interactions with other medicinal products and other forms of interaction

Aredia displays little potential for drug-drug interactions (see section 11 Clinical pharmacology/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 ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Read all of this leaflet carefully before you start treatment with AREDIA[®]

Keep this leaflet. You may need to read it again. If any of the side effects gets serious, or if you notice side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist. If you have any further questions, please ask your doctor or pharmacist.

In this leaflet

- 1 What Aredia[®] is and what it is used for
- 2 Before you start treatment with Aredia
- 3 How to use Aredia
- 4 Possible side effects
- 5 Storing Aredia
- 6 Further information

Aredia 30 mg or 90 mg

Powder and solvent for concentrate for solution for infusion

- The **active substance** of Aredia is pamidronate disodium. It is supplied as powder in vials together with solvent ampoules of water for injections in which to dissolve the powder.
- The **other ingredients** are mannitol and phosphoric acid.

Manufacturer and Marketing Authorisation Holder

Novartis Pharmaceuticals UK Limited,
Frimley Business Park,
Frimley,
Surrey GU16 7SR, England

1 WHAT AREDIA IS AND WHAT IT IS USED FOR

Powder and solvent for concentrate for solution for infusion.

One vial contains 30 mg or 90 mg of pamidronate disodium in powder form.

One solvent ampoule contains 10 mL of water for injection.

Aredia is given as an infusion into a vein after appropriate dilution.

Aredia is used to treat:

- the increased amount of calcium in the blood (hypercalcaemia) in certain conditions,
- Paget's disease of bone.

Aredia belongs to a group of medicines called bisphosphonates which strongly bind to the bone and slow down the rate of bone change. They are used to reduce the amount of calcium in the blood of some patients who have too much calcium in their blood circulation. Aredia can also be used in other conditions with increased bone change or pain.

2 BEFORE YOU START TREATMENT WITH AREDIA

Be sure that you have discussed treatment with Aredia with your doctor. You may only be given Aredia after a full medical examination.

You should not be given Aredia

- if you are allergic (hypersensitive) to pamidronate or other bisphosphonates (the group of substances to which Aredia belongs), or any of the other ingredients of Aredia

Before you are given Aredia, tell your doctor

- **If you have** a serious liver problem.
- **If you had or have** a kidney problem.
- **If you had or have** a heart problem.
- **If you** suffer from calcium or vitamin D deficiency (for example owing to your diet or as a result of digestive problems).
- **If you had or have** pain, swelling or numbness of the jaw or a "heavy jaw feeling" or loosening of a tooth.

If you are under dental treatment or will undergo a dental surgery, tell your dentist that you are being treated with Aredia.

You are advised to have a dental examination prior to treatment with Aredia and should avoid invasive dental procedures during treatment. Be informed of the importance of good dental hygiene and routine dental care.

Ensure sufficient intake of fluids prior to infusions as directed by your doctor as this will help to prevent dehydration.

Your treatment may need to be supplemented with Calcium and Vitamin D.

Your doctor will check your response to treatment at regular intervals. Since bisphosphonates (the class of drugs to which Aredia belongs) may cause damage to the kidneys, your doctor may want to take repeated blood tests, especially when you start treatment with Aredia and before each additional dose. Your doctor will tell you when to withhold the treatment, if necessary. Make sure you inform your doctor if your medical condition changes.

Aredia and older people

Patients at the age of 65 years or older may be safely treated with Aredia, provided that they do not have a serious heart, kidney or liver problem. Ask your doctor if you have any questions about this.

Aredia and children

So far children have not been treated with Aredia.

Pregnant women

You should tell your doctor if you are pregnant, or planning to become pregnant before you receive Aredia. Aredia should not be given during pregnancy.

Breast-feeding mothers

Ask your doctor for advice if you are breast-feeding or intend to breast feed. Mothers treated with Aredia should not breast-feed their babies.

Driving and using machines

Aredia may cause some patients to become sleepy or dizzy, especially immediately after the infusion. If this happens, you should not drive, use machinery or perform other tasks that need full attention.

Using other medicines

Before starting treatment with Aredia, talk to your doctor about any other medicines that you are using or intend to use. It is especially important that your doctor knows if you are being treated with another bisphosphonate, calcitonin or thalidomide.

3 HOW TO USE AREDIA

Aredia can only be given by slow infusion into a vein. The dose will be decided by your doctor. It is 30 to 90 mg for patients with increased blood calcium. Patients with Paget's disease of bone usually receive between 30 to 60 mg in one infusion. An infusion may last several hours, depending on the dose given, and the condition of your kidney. Your doctor will decide how many infusions you need, how often you should receive them and if you will receive additional saline solution for rehydration.

4 POSSIBLE SIDE EFFECTS

Patients taking Aredia may experience side effects, although not everybody gets them.

Some side effects could be serious and might need immediate medical attention.

Some are common (affect between 1 and 10 in every 100 patients).

- Spontaneous bleeding and bruising due to low level of blood platelets
- Fever, sore throat or mouth ulcers due to infections, signs of low level of lymphocytes and leukocytes (a specific type of white blood cells with important functions in the immune system).

- Tingling or numbness and muscle spasms and twitching, symptoms of low levels of calcium

Some are uncommon (less than 1 in every 100 but more than 1 in 1000 patients).

- Severe allergic reaction (anaphylaxis) which causes difficulty in breathing, swollen lips and tongue or a sudden fall in blood pressure
- Seizures
- Severe damage to the kidney
- Uncommonly, in some patients bone damage in the jaw (osteonecrosis) may occur. Signs of this condition can be: pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a “heavy jaw feeling” or loosening of a tooth. Tell your oncologist and dentist immediately if you experience such symptoms.

Some are very rare (less than 1 in every 10,000 patients).

- Heart disease characterized by breathlessness and fluid retention in the body

If you experience any of these, tell your doctor immediately.

Other side effects

Some are very common (more than 1 in 10 patients).

- Short-lasting fever and flu-like condition with chills, sometimes together with a feeling of tiredness and general discomfort
- Low level of phosphate in the blood

Some are common (affect between 1 and 10 in every 100 patients).

- Low level of red blood cells
- Headache
- Sleep disturbances
- Eye irritation
- High blood pressure
- Vomiting
- Loss of appetite
- Abdominal pain
- Diarrhoea
- Constipation
- Stomach pain
- Sickness
- Skin rash

- Short-lasting bone, muscle or joint pain
- Generalised pain
- Redness or swelling at the site of infusion
- Changes in blood tests results

Some are uncommon (less than 1 in every 100 but more than 1 in 1000 patients)

- Agitation
- Dizziness
- Tiredness, lack of energy
- Muscle cramps
- Painful red eye
- Low blood pressure
- Stomach discomfort after meal
- Itching
- Abnormal liver function test

Some are very rare (less than 1 in every 10,000 patients)

- Reactivation of Herpes infection
- Painful eyeball and/or swollen eye

If any of these side effects affects you severely and if you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist. Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving Aredia. It is currently unclear whether Aredia causes this irregular heart rhythm. You should report to your doctor if you experience irregular heart beat during treatment with Aredia.

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

5 STORING AREDIA

- Do not use after the expiry date shown on the vial label or box after 'Exp'. The expiry date refers to the last day of the month.
- Store in the original package.
- Do not store above 30°C.
- Keep out of the sight and reach of children.

6 FURTHER INFORMATION

If you have any questions about this medicinal product, please contact your doctor or pharmacist.

This leaflet was last updated in May 2014

Infections and infestations

Very rare: reactivation of Herpes simplex, reactivation of Herpes zoster.

Blood and lymphatic system 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 (paresthesia, tetany), headache, insomnia, somnolence

Uncommon: seizures, agitation, dizziness, lethargy

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: pruritis

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, glomerulonephropathy.

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: hypokalaemia, hypomagnesaemia, 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 6 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

Pharmacotherapeutic group ATC:

Inhibitor of bone resorption (ATC code: M05B A03)

5.1 Pharmacodynamic Properties

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 sites 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 2-3 hours' duration. Peak plasma pamidronate concentrations of about 10nmol/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 20-55% of the dose is recovered in the urine within 72 hours as unchanged pamidronate.

Within the time frame of experimental studies the remaining fraction of the dose is retained in the body. The percentage of the dose retained in the body is independent of both the dose (range 15-180 mg) and the infusion rate (range 1.25-60 mg/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 180 ml/min and the apparent renal clearance is about 54 mL/min, and there is a tendency for the renal clearance to correlate with creatinine clearance.

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 C_{max} (28,6%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 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 <30mL/min), the AUC of pamidronate was approximately 3 times higher than in patients with normal renal function (creatinine clearance >90mL/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 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 (for pH-adjustment)

Ampoules

Water for injections

6.2 Incompatibilities

Aredia must not be admixed with calcium or other divalent cation-containing infusion solutions such as Ringer's, Hartmann's solution.

6.3 Shelf life

3 years.

Following reconstitution and dilution, use solutions immediately.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

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

Aredia Dry Powder 30mg: Packs containing 2 Aredia Dry Powder 30mg vials and 2 10ml ampoules of Water for Injections.

Aredia Dry Powder 90mg: Packs containing 1 Aredia Dry Powder 90mg vial and 1 10ml ampoule of Water for Injections.

6.6 Instructions for use and handling

Powder in vials should be first dissolved in Water for Injection, i.e. 30mg or 90mg in 10ml. 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 6.0-7.04.

The reconstituted solution should be further diluted with calcium free infusion solution (0.9% sodium chloride or 5% glucose only) 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 NAME AND ADDRESS OF THE HOLDER OF THE MARKETING AUTHORISATION

Novartis Pharmaceuticals UK Limited

Frimley Business Park

Frimley, Camberley

Surrey GU16 7SR

U.K.

8 MARKETING AUTHORISATION NUMBER

PA 13/90/2, PA 13/90/4

8 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Aredia Dry Powder 30mg:

11th November 1993 / 11th November 2003

Aredia Dry Powder 90mg:

5th July 1995 / 30th October 2004

9 DATE OF REVISION OF TEXT

June 2014