

PRESCRIBING INFORMATION

^{Pr}**AREDIA***

(pamidronate disodium for injection)

30 mg, 90 mg

For i.v. infusion only

Bone Metabolism Regulator

Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec, H9S 1A9

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^{Pr}AREDIA* is a registered trademark

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Pr AREDIA*

(pamidronate disodium)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
I.V. infusion	sterile lyophilized powder: <ul style="list-style-type: none">▪ 30 mg/vial▪ 90 mg/vial	<ul style="list-style-type: none">▪ mannitol▪ phosphoric acid

INDICATIONS AND CLINICAL USE

- **Tumour-induced hypercalcemia following adequate saline rehydration.**
Prior to treatment with AREDIA* (pamidronate disodium), renal excretion of excess calcium should be promoted by restoring and maintaining adequate fluid balance and urine output.
- **Conditions associated with increased osteoclast activity: predominantly lytic bone metastases and multiple myeloma.**
- **Symptomatic Paget*s disease of bone.**

CONTRAINDICATIONS

AREDIA* is contraindicated

- in patients with known or suspected hypersensitivity to AREDIA* (pamidronate disodium), to any of its excipients (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**), or to other bisphosphonates.
- in pregnancy,
- in breast-feeding women

WARNINGS AND PRECAUTIONS

General

AREDIA* (pamidronate disodium) MUST NEVER BE GIVEN AS A BOLUS INJECTION SINCE SEVERE LOCAL REACTIONS AND THROMBOPHLEBITIS MAY RESULT FROM HIGH LOCAL CONCENTRATIONS.

AREDIA* SHOULD ALWAYS BE DILUTED AND ADMINISTERED AS A SLOW INTRAVENOUS INFUSION (see DOSAGE AND ADMINISTRATION). REGARDLESS OF THE VOLUME OF SOLUTION IN WHICH AREDIA* IS DILUTED, SLOW INTRAVENOUS INFUSION IS ABSOLUTELY NECESSARY FOR SAFETY.

AREDIA* should not be given together with other bisphosphonates to treat hypercalcemia since the combined effects of these agents are unknown.

AREDIA* should not be mixed with calcium-containing intravenous infusions.

Patients must be assessed prior to and during administration of AREDIA* to assure that they are appropriately hydrated. This is especially important for patients receiving diuretic therapy.

It is essential in the initial treatment of tumour-induced hypercalcemia that intravenous rehydration be instituted to restore urine output. Patients should be hydrated adequately throughout treatment but overhydration must be avoided.

Cardiovascular

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.

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%). Previously, it has been observed in a clinical trial investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased rate of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism of this increased incidence of atrial fibrillation in isolated studies with some bisphosphonates, including AREDIA*, is unknown.

Effects on ability to drive or use machines

Somnolence and/or dizziness may occur following AREDIA* infusion, in which case the patient should not drive, operate potentially dangerous machinery or engage in other activities that may be hazardous because of decreased alertness.

Endocrine and Metabolism

Paget's disease

Pre-existing hypocalcemia must be treated by adequate intake of calcium and Vitamin D before initiating AREDIA*. Other disturbances of mineral metabolism (e.g., parathyroidectomy resulting in partial or complete hypoparathyroidism) must also be effectively managed. It is recommended that patients with Paget's disease of bone have their serum calcium levels assessed before and during treatment with AREDIA* (e.g., as part of their annual examination). All patients should be counselled regarding the importance of calcium and vitamin D supplementation in maintaining serum calcium levels and on the symptoms of hypocalcemia.

Lytic bone metastases or multiple myeloma

In the absence of hypercalcemia, patients who are at risk of calcium or vitamin D deficiency, should be given oral calcium and Vitamin D supplementation in order to minimize the risk of hypocalcemia. In the event that hypercalcemia develops, calcium and Vitamin D supplements should be discontinued immediately.

Hepatic/Biliary/Pancreatic

There are no clinical data available in patients with severe hepatic insufficiency.

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports occur rarely. This category of drugs includes AREDIA* (pamidronate disodium for injection). 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 of patients had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported in cancer patients treated with bisphosphonates, including AREDIA*. Although no causal relationship has been established, there is an association between bisphosphonate use and the development of ONJ. Post-marketing experience suggests a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma) and dental status (dental extractions, periodontal disease and local trauma including poorly fitting dentures); these are associated with a greater risk of developing ONJ. Cancer patients also receive other treatments that may play a role in the development of ONJ, such as chemotherapy and glucocorticosteroids. Many patients had signs of local infection including osteomyelitis.

Presentation of ONJ may include altered local sensation (hyperaesthesia or numbness), maxillofacial pain, “toothaches”, denture sore spots, loose teeth, exposed bone in the oral cavity, impaired healing, recurrent or persistent soft tissue infection in the oral cavity and marked oral odour. The onset can be from months to years after commencing bisphosphonate therapy. Cancer patients should maintain good oral hygiene; it is recommended that advanced cancer patients be encouraged to have an oral examination of both hard and soft tissues, with preventive dentistry prior to treatment with bisphosphonates, and that such assessments continue at regularly scheduled intervals after bisphosphonate therapy is initiated. While on bisphosphonate treatment, these patients should avoid invasive dental procedures if possible. Biopsies are not recommended unless metastasis to the jaw is suspected. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there is no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal

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 (some with fatal outcome) have been reported very rarely 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.

Due to the risk of clinically significant deterioration in renal function which may progress to renal failure, single doses of AREDIA* should not exceed 90 mg, and the recommended infusion time should be observed (see **DOSAGE AND ADMINISTRATION**).

AREDIA* is excreted intact primarily via the kidney (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**), thus the risk of adverse reactions may be greater in patients with impaired renal function.

As with other i.v. bisphosphonates renal monitoring is recommended, for instance, measurement of serum creatinine prior to each dose of AREDIA*. Experience with AREDIA* in patients with severe renal impairment (serum creatinine >440 $\mu\text{mol/L}$ in T1H patients; >180 $\mu\text{mol/L}$ in multiple myeloma patients) is limited. If clinical judgment determines that the potential benefits outweigh the risk in such cases, AREDIA* should be used cautiously and renal function carefully monitored. Patients treated with AREDIA* for bone metastases or multiple myeloma should have their dose withheld if renal function has deteriorated (see **DOSAGE AND ADMINISTRATION, Renal Impairment**).

Special Populations

Pregnant Women:

It has been shown that AREDIA* can cross the placenta in rats and has produced marked maternal and embryo/fetal adverse effects in rats and rabbits (see **TOXICOLOGY/Reproductive Toxicity**).

There are no adequate and well-controlled studies in pregnant women and no clinical evidence to support the use of AREDIA* in pregnant women. Therefore, AREDIA* should not be used during pregnancy (see **CONTRAINDICATIONS**).

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.

Nursing Women:

There is no clinical experience with AREDIA* in lactating women. A study in lactating rats has shown that pamidronate passes into the milk. Mothers treated with AREDIA* should therefore not breast feed their infants.

Pediatrics:

The safety and efficacy of AREDIA* in children has not been established. Until further experience is gained, AREDIA* is only recommended for use in adult patients.

Monitoring and Laboratory Tests

Patients should have standard serum creatinine and clinical renal function parameters periodically evaluated. Patients receiving frequent AREDIA* infusions over a prolonged period of time, and those with pre-existing renal disease or a predisposition to renal impairment (e.g., patients with multiple myeloma and/or tumour-induced hypercalcemia) should have evaluations of standard laboratory and clinical parameters of renal function prior to each dose of AREDIA*. Fluid balance (urine output, daily weights) should also be followed carefully. If there is deterioration of renal function during AREDIA* therapy, the infusion must be stopped (see **WARNINGS AND PRECAUTIONS**).

AREDIA* is excreted intact primarily via the kidney, thus the risk of renal adverse reactions may be greater in patients with impaired renal function.

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy with AREDIA*. Patients with anemia, leukopenia or thrombocytopenia should have regular hematology assessments. Occasional cases of mild, transient hypocalcemia, usually asymptomatic, have been reported. Symptomatic hypocalcemia occurs rarely and can be reversed with calcium gluconate. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcemia due to relative hypoparathyroidism.

In tumour-induced hypercalcemia, either ionized calcium or total serum calcium corrected (adjusted) for albumin should be monitored during treatment with AREDIA*. Serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since hypoalbuminemia is commonly present. Corrected serum calcium values should be calculated using established algorithms, such as:

$$cCa = tCa + (0.02 \times [40 - ALB])$$

where:

cCa = adjusted calcium concentration (mmol/L)

tCa = measured total calcium concentration (mmol/L)

ALB = measured albumin concentration (g/L)

Although mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia is usually associated with a variety of signs and symptoms, and can be life-threatening if not promptly recognized and treated. Individuals at risk and their caregivers should be made aware that signs and symptoms of hypercalcemia include: lethargy, fatigue, confusion, loss of appetite, nausea and vomiting, constipation, excessive thirst and urination. Measures such as maintaining

mobility and ensuring adequate hydration could diminish the symptoms of hypercalcemia. However, when symptoms of hypercalcemia are detected, it is important to seek medical assistance promptly.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions with AREDIA* (pamidronate disodium) are usually mild and transient. The most common adverse reactions are influenza-like symptoms and mild fever (an increase in body temperature of >1°C, which may last up to 48 hours). Fever usually resolves spontaneously and does not require treatment. Acute "influenza-like" reactions usually occur only with the first AREDIA* infusion. The tables below show the incidence of the more commonly observed adverse effects overall and by indication.

Clinical Trial Adverse Drug Reactions

Adverse events by body system:

Biochemical Changes

Very Common: hypocalcemia, hypophosphatemia

Common: hypokalemia, hypomagnesemia, increase in serum creatinine

Uncommon: abnormal liver function tests, increase in serum urea

Very Rare: hyperkalemia, hyponatremia

Blood

Common: anemia, thrombocytopenia, lymphocytopenia

Very Rare: leukopenia

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

Body as a whole

Very common: fever and influenza-like symptoms sometimes accompanied by malaise, rigor, fatigue and flushes

Cardiovascular system

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%). Previously, it has been observed in a clinical trial investigating patients with postmenopausal osteoporosis, that zoledronic acid treated patients (5 mg) had an increased rate of atrial fibrillation serious adverse events compared to placebo (1.3% compared to 0.6%). The mechanism of this increased incidence of atrial fibrillation in isolated studies with some bisphosphonates, including AREDIA*, is unknown.

Common: hypertension

Uncommon: hypotension

Very Rare: left ventricular failure (dyspnea, pulmonary edema), congestive heart failure (edema) due to fluid overload

Central nervous system

Common: symptomatic hypocalcemia (paresthesia, tetany), headache, insomnia, somnolence

Uncommon: seizures, agitation, dizziness, lethargy

Very Rare: confusion, visual hallucinations

Gastrointestinal tract

Common: nausea, vomiting, anorexia, abdominal pain, diarrhea, constipation, gastritis

Uncommon: dyspepsia

Immune System

Uncommon: allergic reactions including anaphylactoid reactions, bronchospasm, dyspnea, Quincke's (angioneurotic) oedema.

Very Rare: anaphylactic shock

Infection

Very Rare: reactivation of Herpes simplex and Herpes zoster

Local reactions

Common: reactions at the infusion site: pain, redness, swelling, induration, phlebitis, thrombophlebitis)

Musculoskeletal system

Common: transient bone pain, arthralgia, myalgia, generalized pain

Uncommon: osteonecrosis of the jaw (ONJ), muscle cramps

Renal system

Uncommon: acute renal failure

Rare: focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome

Very Rare: hematuria, deterioration of pre-existing renal disease

Respiratory system

Rare: adult respiratory distress syndrome, interstitial pneumonitis

Skin

Common: rash

Uncommon: pruritus

Special senses

Common: conjunctivitis

Uncommon: uveitis (iritis, iridocyclitis)

Very Rare: scleritis, episcleritis, xanthopsia

Many of these adverse events may have been related to the underlying disease.

Tumour-Induced Hypercalcemia and Paget's Disease

Adverse events considered to be related to AREDIA* occurring in $\geq 1\%$ patients in the specified indication:

Adverse events	Tumour-induced hypercalcemia	Paget's disease
no. of patients	n=910	n=395
	(%)	(%)
Fever	6.9	8.9
Headache	0.0	4.8
Hypocalcemia	3.2	0.8
Influenza-like symptoms	0.0	11.9
Infusion site reaction	1.7	1.8
Malaise	0.0	5.8
Myalgia	0.0	2.0
Nausea	0.9	2.0
Pain (bone)	0.0	8.9
Pain (unspecified)	0.0	7.9
Rigors	0.0	2.8

Bisphosphonates, including AREDIA*, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure (see **WARNINGS AND PRECAUTIONS**). Since many patients with tumour-induced hypercalcemia have compromised renal function prior to receiving antihypercalcemia therapy (see **WARNINGS AND PRECAUTIONS**), it is difficult to estimate the role of individual bisphosphonates in subsequent changes in renal function. Deterioration of renal function (elevation of serum creatinine of $>20\%$ above baseline) which could not be readily explained in terms of pre-existing renal disease, prior nephrotoxic chemotherapies or compromised intravascular volume status has been noted in 7 cases of 404 patients treated with AREDIA* where these data have been reported. As with other i.v. bisphosphonates, renal monitoring is recommended (see **WARNINGS AND PRECAUTIONS - Patient Monitoring**).

Bone Metastases and Multiple Myeloma

The most commonly reported adverse events regardless of relationship to therapy are shown in the table below.

Deterioration of renal function (including renal failure) has been associated with

bisphosphonates including AREDIA*. Renal monitoring is recommended (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

Commonly Reported Adverse Events in Three Controlled Trials (regardless of causality)		
Bone metastases and multiple myeloma patients		
Adverse Event	AREDIA* 90 mg	Placebo
	n=572	n=573
General		
Asthenia	16.4	15.4
Fatigue	30.4	35.5
Fever	35.5	30.5
Metastases	14.0	13.6
Digestive System		
Anorexia	20.8	18.0
Constipation	27.6	30.9
Diarrhea	24.3	26.2
Dyspepsia	13.6	12.4
Nausea	48.4	46.4
Pain Abdominal	17.3	14.0
Vomiting	30.9	28.1
Hemic and Lymphatic System		
Anemia	35.1	32.6
Granulocytopenia	16.8	17.3
Thrombocytopenia	11.0	13.1
Musculoskeletal System		
Myalgias	22.6	16.9
Skeletal Pain	59.4	69.1
CNS		
Headache	24.0	19.7
Insomnia	18.2	17.3
Respiratory System		
Coughing	21.2	18.8
Dyspnea	23.3	18.7

Commonly Reported Adverse Events in Three Controlled Trials (regardless of causality)		
Bone metastases and multiple myeloma patients		
Adverse Event	AREDIA* 90 mg	Placebo
	n=572	n=573
Upper Respiratory Infection	19.8	20.9
Urogenital System		
Urinary Tract Infection	14.5	10.8

Post-marketing Experience

Cases of osteonecrosis of the jaw (ONJ) are uncommon, although data suggest a higher number of reported cases in certain cancers, such as advanced breast cancer and multiple myeloma. The majority of reported cases of ONJ are associated with invasive dental procedures (such as tooth extraction or dental surgery and local trauma including poorly fitting dentures) or periodontal disease. Many patients had signs of local infection including osteomyelitis.

The following adverse reactions have been reported in post-marketing use: **General:** reactivation of Herpes simplex and Herpes zoster, influenza-like symptoms; **CNS:** confusion and visual hallucinations, sometimes in the presence of electrolyte imbalance; **Skin:** rash, pruritus; **Special senses:** conjunctivitis; **Renal:** focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome; **Laboratory abnormalities:** hyperkalemia, hypernatremia, hematuria. Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and, very rarely, anaphylactic shock.

DRUG INTERACTIONS

Drug interaction studies with AREDIA* in humans have not been conducted.

Caution is warranted when AREDIA* is used with other potentially nephrotoxic drugs.

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

AREDIA* should not be used in combination with other bisphosphonates.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing recommendations differ for tumour-induced hypercalcemia, lytic bone metastases and multiple myeloma, and Paget's disease. For patients suffering from TIH and multiple myeloma,

see the TIH dosage guidelines.

AREDIA* (pamidronate disodium) must never be given as a bolus injection (see WARNINGS AND PRECAUTIONS). AREDIA* should be administered in a compatible calcium-free intravenous solution (e.g., sterile normal saline or dextrose 5% in water). AREDIA* should be infused slowly.

To minimize local reactions the cannula should be carefully inserted in a relatively large vein.

The infusion rate should never exceed 60 mg/h (1 mg/min) and the concentration of AREDIA* in the infusion solution should not exceed 90 mg/250 mL. A dose of 90 mg should normally be administered as a 2-hour infusion in 250 mL infusion solution. **However, in patients with multiple myeloma and in patients with tumour-induced hypercalcemia it is recommended not to exceed 90 mg in 500 mL over 4 hours (i.e., an infusion rate of 22.5 mg/h).**

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 hypercalcemia 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 **DETAILED PHARMACOLOGY - Hepatic impairment**). AREDIA* has not been studied in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Recommended Dose and Dosage Adjustment

Dosing Guidelines for Tumour-Induced Hypercalcemia

Patients must be adequately rehydrated prior to and during administration of AREDIA*.

In tumour-induced hypercalcemia, either ionized calcium or total serum calcium corrected (adjusted) for albumin should be monitored during treatment with AREDIA*. Serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since hypoalbuminemia is commonly present. Corrected serum calcium values should be calculated using established algorithms, such as:

$cCa = tCa + (0.02 \times [40 - ALB])$
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where:

cCa = adjusted calcium concentration (mmol/L)

tCa = measured total calcium concentration (mmol/L)

ALB = measured albumin concentration (g/L)

Although mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia usually associated with a variety of signs and symptoms, and can be life-threatening if not promptly recognized and treated. Individuals at risk and their caregivers should be made aware that signs and symptoms of hypercalcemia include: lethargy, fatigue, confusion, loss of appetite, nausea and vomiting, constipation, excessive thirst and urination. Measures such as maintaining mobility and ensuring adequate hydration could diminish the symptoms of hypercalcemia. However, when symptoms of hypercalcemia are detected, it is important to seek medical assistance promptly.

The recommended total dose of AREDIA* for a treatment course depends upon initial plasma calcium levels. Doses should be adapted to the degree of severity of hypercalcemia to ensure normalization of plasma calcium and to optimize the duration of response. **A dose of 90 mg should be administered in 500 mL of infusion solution. The infusion rate should not exceed 22.5 mg/hour.**

The total dose for a treatment course may be given as a single infusion, or in multiple infusions spread over 2 to 4 consecutive days. The **maximum dose** of AREDIA* per treatment course is 90 mg whether for initial or repeat treatment courses. Higher doses have not been associated with increased clinical effect.

The following table presents dosing guidelines for AREDIA* derived from clinical data on uncorrected calcium values. These dose ranges also apply for calcium corrected for serum protein.

Tumour-induced Hypercalcemia				
Initial Serum Calcium		Total Dose (mg)	Concentration of Infusate (mg/mL)	Maximum Infusion Rate (mg/h)
(mmol/L)	(mg %)			
Up to 3.0	Up to 12.0	30	30 mg/ 125 mL	22.5 mg/h
3.0 - 3.5	12.0 - 14.0	30 or 60 ^s	30 mg/ 125 mL 60 mg/ 250 mL	22.5 mg/h 22.5 mg/h

3.5- 4.0	14.0 - 16.0	60 [§] or 90	60 mg/ 250 mL 90 mg/ 500 mL	22.5 mg/h 22.5 mg/h
>4.0	>16.0	90	90 mg/ 500 mL	22.5 mg/h

[§]Two vials of 30 mg each may be used

Decreases in serum calcium levels are generally observed within 24 to 48 hours after drug administration, with maximum lowering occurring by 3 to 7 days. If hypercalcemia recurs, or if plasma calcium does not decrease within 2 days, repeat infusions of AREDIA* may be given, according to the dosing guidelines. The limited clinical experience available to date has suggested the possibility that AREDIA* may produce a weaker therapeutic response with repeat treatment in patients with advanced cancer.

Dosing Guidelines for Bone Metastases and Multiple Myeloma

The recommended dose of AREDIA* for the treatment of predominantly lytic bone metastases and multiple myeloma is 90 mg administered as a single infusion every 4 weeks. In patients with bone metastases who receive chemotherapy at 3-weekly intervals, AREDIA* 90 mg may also be given every 3 weeks. A dose of 90 mg should normally be administered as a 2-hour infusion in 250 mL of infusion solution. However, in patients with multiple myeloma it is recommended not to exceed 90 mg in 500 mL over 4 hours.

Radiotherapy is the treatment of choice for patients with solitary lesions in weight bearing bones.

Bone Metastases		
Disease State	Dosing Schedule	Concentration of Infusate (mg/mL)
Bone metastases	90 mg/2 hours every 3 [*] -4 weeks	90 mg/250 mL
Multiple myeloma	90 mg/4 hours every 4 weeks	90 mg/500 mL

* for patients receiving chemotherapy every 3 weeks

Dosing Guidelines for Paget's Disease of Bone

The recommended total dose of AREDIA* for a treatment course is 180 to 210 mg. This may be administered as 6 doses of 30 mg once a week (total dose 180 mg). Alternatively, 3 doses of 60 mg may be administered every second week, but treatment should be initiated with a 30 mg dose (total dose 210 mg) as influenza-like reactions are common only with the first infusion. Each dose of 30 mg or 60 mg should be diluted in at least 250 mL or 500 mL, respectively, of normal saline or D5W. An infusion rate of 15 mg per hour is recommended. This regimen, omitting the initial dose, can be repeated after 6 months until remission of disease is achieved, and when relapse occurs (see table below).

Paget's Disease			
Recommended total dose/treatment course: 180-210 mg			
Regimen	Dosing Schedule	Concentration of Infusate (mg/mL)	Infusion Rate (mg/h)
Regimen 1 Total dose 180 mg	30 mg once weekly for 6 weeks	30 mg in ≥ 250 -500 mL	15 mg/h
Regimen 2 Total dose 210 mg	Infusions administered every 2 weeks. Initial dose (week 1) = 30 mg; Subsequent doses (weeks 3, 5 & 7) = 60 mg	30/60 mg [§] in ≥ 250 -500 mL	15 mg/h
Re-treatment Regimen Total dose 180 mg	60 mg every 2 weeks for a total of 3 infusions.	60 mg [§] in 500 mL	15 mg/h

[§]Two vials of 30 mg each may be used

Administration

Reconstitution:

Each vial of sterile lyophilized powder should be reconstituted with Sterile Water for Injection prior to dilution as given in the following table:

RECONSTITUTION TABLE			
Vial size	Volume of diluent to be added to the vial	Approximate available volume	Nominal concentration
30 mg/10 mL vial	10 mL	10 mL	3 mg/mL
90 mg/10 mL vial	10 mL	10 mL	9 mg/mL

Dilution of Reconstituted Solution for I.V. Infusion:

Reconstituted solutions that have been prepared with Sterile Water for Injection should be further diluted with either 0.9% w/v sodium chloride or 5% w/v glucose solution prior to intravenous infusion administration. The reconstituted solution is chemically and physically stable for 24 hours at room temperature. However, from a microbiological point of view, it is preferable to use the product immediately after aseptic reconstitution and dilution.

If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between reconstitution, dilution and end of administration must not exceed 24 hours.

All parenteral products should be visually inspected for particulate matter and discoloration prior

to administration. Any solution found to have particulate matter or discoloration should be discarded.

Incompatibilities

Pamidronate forms complexes with divalent cations. For this reason, AREDIA* reconstituted solution must not be mixed with calcium-containing intravenous solutions such as Ringer's solution. AREDIA* reconstituted solution should be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution. Studies with containers and infusion sets/devices for infusion made of glass, polyethylene and polyvinylchloride have been shown to be compatible with diluted AREDIA* solution.

OVERDOSAGE

Patients who have received doses higher than those recommended should be carefully monitored. Clinically significant hypocalcemia with paresthesia, tetany and hypotension, may be reversed by an infusion of calcium gluconate. Acute hypocalcemia is not expected to occur with AREDIA* (pamidronate disodium) since plasma calcium levels fall progressively for several days after treatment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AREDIA* (pamidronate disodium) belongs to a class of bisphosphonates (previously termed diphosphonate), which inhibit bone resorption. The therapeutic activity of AREDIA* is attributable to its potent anti-osteoclastic activity on bone. In animal studies, at therapeutic doses, pamidronate disodium inhibits bone resorption apparently without inhibiting bone formation and mineralization.

The predominant means by which AREDIA* reduces bone turnover both *in vitro* and *in vivo* appears to be through the local, direct antiresorptive effect of bone-bound bisphosphonate. Pamidronate disodium binds to calcium phosphate (hydroxyapatite) crystals and directly inhibits the formation and dissolution of this bone mineral component *in vitro*. *In vitro* studies indicate that pamidronate disodium is a potent inhibitor of osteoclastic bone resorption. Pamidronate disodium also suppresses the migration of osteoclast precursors onto the bone and their subsequent transformation into the mature resorbing osteoclast.

Tumour-induced hypercalcemia

In tumour-induced hypercalcemia, AREDIA* normalizes plasma calcium between 3 and 7 days following the initiation of treatment irrespective of the type of malignancy or presence of detectable metastases. This effect is dependent on initial calcium levels.

AREDIA* improves symptoms associated with hypercalcemia, e.g. anorexia, nausea, vomiting

and diminished mental status.

The kidneys play a prominent role in calcium homeostasis. In addition to skeletal osteolysis, renal dysfunction contributes to the pathogenesis of tumour-induced hypercalcemia. When diagnosed, most hypercalcemic patients are significantly dehydrated. Elevated plasma calcium antagonizes antidiuretic hormone-induced renal concentration, and thus results in polyuria and excessive fluid loss. Hydration status is further compromised by reduced fluid intake due to nausea, vomiting and diminished mental status. Furthermore, dehydration often leads to a fall in glomerular filtration rate (GFR).

Before AREDIA* therapy is initiated, patients should be adequately rehydrated with isotonic saline (0.9%) (see **WARNINGS AND PRECAUTIONS, General**). Normalization of plasma calcium levels by AREDIA* in adequately hydrated patients may also normalize plasma parathyroid hormone (PTH) which is suppressed by hypercalcemia.

The duration of normocalcemia following AREDIA* treatment varies in patients with tumour-induced hypercalcemia because of early mortality, and the heterogeneity of diseases and cancer therapies. In general, recurrences tend to occur preferentially after treatment with lower doses: at doses of 30 mg or less, plasma calcium levels tend to increase after approximately 1 week, while at high doses (total treatment doses of 45 to 90 mg) plasma calcium levels remained normal for at least 2 weeks and up to several months. One study has shown a clear relationship between recurrence rates and AREDIA* dose: in patients treated with single i.v. infusions of 30, 45, 60 and 90 mg AREDIA*, recurrence rates were lower for the higher dose group 9 months after initial treatment. In patients in whom the underlying disease is well controlled by cancer therapy, the duration of response tends to be more prolonged.

Clinical experience with AREDIA* in relapsed tumour-induced hypercalcemia is limited. In general, with re-treatment, the response is similar to that with the first AREDIA* treatment, unless the cancer has progressed significantly. Therefore, AREDIA* treatment appears effective for recurrent hypercalcemia at doses established for the initial treatment course (see **DOSAGE AND ADMINISTRATION**). The mechanisms underlying possible decreased effects of repeat treatment with AREDIA* in advanced cancer are unknown.

In severe forms of hypercalcemia the dose of AREDIA* may be increased, or eventually, a combination drug therapy should be considered (see **WARNINGS AND PRECAUTIONS**).

Bone metastases and multiple myeloma

Lytic bone metastases in cancer patients are caused by increased osteoclast activity. Metastatic tumour cells secrete paracrine factors which stimulate neighboring osteoclasts to resorb bone. By inhibiting osteoclast function, bisphosphonates interrupt the cascade of events which lead to tumour-induced osteolysis. Lytic bone destruction causes significant complications and associated morbidity.

Clinical trials in patients with predominantly lytic bone metastases or multiple myeloma showed that AREDIA* prevented or delayed skeletal-related events, (SREs: hypercalcemia, pathologic fractures, radiation therapy to bone, orthopedic surgery, 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.

A significant reduction in bone pain was also demonstrated, which in some patients led to decreased analgesic intake and increased mobility. Greater deteriorations in ECOG performance status and Spitzer quality of life scores were seen in the placebo patients compared to AREDIA*-treated patients.

Paget's disease

Paget's disease of bone, which is characterized by local areas of increased bone resorption and formation with qualitative changes in remodelling, responds well to treatment with AREDIA*. Repeated infusions of pamidronate disodium do not lead to reduced efficacy. In addition, patients resistant to etidronate and calcitonin respond well to AREDIA* infusions. In long-term follow-up to clinical trials, bone fracture rate does not appear to be increased following treatment with pamidronate disodium relative to the normally occurring rate in patients with Paget's disease.

Clinical and biochemical remission of Paget's disease has been demonstrated by bone scintigraphy, by decreases in urinary hydroxyproline and serum alkaline phosphatase, and by symptomatic improvement. Bone scans show that AREDIA* reduces the number of bones and the percent of the skeleton affected and that bone scintigraphy significantly improves. Bone biopsies consistently show histological and histomorphometric improvement indicating the reversal of the disease process. Symptoms improve even in those with severe disease.

Pharmacokinetics

Plasma concentrations of pamidronate rise rapidly after infusion is started and fall rapidly when the infusion is stopped. The apparent plasma half-life is about 0.8 hours. Apparent steady state is therefore achieved with infusions of more than about 2 to 3 hours' duration. When infused i.v. at 60 mg over 1 hour, the peak plasma concentration is about 10 nmol/mL and the apparent total plasma clearance is about 180 mL/min.

As pamidronate has a strong affinity for calcified tissues, total elimination is not observed within the time frame of experimental studies.

After an i.v. infusion, about 20 to 55% of the dose is recovered in the urine within 72 hours as unchanged pamidronate, the majority being excreted within the first 24 hours. Pamidronate does not appear to be metabolized, and the remaining fraction of the dose is retained in the body (within the time frame of the studies). The percentage of the dose retained is independent of both the dose (range 15 to 180 mg) and the infusion rate (range 1.25 to 60 mg/h).

Retention is similar after each dose of pamidronate disodium. Thus, accumulation in bone is not capacity limited and is dependent solely on the cumulative dose.

Urinary elimination is biphasic ($t_{1/2\alpha} = 1.6$ h; $t_{1/2\beta} = 27.2$ h). The apparent renal clearance is about 54 mL/min, and there is a tendency for renal clearance to correlate with creatinine clearance.

Pamidronate disodium binding to human serum proteins is relatively low (about 54%) but increases to approximately 5 mmol when exogenous 95% calcium is added to human plasma.

Special Populations and Conditions

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 AUC (39.7%) and C_{max} (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 **DOSAGE AND ADMINISTRATION**).

Hepatic and metabolic clearance of AREDIA* are insignificant. AREDIA* thus displays little potential for drug interactions at either the metabolic or protein binding level.

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) (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Protect vials from heat (i.e., store below 30°C).

AREDIA* must be kept out of the reach and sight of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

^{Pr}AREDIA* 30 mg (pamidronate disodium) vials for injection:

Each vial of white to practically white lyophilisate contains pamidronate disodium (30 mg). Available in cartons of 1 vial.

Pr AREDIA* 90 mg (pamidronate disodium) vials for injection:

Each vial of white to practically white lyophilisate contains pamidronate disodium (90 mg). Available in cartons of 1 vial.

Composition

AREDIA* 30 mg/vial for injection:

Each vial of sterile lyophilized powder contains anhydrous pamidronate disodium (30 mg) and mannitol (470 mg). Phosphoric acid is employed to adjust the pH to 6.3.

AREDIA* 90 mg/vial for injection:

Each vial of sterile lyophilized powder contains anhydrous pamidronate disodium (90 mg) and mannitol (375 mg). Phosphoric acid is employed to adjust the pH to 6.3.

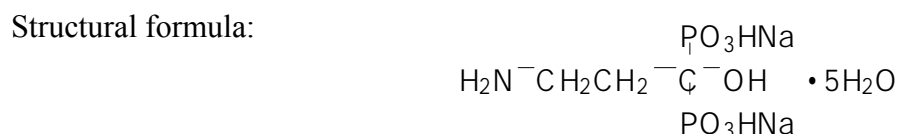
These preparations contain **NO** preservatives.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Pamidronate disodium
Chemical name:	Disodium-3-amino-1-hydroxypropylidene-1,1-bisphosphonate
Molecular formula:	$C_3H_9NO_7P_2Na_2 \cdot 5H_2O$
Molecular mass:	369.1



Physicochemical properties:	Description: Colourless, crystalline powder
	Solubility: Soluble in water or 2N sodium hydroxide, poorly soluble in 0.1N hydrochloric acid and 0.1N acetic acid and insoluble in organic solvents
	pH: The pH of a 1% solution in water is approximately 8.2.

CLINICAL TRIALS

The potent inhibitory effect of pamidronate disodium on bone resorption has been demonstrated in clinical studies which have shown pamidronate disodium to be highly effective in the treatment of malignant hypercalcemia, bone metastases and Paget's disease of the bone.

Tumour-induced Hypercalcemia

Pamidronate disodium lowered plasma calcium between 3 to 7 days following the initiation of treatment irrespective of the tumour type or presence of detectable bone metastases. In controlled clinical trials, pamidronate disodium was infused at up to 15 mg per hour for doses up

to 60 mg whereas 90 mg was infused over 24 hours.

Normalization of plasma calcium levels was accompanied by a decrease in urinary calcium levels to normal, and in some cases, to below normal levels. Since it has been reported that calcium absorption from the kidney and gut are not increased by pamidronate disodium administration, the decreases in urinary calcium observed can be regarded as solely reflecting inhibition of bone resorption rather than effects on the kidney and gut.

Normalization of plasma calcium, including transient hypocalcemia, is dependent on the initial levels of plasma calcium and the dose of pamidronate disodium selected. Severe hypercalcemia (plasma calcium >4.0 mmol/L) required higher doses of pamidronate disodium for normalization than moderate hypercalcemia. However, treatment of moderate hypercalcemia with high doses of pamidronate disodium (60 to 90 mg) can lead to transient hypocalcemia. A single infusion of 90 mg is indicated only for cases of severe hypercalcemia.

Several changes in biochemical parameters occur secondary to the normalization of plasma calcium which reflect the antiresorptive activity of pamidronate disodium. Parathyroid hormone levels, which are usually suppressed in hypercalcemia of malignancy, typically recover after treatment with pamidronate disodium. This is considered to be a physiological response to lowering of blood calcium levels. Previously suppressed parathyroid hormone levels have not been observed to increase above the upper limits of normal.

Urinary calcium/creatinine and urinary hydroxyproline/creatinine ratios decrease and usually return to within or below normal after treatment with pamidronate disodium. These changes occur within the first week after treatment, as do decreases in serum calcium levels, and are consistent with the antiresorptive pharmacologic action of pamidronate disodium.

The decrease in urinary phosphate excretion despite a rise in glomerular filtration rate after pamidronate disodium administration suggests a positive phosphorus balance. This effect may be related to increased phosphate uptake into bone since the lowering of phosphate excretion occurred after reductions in plasma calcium, plasma phosphate, and urinary hydroxyproline. Phosphate levels usually returned to normal within 7-10 days. The ratio of plasma phosphate to the renal phosphate threshold ($TmPO_4/GFR$) is also decreased with pamidronate disodium treatment, probably reflecting a rise in PTH secretion due to the sharp fall in plasma calcium.

Pamidronate disodium had no consistent effects on plasma magnesium levels, thus confirming the absence of effect of pamidronate disodium on magnesium metabolism.

Bone metastases and multiple myeloma

Three large Phase III trials, one in multiple myeloma and two in breast cancer (one versus standard chemotherapy and one versus hormonal therapy) showed that 90 mg AREDIA* (pamidronate disodium) infused every 3-4 weeks significantly decreased the skeletal morbidity rate (number of SREs/year) in all patient groups (see below for a more detailed description of the results). Skeletal-related events (SREs) were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Radiation to bone was also significantly lower in all AREDIA* groups. The proportion of patients experiencing an SRE was significantly smaller, and the time to first SRE was significantly longer

in AREDIA*-treated multiple myeloma and breast cancer + chemotherapy patients. The same trend was seen in the hormonally-treated breast cancer patients. Fewer AREDIA*-treated multiple myeloma patients suffered vertebral pathologic fractures.

Multiple Myeloma

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myeloma were enrolled to receive AREDIA* or placebo in addition to their underlying antimyeloma therapy to determine the effect of AREDIA* on the occurrence of skeletal-related events (SREs). SREs were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Patients received either 90 mg of AREDIA* or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 AREDIA*, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the AREDIA* group (24% vs. 41%, $p<0.001$), and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for AREDIA* patients than for placebo patients (mean: 1.1 vs. 2.1, $p<0.02$). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the AREDIA* group ($p=0.001$, 0.006, and 0.046, respectively). Moreover, fewer AREDIA* patients suffered any pathologic fracture (17% vs. 30%, $p=0.004$) or needed radiation to bone (14% vs. 22%, $p=0.049$).

In addition, decreases in pain scores from baseline occurred at the last measurement for those AREDIA* patients with pain at baseline ($p=0.026$) but not in the placebo group. At the last measurement, a worsening from baseline was observed in the placebo group for the Spitzer quality of life variable ($p<0.001$) and ECOG performance status ($p<0.011$) while there was no significant deterioration from baseline in these parameters observed in AREDIA*-treated patients.

After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the AREDIA* group than the placebo group ($p=0.015$). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs. 2.2 for AREDIA* patients vs. placebo patients ($p=0.008$), and time to first SRE was significantly longer in the AREDIA* group compared to placebo ($p=0.016$). Fewer AREDIA* patients suffered vertebral pathologic fractures (16% vs. 27%, $p=0.005$). Survival of all patients was not different between treatment groups.

Bone Metastases

Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of AREDIA* infused over two hours every three to four weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had at least two lytic metastases, one of which was at least 1 cm in diameter. In one trial patients were receiving hormonal therapy and in the second patients were being treated with chemotherapy, at trial entry.

Breast Cancer Patients Receiving Hormonal Therapy:

372 patients receiving hormonal therapy were randomized to received either 90 mg of AREDIA* (182) or placebo (190) each given as a two-hour infusion at intervals of three to four weeks for

24 months. The proportion of patients developing an SRE was smaller in the AREDIA* treatment group than in the placebo treatment group throughout the trial (3, 6, 9, 12, 15, 18, 21 and 24 months). At the end of the 24 monthly cycles of the trial, the proportion of patients having an SRE (+HCM) was significantly lower for AREDIA* patients than for placebo patients (56% vs. 67% $p=0.027$) and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for AREDIA* patients than for placebo patients (mean: 2.4 vs. 3.8, $p=0.008$). The median time to the first SRE (+HCM) and for radiation to bone significantly greater for AREDIA* patients compared to placebo patients ($p=0.049$ and 0.016 , respectively).

Bone lesion partial response, assessed radiologically, was 30% for the AREDIA* group and 24% for the placebo group ($p=0.202$). In addition, pain and analgesic scores increased significantly less ($p=0.007$, and $p<0.001$, respectively) from baseline in the AREDIA* group than in the placebo group at last measurement.

Breast Cancer Patients Receiving Chemotherapy:

382 patients receiving chemotherapy were randomized to receive either 90 mg of AREDIA* ($n=185$) or placebo ($n=197$) each given as a two-hour infusion at intervals of three to four weeks for 24 months. The proportion of patients developing any SRE was significantly lower on AREDIA* than on placebo at 15 months, 18 months, 21 months and 24 months. At the end of the 24 monthly cycles of the trial, the proportion of patients having any SRE (+HCM) was significantly lower for AREDIA* patients than for placebo patients (50% vs. 70% $p<0.001$) and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for AREDIA* patients than for placebo patients (mean: 2.6 vs. 4.3, $p<0.001$). The times to the first SRE occurrence, any pathologic fracture, non-vertebral pathologic fracture, and radiation to bone was statistically significantly shorter for placebo compared to AREDIA* patients ($p<0.001$, 0.009 , 0.001 and 0.001 , respectively).

Bone lesion complete and partial response, assessed radiologically, was significantly higher in AREDIA* vs. placebo breast cancer patients receiving chemotherapy (34% vs. 19%, $p=0.002$). In addition, pain and analgesic scores increased significantly less ($p=0.050$ and $p=0.009$, respectively) from baseline in the AREDIA* group than in the placebo group at last measurement. In both treatment groups, the ECOG performance status worsened from baseline to endpoint, but the worsening was significantly ($p=0.002$) larger in the placebo group than in the AREDIA* group.

Paget's Disease:

A clear dose response was demonstrated in a randomized, double-blind clinical trial in which patients received a single dose of pamidronate disodium ($N=64$). A single infusion of pamidronate disodium 15 mg was not effective; 90 mg was most effective. A 50% fall from baseline was achieved in both ALP (alkaline phosphatase) and OHP:Cr (hydroxyproline:creatinine ratio) in >20% of patients with both 45 and 90 mg pamidronate disodium ($p<0.05$).

In a multiple-dose infusion study, pamidronate disodium was infused i.v. at 15 mg/2 hours daily for 5 consecutive days ($N=12$). ALP normalized in 4 patients. Five patients required re-treatment within 6 months and 6 patients after 6 months.

In an open clinical trial, patients were stratified according to initial ALP. Those with ALP <500 (Group A; N=65) or >500 I.U./L (Group B; N=11) were administered 180-195 mg or 360-375 mg pamidronate disodium, respectively, as 30 mg weekly infusions. In Group A, ALP normalized in 80% and OHP:Cr in 88% patients. In addition, bone scan results significantly improved. The duration of remission was 543 and 388 days, respectively. In Group B, ALP and OHP:Cr were reduced 80% and 73%, respectively. These patients had particularly severe disease and only 25% remitted on the basis of OHP:Cr and the median duration of remission was relatively short (52 days). In both groups there were subjective clinical improvements in over 50% patients.

In a larger, open clinical trial of similar design, patients were also stratified according to initial ALP. However, those with ALP <500 (Group A; N=159) or >500 I.U./L (Group B; N=52) were administered 210 mg or 390 mg pamidronate disodium, respectively, as infusions of 30 mg initially then 60 mg every 2 weeks. In Group A, ALP normalized in 81% and OHP:Cr in 93% patients. In addition, bone scan results significantly improved (scintigraphic index, % of skeleton affected and number of bones affected). The median duration of remission was 780 and 494 days, respectively. In Group B, results were similar to those achieved in the previous study. Symptom evaluation demonstrated improvement in 50-60% patients.

DETAILED PHARMACOLOGY

Animal Pharmacology

Subcutaneous administration of pamidronate disodium to rats reduced urinary hydroxyproline excretion within 2 to 8 days starting at 0.16 $\mu\text{mol/kg/day}$ and reaching a maximum at 16 $\mu\text{mol/kg/day}$. At higher doses (>40 $\mu\text{mol/kg/day}$) pamidronate disodium inhibited bone mineralization as assessed by the molar ratio of calcium to hydroxyproline in metaphyseal bone. Doses below this level reduced bone alkaline phosphatase activity, hydroxyproline synthesis and calcium content. These changes in bone apposition parameters required at least 23 days exposure for a maximal effect, compared to 8 days for effects on bone resorption. Thus, pamidronate disodium inhibits bone resorption in rats at doses several-fold lower than those that affect bone growth and mineralization.

Low doses of pamidronate disodium increased both elastic and ultimate bone strength in the rat, whereas high doses (>14 mg/kg/day I.P.) produced opposite effects. The latter doses were far above those required to completely suppress calcium mobilization in rats.

In dogs, long-term intermittent treatment with pamidronate disodium retains structural integrity in cortical and vertebral bone. Intermittent oral pamidronate disodium treatment for 12 weeks caused no changes in the mechanical properties of cortical femoral bone but trabecular bone showed a significant increase in compressive stiffness and torsional strength.

In mice, S.C. administration of 16 $\mu\text{mol/kg}$ (4.5 mg/kg) pamidronate disodium for 7 days increased tibial growth plate width without concomitant effects on longitudinal growth.

The intermittent administration of pamidronate disodium to animals was also effective in

inhibiting bone resorption. In 10-week old pigs, administration of 1.6 µg/kg/day pamidronate disodium for 5 out of 21 days produced a significant inhibition of bone resorption that was equivalent to that produced with a continuous 60-day dosing regimen. In mice, once weekly treatment for 1 year augmented diaphyseal wall thickness and the number of persisting trabeculae. This effect was mainly achieved by a suppression of endosteal bone resorption, which occurs during the retrogressive phase of C57BL/Silberberg mice aged more than 4 months. Bones of treated mice also demonstrated a higher femoral calcium content and ash weight, and increased resistance to fracture stress in comparison to untreated controls.

As a result of hormonal regulation, pamidronate disodium does not significantly affect serum calcium in normal, healthy animals. Under various experimental conditions however, changes in serum calcium values will reflect the effects of pamidronate disodium on bone metabolism. In thyroid-parathyroidectomized rats, the 1,25(OH)₂ vitamin D₃-stimulated mobilization of calcium from bone was inhibited by pamidronate disodium at daily doses of 0.02-0.6 mg/kg S.C. Similarly, pamidronate disodium reduced hypercalcemia of malignancy in rats bearing Walker 256 carcinosarcoma tumours. Mice bearing 5T2 myelomas had fewer skeletal lesions if treated with pamidronate disodium, although the myeloma itself was unaffected by pamidronate disodium treatment.

Twenty-four hours after single intravenous administration of 10 mg/kg to growing rats, approximately 50% of the dose is retained in bone, 0.1% in blood, 1.1% in spleen and 30% in liver. Pamidronate disodium is also stored in tracheal cartilage of rats. The percent uptake into the liver increases with dose, ranging from 3.0% at 0.01 mg/kg, to 30% at 10 mg/kg doses. Levels accumulated in liver at 10 mg/kg gradually decline during the 2 weeks after administration, with redistribution and uptake into bone, or elimination by the kidneys over 24-48 hours.

Pamidronate disodium does not undergo significant metabolism in the rat: at 10 mg/kg i.v., approximately 20% of the dose is excreted unchanged in the urine by 24 hours. Bile accounts for less than 0.1% of the administered dose. The biological half-life of pamidronate disodium in rats has been estimated to be approximately 300 days.

A preferential uptake and prolonged storage of ¹⁴C-pamidronate disodium in bone is also observed in dogs following single intravenous administration. Radioactivity is detectable in blood only up to 72 hours.

Human Pharmacology

Pamidronate disodium is a second-generation bisphosphonate. These agents are synthetic analogues of pyrophosphate and specifically inhibit bone resorption. First generation compounds such as 1-hydroxyethylidene-1, 1-biphosphonic acid (HEBP or etidronate disodium) block resorption but may also inhibit bone mineralization. Pamidronate disodium, a second generation bisphosphonate, inhibits bone resorption at doses that do not appear to affect the mineralization of newly-formed osteoid tissue and thus constitutes a rational treatment for pathological bone resorption. The predominant mode of action appears to be a local, direct effect; bisphosphonates complex tightly to, and inhibit the formation and dissolution of, hydroxyapatite crystals.

TOXICOLOGY

Acute Toxicity

In acute toxicity studies, pamidronate disodium was better tolerated when administered as a short-term i.v. infusion or i.p. than as a bolus i.v. dose, presumably because of lower plasma concentrations. In mice, the i.v. bolus and I.P. LD₅₀ of pamidronate disodium were 20.3 mg/kg and 40 mg/kg respectively; in rats 80 mg/kg and 65 mg/kg, and in rabbits, 18.5 mg/kg and 190 mg/kg. In dogs, the LD₅₀ was >10 mg/kg for a bolus i.v. dose and >40 mg/kg when administered as an i.v. infusion.

Subacute and Chronic Toxicity

Pamidronate disodium has been administered to mice, rats, rabbits and dogs for 3 months by intermittent i.v. infusion or a bolus i.v. dose. Repeat dose animal studies demonstrate that intermittent administration of pamidronate disodium by i.v. infusion is better tolerated than the bolus i.v. route. Dose- and regimen-dependent nephropathy occurred in all species except the mouse. These studies indicate that adverse effects with pamidronate disodium correlate strongly with peak plasma concentration. It should therefore be administered intermittently by slow infusion; daily intravenous administration, especially as a bolus, should be avoided.

The no-toxic effect level for rats and dogs administered 2, 6 or 20 mg/kg by i.v. infusion for 1 hour weekly for 3 months was 2 mg/kg for both species. In all dose groups in the dog, but only at the highest dose in the rat, pharmacological effects were evident as non-reversible, dose-related increase in primary spongy bone formation with a widened metaphyses, increased calcification and impaired remodeling with no impairment of mineralization. This was accompanied by reduced AP and serum phosphate. The major target organ for toxic effects was the kidney, but following high i.v. doses, especially those administered as a bolus, inflammation/degeneration was also observed in the stomach and the lung, and to a lesser extent in the spleen, liver and heart.

Reproductive Toxicity

Pamidronate crosses the placenta barrier readily and accumulates primarily in the fetal bones in rats. Reproductive toxicological studies conducted in rats and rabbits by peroral or intravenous administration at dose levels comparable to human therapeutic dose revealed that pamidronate causes the following adverse events and developmental abnormalities: reduced fertility in both sexes and the first generation of the offspring, distress and prolongation of parturition process with fatal outcome, marked increases in resorption, pre- and post-implantation losses, reduced number of viable pups born, delayed skeletal maturation and ossification, shortening of long bones and visceral and external abnormality (dilated and kinked ureters, displaced testis, shortened body, curved or hooked joints, mal-rotated hind limbs, subcutaneous hemorrhage and edema, etc.).

Carcinogenesis and Mutagenesis

Mutagenic potential was assessed by three different methods both *in vitro* (Ames test, point mutation test, and a cytogenetic test) and *in vivo* (nucleus anomaly test, sister chromatid

exchange study and a micronucleus test). There was no evidence of mutagenic potential *in vivo*. *In vitro* tests were also negative apart from a slight increase in the number of chromosome aberrations in Chinese hamster ovary cells at the highest concentration only (2500 µg/mL).

Carcinogenic potential was assessed in both mice and rats treated with pamidronate disodium ≤40 mg/kg/day and ≤75 mg/kg/day, respectively, by gavage for 2 years. These studies repeated earlier studies completed in the 1970's, in which pamidronate disodium ≤1000 mg/kg was added to the food supply. From these studies, pamidronate disodium does not appear to have carcinogenic potential.

The only unexpected finding in these repeat carcinogenicity studies was hydrocephaly observed in the mouse study. This event occurred at all dose levels, and was probably caused by changes in cranial bones as a result of the pharmacological activity of the compound in the young, growing animals. It is not thought to be of relevance in adult patients in whom bone growth is complete.

In mice receiving pamidronate disodium ≤40 mg/kg daily, there was dose-dependent reduction in the incidence of neoplasms, which was attributed to pamidronate disodium-related decreases in food consumption; mice fed a restricted diet have been shown to develop fewer tumours than those fed *ad libitum*. In this study, the incidence of liver tumours was reduced relative to control animals. In female mice fed with pamidronate disodium 879 mg/kg/day in the diet, the incidence of benign hepatomas was increased relative to control animals.

In both rat carcinogenicity studies, the incidence of neoplastic lesions was within the range observed with historical controls, apart from a slight increase in intestinal leiomyomas observed in females in one study only. Intestinal leiomyomas occur spontaneously in 0.44% Wistar rats (range 0-2%) used as controls in carcinogenicity studies. The mean incidence of these tumours in female Wistar rats administered 1000 mg/kg/day in the diet was 1.2% (range 0-3.7%). As no intestinal leiomyomas were observed in female rats in the other rat study, it is unlikely that these benign, non-fatal tumours are of biological or clinical significance.

REFERENCES

1. BERENSON JR, LICHTENSTEIN A, PORTER L, DIMOPOULOS M, BORDONI R et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *NEJM* 1996; 334: 488-493
2. BODY JJ, MAGRITTE A, SERA J, SCULIER JP, and BORKOWSKI A. Aminohydroxypropylidene bisphosphonate (APD) treatment for tumor-associated hypercalcemia: A randomized comparison between a 3-day treatment and single 24-hour infusions. *J Bone Miner Res* 1989; 4 (6): 923-928
3. BODY JJ, BORKOWSKI A, CLEEREN A, and BIJVOET OLM. Treatment of malignancy-associated hypercalcemia with intravenous aminohydroxypropylidene diphosphonate. *J Clin Oncol* 1986; 4 (8): 1177-1183
4. BODY JJ, POT M, BORKOWSKI A, SCULIER JP, and KLASTERSKY J. Dose/response study of aminohydroxypropylidene bisphosphonate in tumor-associated hypercalcemia. *Am J Med* 1987; 82: 957-963
5. BOONEKAMP PM, van der WEE-PALS LJA, van WIJK-VAN LENNEP MML, THESING CW, and BIJVOET OLM. Two modes of action of bisphosphonates on osteoclastic resorption of mineralized matrix. *Bone Miner* 1986; 1: 27-39
6. CAL JC, and DALEY-YATES PT. Disposition and nephrotoxicity of 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) in rats and mice. *Toxicology* 1990; 65: 179-197
7. COLEMAN RE, and PUROHIT OP. Osteoclast inhibition for the treatment of bone metastases. *Cancer Treatment Reviews* 1993; 19:79-103
8. COLEMAN RE, and RUBENS RD. 3(amino-1,1-hydroxypropylidene) bisphosphonate (APD) for hypercalcemia of breast cancer. *Br J Cancer* 1987; 56: 465-469
9. COLEMAN RE, WOLL PJ, SCRIVENER W, RUBENS RD. Treatment of bone metastases from breast cancer with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Br J Cancer* 1988;58:621-625
10. DALEY-YATES PT, DODWELL DJ, PONGCHAIDECHA M, COLEMAN RE and HOWELL A. The clearance and bioavailability of pamidronate in patients with breast cancer and bone metastases. *Calcif Tissue Int* 1991;49:433-435
11. FITTON A, and McTAVISH D. Pamidronate. A review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1991; 41: 289-318
12. FLANAGAN AM, and CHAMBERS TJ. Inhibition of bone resorption by bisphosphonate; interactions between bisphosphonates, osteoclasts, and bone. *Calcif Tissue Int* 1991; 49:407-415

13. FOLAY-NOLAN D, DALY MJ, WILLIAMS D, WASTI A, and MARTIN M. Pamidronate associated hallucinations. *Ann Rheum Dis* 1992; 51: 927-928
14. GRAEPEL P, BENTLEY P, FRITZ H, MIYAMOTO M, and SLATER SR. Reproduction toxicity studies with pamidronate. *Arzneim Forsch / Drug Res* 1992; 42: 654-667
15. HARINCK HIJ, BIJVOET OLM, PLANTINGH AST, BODY JJ, ELTE JWF, SLEEBOOM HP, WILDIERS J, and NEIJT JP. Role of bone and kidney in tumor-induced hypercalcemia and its treatment with bisphosphonate and sodium chloride. *Am J Med* 1987; 82: 1133-1142
16. HARINCK HIJ, PAPAPOULOS SE, BLANKSMA HJ, MOOLENAAR AJ, VERMEIJ P, and BIJVOET OLM. Paget's disease of bone: early and late responses to three different modes of treatment with aminohydroxypropylidene bisphosphonate (APD). *Br Med J* 1987; 295: 1301-1305
17. HOSKING DJ, COWLEY A, and BUCKNALL CA. Rehydration in the treatment of severe hypercalcemia. *Q J Med* 1981; 200: 473-481
18. HUGHES DE, MIAN M, GUILLARD-CUMMING DF, and RUSSELL RGG. The cellular mechanism of action of bisphosphonates. *Drugs Exptl Clin Res* 1991; 17: 109-114
19. KELLIHAN MJ, and MANGINO PD. Pamidronate. *Ann of Pharmacother* 1992; 26: 1262-1269
20. LEYVRAZ S, HESS U, FLESCH G, BAUER J, SAUFFE S, FORD JM, and BURCKHARDT P. Pharmacokinetics of pamidronate in patients with bone metastases. *J Natl Cancer Inst* 1992;84:788-792
21. LOWIK CWGM, VAN DER PLUIJM G, VAN DER WEE-PALS LJA, BLOYS VAN TRESLONG-DE GROOT H, and BIJVOET OLM. Migration and phenotypic transformation of osteoclast precursors into mature osteoclasts: The effect of bisphosphonate. *J Bone Miner Res* 1988; 3 (2): 185-192
22. MASUD T, and FRANCIS RM. Adverse effects of drugs for bone disease. *Adv Drug React Bull* 1992; (155): 583-586
23. MORTON AR, CANTRILL JA, CRAIG AE, HOWELL A, DAVIES M, and ANDERSON DC. Single dose versus daily intravenous aminohydroxypropylidene biphosphonate (APD) for the hypercalcemia of malignancy. *Br Med J* 1988; 296: 811-814
24. MORTON AR, CANTRILL JA, PILLAI GV, MCMAHON A, ANDERSON DC, and HOWELL A. Sclerosis of lytic bone metastases after disodium aminohydroxypropylidene bisphosphonate (APD) in patients with breast carcinoma. *Br Med J* 1988; 297: 772-773

25. PUROHIT OP, ANTHONY C, RADSTONE CR, OWEN J and COLEMAN RE. High-dose intravenous pamidronate for metastatic bone pain. *Br J Cancer* 1994; 70: 554-558
26. RALSTON SH, GALLAGHER SJ, PATEL U, DRYBURGH FJ, FRASER WD, COWAN RA, and BOYLE IT. Comparison of three intravenous bisphosphonates in cancer-associated hypercalcemia. *Lancet* 1989; II (8673): 1180-1182
27. RALSTON SH, GALLACHER SJ, PATEL U, CAMPBELL J, and BOYLE IT. Cancer-associated hypercalcemia: Morbidity and mortality. Clinical experience in 126 treated patients. *Ann Intern Med* 1990; 112 (7): 499-504
28. RITCH PS. Treatment of cancer-related hypercalcemia. *Semin Oncol* 1990; 17 (2 Suppl 5): 26-33
29. SATO M, GRASSER W, ENDO N, AKINS R, SIMMONS H, THOMPSON DD, GOLUB E, and RODAN GA. Bisphosphonate action; Alendronate localization in rat bone and effects on osteoclast ultrastructure. *J Clin Invest* 1991; 88: 2095-2105
30. SAWYER N, NEWSTEAD C, DRUMMOND A, NEWLAND A, and CUNNINGHAM J. One-shot high-dose pamidronate disodium (APD): effective, simple treatment for hypercalcemia in haematological malignancy. *Clin Lab Haematol* 1989; 11: 179-184
31. SERIS ES. Perspectives: a practical guide to the use of pamidronate in the treatment of Paget's disease. *J Bone Mineral Res* 1994; 9 (3):303-304
32. SHINODA H, ADAMEK G, FELIX R, FLEISCH H, SCHENK R, and HAGAN P. Structure-activity relationships of various bisphosphonates. *Calcif Tissue Int* 1983; 35: 87-99
33. SILVERMAN P, and DISTELHORST CW. Metabolic emergencies in clinical oncology. *Semin Oncol* 1989; 16 (6): 504-515
34. THIEBAUD D, JAEGER PH, JACQUET AF, and BURCKHARDT P. Dose response in the treatment of malignant hypercalcemia by a single infusion of the bisphosphonate AHPBP (APD). *J Clin Oncol* 1988; 6 (5): 762-768
35. THURLIMANN B, MORANT R, JUNGI WF, and RADZIWILL A. Pamidronate for pain control in patients with malignant osteolytic bone disease: a prospective dose-effect study. *Supportive Care Cancer* 1992; 2: 61-65
36. WINGEN F, and SCHMAHL D. Pharmacokinetics of the osteotropic diphosphonate 3-amino-1-hydroxypropane-1,1-diphosphonic acid in mammals. *Arzneimittelforschung* 1987; 37 (II) (9): 1037-1042

37. YATES AJP, MURRAY RML, JERUMS GJ, and MARTIN TJ. A comparison of single and multiple intravenous infusions of 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) in the treatment of hypercalcemia of malignancy. Aust N Z J Med 1987; 17: 387-391
38. VALENTIN-OPRAN A, CHARHON SA, MEUNIER PJ, EDOUARD CM, ARLOT ME. Quantitative histology of myeloma-induced bone changes. Br J Haematol 1982; 52:601-10

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