CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-594

Generic Name: Pamidronate Disodium for Injection, 30 mg/ vial and 90 mg/ vial

Sponsor: Gensia Sicor Pharmaceuticals, Inc.

Approval Date: May 6, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

APPROVAL LETTER

ANDA 75-594

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia Gustavson
U.S. Agent for Aesgen, Inc.
19 Hughes
Irvine, CA 92618-1902

MAY 6 2002

Dear Madam:

This is in reference to your abbreviated new drug application dated February 17, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial.

Reference is also made to our tentative approval letter dated November 28, 2001 and to your amendment dated February 26, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Aredia® Injection, 30 mg/vial and 90 mg/vial, respectively, of Novartis Pharmaceuticals Corporation).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

/S/

Gary Buehler 5/6/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

TENTATIVE APPROVAL LETTER

ANDA 75-594

NOV 28 2001

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia Gustavson
U.S. Agent for Aesgen, Inc.
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 17, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial.

Reference is also made to your amendments dated June 21, August 1, August 16, August 22, and August 23, 2001. We also reference your patent/exclusivity-related correspondences dated May 14 and June 23, 1999; May 26, June 21, and August 7, 2000; and June 18, July 10, August 13, and September 27, 2001.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product. The determination is subject to change on the basis of new information that may come to our attention.

The listed drug product (RLD) referenced in your application, Aredia® Injection of Novartis Pharmaceuticals Corporation, is subject to a period of patent protection which expires on July 29, 2005, (U.S. Patent No. 4,711,880 [the '880 patent]). Your application contains a Paragraph IV Certification to the '880 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your commercial manufacture, use, or sale of this drug product will not infringe on this patent. You have

notified the Agency that Aesgen, Inc. (Aesgen) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no legal action regarding the '880 patent was brought against Aesgen within the statutory forty-five day period.

However, we are unable to grant final approval to your application at this time. This is because the Act provides that approval of an ANDA containing a certification described in section 505(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification"), and that is for a drug product for which a previous ANDA has been submitted which also contains a Paragraph IV Certification, shall be made effective not earlier than one hundred and eighty days after:

(1) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

(2) the date of a decision of a court holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier (section 505(j)(5)(B)(iv)).

With respect to Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial, a previous abbreviated application containing a Paragraph IV Certification was accepted for filing by this office prior to receipt of your application. Furthermore, we are aware that a court decision finding non-infringement of the '880 patent was rendered by the U.S. District Court for the Northern District of Illinois on November 6, 2001. Accordingly, your application will be eligible for final approval beginning on the date that is one hundred and eighty days after the date of this court decision as described under section 505(j)(5)(B)(iv). We refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

In order to reactivate this application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. Please note

that this amendment should be submitted even if none of these changes were made. The amendment should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

For subsequent information on the status of your application and prior to submitting the amendment referenced above, please contact Sarah Ho, R.Ph., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,

/s/ for

11/28/2001

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

Final Printed Labeling

Y36-000-41A
Package Insert

APPROVED
MAY - 6 2002

R_x only

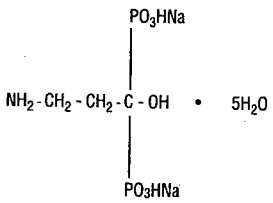
GensiaSicor® PHARMACEUTICALS

Pamidronate Disodium
for Injection

For Intravenous Infusion

DESCRIPTION

Pamidronate Disodium for Injection, is a bone-resorption inhibitor available in 30-mg or 90-mg vials for intravenous administration. Each 30,-mg and 90-mg vial contains, respectively, 30 mg and 90 mg of sterile, lyophilized pamidronate disodium and 470 mg and 375 mg of mannitol, USP. The pH of a 1% solution of pamidronate disodium in distilled water is approximately 8.3. Pamidronate disodium, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, pentahydrate, and its structural formula is:



Pamidronate disodium is a white-to-practically-white powder. It is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2{\cdot}5H_2O$ and its molecular weight is 369.1.

Inactive Ingredients. Mannitol, USP, and phosphoric acid (for adjustment to pH 6.5 prior to lyophilization).

CLINICAL PHARMACOLOGY

The principal pharmacologic action of pamidronate disodium is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Pamidronate disodium adsorbs to calcium phosphate (hydroxyapatite) crystals in bone and may directly block dissolution of this mineral component of bone. In vitro studies also suggest that inhibition of osteoclast activity contributes to inhibition of bone resorption. In animal studies, at doses recommended for the treatment of hypercalcemia, pamidronate disodium inhibits bone resorption apparently without inhibiting bone formation and mineralization. Of relevance to the treatment of hypercalcemia of malignancy is the finding that pamidronate disodium inhibits the accelerated bone resorption that results from osteoclast hyperactivity induced by various tumors in animal studies.

Pharmacokinetics

Cancer patients (n=24) who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of pamidronate disodium over 4 hours and 90 mg of pamidronate disodium over 24 hours (Table 1).

Distribution: The mean ± SD body retention of pamidronate was calculated to be 54 ± 16% of the dose over 120 hours.

Metabolism: Pamidronate is not metabolized and is exclusively eliminated by renal excretion.

Excretion: After administration of 30, 60, and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate disodium over 24 hours, an overall mean ± SD of 46 ± 16% of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean ± SD elimination half-life is 28 ± 7 hours. Mean ± SD total and renal clearances of pamidronate were 107 ± 50 mL/min and 49 ± 28 mL/min, respectively. The rate of elimination from bone has not been determined.

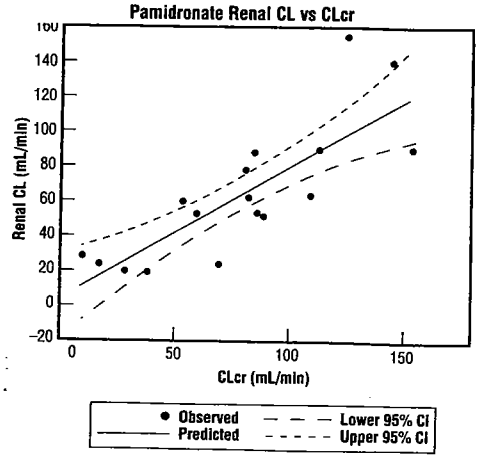
Special Populations

There are no data available on the effects of age, gender, or race on the pharmacokinetics of pamidronate.

Pediatric: Pamidronate is not labeled for use in the pediatric population.

Renal Insufficiency: The pharmacokinetics of pamidronate were studied in cancer patients (n=19) with normal and varying degrees of renal impairment. Each patient received a single 90-mg dose of pamidronate disodium infused over 4 hours. The renal clearance of pamidronate in patients was found to closely correlate with creatinine clearance (see Figure 1). A trend toward a lower percentage of drug excreted unchanged in urine was observed in renally impaired patients. Adverse experiences noted were not found to be related to changes in renal clearance of pamidronate. Given the recommended dose, 90 mg infused over 4 hours, excessive accumulation of pamidronate in renally impaired patients is not anticipated if pamidronate disodium is administered on a monthly basis.

Figure 1: Pamidronate renal clearance as a function of creatinine clearance in patients with normal and impaired renal function. The lines are the mean prediction line and 95% confidence intervals.



Hepatic Insufficiency: There are no human pharmacokinetic data for pamidronate disodium in patients who have hepatic insufficiency.

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorp bone disease and hypercalcemia of malignancy. Excessive rele and gastrointestinal disturbances, with progressive dehydrati increased renal resorption of calcium, setting up a cycle of resorption and adequate fluid administration to correct hypercalcemia.

Most cases of hypercalcemia associated with malignancy occ lung or head and neck; renal-cell carcinoma; and certain hema lymphomas. A few less-common malignancies, incl cholangiocarcinoma, have a high incidence of hypercalcemia malignancy can generally be divided into two groups, accordi

In humoral hypercalcemia, osteoclasts are activated and bone related protein, which are elaborated by the tumor and circulate cell malignancies of the lung or head and neck or in genitourin metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result ir resorption by osteoclasts. Tumors commonly associated with myeloma.

Total serum calcium levels in patients who have hypercalcemia concomitant hypoalbuminemia is commonly present. Ideally hypercalcemic conditions; however, these are not commonly o of the total serum calcium value for differences in albumin level nomograms are in use for this type of calculation (see **DOSAGE**

Clinical Trials

In one double-blind clinical trial, 52 patients who had hyperca 90 mg of pamidronate disodium as a single 24-hour intravenous after 48 hours of saline hydration.

The mean baseline-corrected serum calcium for the 30-mg, 13.3 mg/dL, respectively.

The majority of patients (64%) had decreases in albumin-corre Mean-corrected serum calcium levels at days 2-7 after initia reduced from baseline in all three dosage groups. As a result, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg corrected serum calcium levels. Many patients (33%-53%) in t corrected serum calcium levels, or a partial response (≥15% de

In a second double-blind, controlled clinical trial, 65 cancer patie at least 24 hours of saline hydration were randomized to recei infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intra to receive pamidronate and 35 to receive etidronate.

The mean baseline-corrected serum calcium for the pamidrona 13.8 mg/dL, respectively

By day 7, 70% of the patients in the pamidronate disodium gro normal-corrected serum calcium levels (P<0.05). When partial r also included, the response rates were 97% for the pamidron (P<0.01). Mean-corrected serum calcium for the pamidronate di values to 10.4 and 11.2 mg/dL, respectively, on day 7. At day 1 of patients in the etidronate disodium group still had normal-corr For responders in the pamidronate disodium and etidronate gro respectively). The time course of effect on corrected serum calc

	Change in Corrected S from Initiation
Time (hr)	Mean Change from Base
	Pamidronate disodium
Baseline	14.6
24	-0.3
48	-1.5
72	-2.6
96	-3.5
168	-4.1

[1]Comparison between treatment groups

In a third multicenter, randomized, parallel double-blind trial, a g receive 60 mg of pamidronate disodium as a 4- or 24-hour infus who had a corrected serum calcium level of ≥12.0 mg/dL after 2

The mean baseline-corrected serum calcium levels for pamidro 60-mg 24-hour infusion, and saline infusion were 14.2 mg/dL, 13

By day 7 after initiation of treatment, 78%, 61%, and 22% of th 60-mg 4-hour infusion, 60-mg 24-hour infusion, and saline i pamidronate disodium 60-mg 4-hour infusion group and 26% of th group had normal-corrected serum calcium levels or maintenanc

For responders, the median duration of complete responses was infusion and pamidronate disodium 60-mg 24-hour infusion, resp

In all three trials, patients treated with pamidronate disodium ha metastases. Concomitant administration of furosemide did not aff

Thirty-two patients who had recurrent or refractory hypercalcer pamidronate disodium over a 4- or 24-hour period. Of these, 4 response to the retreatment, and these responders had about a 3- retreatment.

Unlike pamidronate disodium 60 mg, the drug has not been inve infused over a 4-hour period.

Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic dise complicated by concurrent excessive bone repair, affecting one or bones that may fracture or bend under stress. Signs and symptoms resulting from cranial and spinal nerve entrapment and from spina to the involved bone, increased serum alkaline phosphatase hydroxyproline excretion (reflecting increased bone resorption).

Clinical Trials

In one double-blind clinical trial, 64 patients with moderate to sev mg, or 30 mg of pamidronate disodium as a single 4-hour infusion 90 mg of pamidronate disodium

in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2 \cdot 5H_2O$ and its molecular weight is 369.1.

Inactive Ingredients. Mannitol, USP, and phosphoric acid (for adjustment to pH 6.5 prior to lyophilization).

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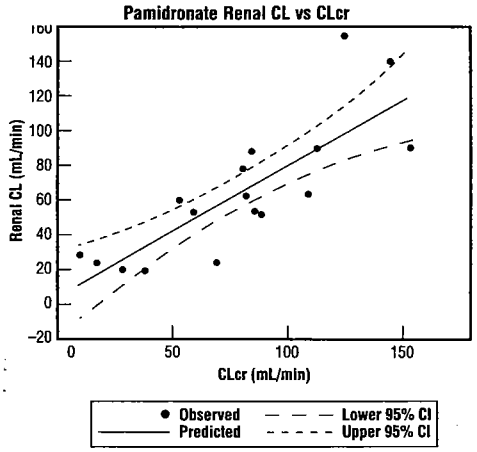
Special Populations

There are no data available on the effects of age, gender, or race on the pharmacokinetics of pamidronate.

Pediatric: Pamidronate is not labeled for use in the pediatric population.

Renal Insufficiency: The pharmacokinetics of pamidronate were studied in cancer patients (n=19) with normal and varying degrees of renal impairment. Each patient received a single 90-mg dose of pamidronate disodium infused over 4 hours. The renal clearance of pamidronate in patients was found to closely correlate with creatinine clearance (see Figure 1). A trend toward a lower percentage of drug excreted unchanged in urine was observed in renally impaired patients. Adverse experiences noted were not found to be related to changes in renal clearance of pamidronate. Given the recommended dose, 90 mg infused over 4 hours, excessive accumulation of pamidronate in renally impaired patients is not anticipated if pamidronate disodium is administered on a monthly basis.

Figure 1: Pamidronate renal clearance as a function of creatinine clearance in patients with normal and impaired renal function. The lines are the mean prediction line and 95% confidence intervals.



Hepatic Insufficiency: There are no human pharmacokinetic data for pamidronate disodium in patients who have hepatic insufficiency.

Drug-Drug Interactions: There are no human pharmacokinetic data for drug interactions with pamidronate disodium.

Table 1

Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients (n=6 for each group)

Dose (infusion rate)	Maximum Concentration (mcg/mL)	Percent of dose excreted in urine	Total Clearance (mL/min)	Renal Clearance (mL/min)
30 mg	0.73	43.9	136	58
(4 hrs)	(0.14, 19.1%)	(14.0, 31.9%)	(44, 32.4%)	(27, 46.5%)
60 mg	1.44	47.4	88	42
(4 hrs)	(0.57, 39.6%)	(47.4, 54.4%)	(56, 63.6%)	(28, 66.7%)
90 mg	2.61	45.3	103	44
(4 hrs)	(0.74, 28.3%)	(25.8, 56.9%)	(37, 35.9%)	(16, 36.4%)
90 mg	1.38	47.5	101	52
(24 hrs)	(1.97, 142.7%)	(10.2, 21.5%)	(58, 57.4%)	(42, 80.8%)

After intravenous administration of radiolabeled pamidronate in rats, approximately 50%-60% of the compound was rapidly adsorbed by bone and slowly eliminated from the body by the kidneys. In rats given 10 mg/kg bolus injections of radiolabeled pamidronate disodium, approximately 30% of the compound was found in the liver shortly after administration and was then redistributed to bone or eliminated by the kidneys over 24-48 hours. Studies in rats injected with radiolabeled pamidronate disodium showed that the compound was rapidly cleared from the circulation and taken up mainly by bones, liver, spleen, teeth, and tracheal cartilage. Radioactivity was eliminated from most soft tissues within 1-4 days; was detectable in liver and spleen for 1 and 3 months, respectively; and remained high in bones, trachea, and teeth for 6 months after dosing. Bone uptake occurred preferentially in areas of high bone turnover. The terminal phase of elimination half-life in bone was estimated to be approximately 300 days.

Pharmacodynamics

Serum phosphate levels have been noted to decrease after administration of pamidronate disodium, presumably because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7-10 days.

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

corrected serum calcium levels, or a partial response (≥15% decrease

In a second double-blind, controlled clinical trial, 65 cancer patients wh at least 24 hours of saline hydration were randomized to receive eithe infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous to receive pamidronate and 35 to receive etidronate.

The mean baseline-corrected serum calcium for the pamidronate diso 13.8 mg/dL, respectively

By day 7, 70% of the patients in the pamidronate disodium group and normal-corrected serum calcium levels (P<0.05). When partial respons also included, the response rates were 97% for the pamidronate disc (P<0.01). Mean-corrected serum calcium for the pamidronate disodium values to 10.4 and 11.2 mg/dL, respectively, on day 7. At day 14, 43% of patients in the etidronate disodium group still had normal-corrected s For responders in the pamidronate disodium and etidronate groups, th respectively). The time course of effect on corrected serum calcium is

Change in Corrected Serum from Initiation of Tr

Time (hr)	Mean Change from Baseline in Pamidronate disodium
Baseline	14.6
24	-0.3
48	-1.5
72	-2.6
96	-3.5
168	-4.1

[1]Comparison between treatment groups

In a third multicenter, randomized, parallel double-blind trial, a group receive 60 mg of pamidronate disodium as a 4- or 24-hour infusion, v who had a corrected serum calcium level of ≥12.0 mg/dL after 24 hou

The mean baseline-corrected serum calcium levels for pamidronate 60-mg 24-hour infusion, and saline infusion were 14.2 mg/dL, 13.7 m

By day 7 after initiation of treatment, 78%, 61%, and 22% of the pa 60-mg 4-hour infusion, 60-mg 24-hour infusion, and saline infusic pamidronate disodium 60-mg 4-hour infusion group and 26% of the pat group had normal-corrected serum calcium levels or maintenance of a

For responders, the median duration of complete responses was 4 da infusion and pamidronate disodium 60-mg 24-hour infusion, respectiv

In all three trials, patients treated with pamidronate disodium had sig metastases. Concomitant administration of furosemide did not affect r

Thirty-two patients who had recurrent or refractory hypercalcemia c pamidronate disodium over a 4- or 24-hour period. Of these, 41% r response to the retreatment, and these responders had about a 3-mg/c retreatment.

Unlike pamidronate disodium 60 mg, the drug has not been investig infused over a 4-hour period.

Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic disease complicated by concurrent excessive bone repair, affecting one or mo bones that may fracture or bend under stress. Signs and symptoms ma resulting from cranial and spinal nerve entrapment and from spinal cc to the involved bone, increased serum alkaline phosphatase leve hydroxyproline excretion (reflecting increased bone resorption).

Clinical Trials

In one double-blind clinical trial, 64 patients with moderate to severe I mg, or 30 mg of pamidronate disodium as a single 4-hour infusion on 90 mg of pamidronate disodium.

The mean baseline serum alkaline phosphatase levels were 1409 U/ hydroxyproline/creatinine ratios were 0.25, 0.19, and 0.19 for the 15-n

The effects of pamidronate disodium on serum alkaline phosphatase (S are summarized in the following table:

Percent of Patient Significant % Decreases in S

	SAP		
% Decrease	15 mg	45 mg	90 mg
≥50	26	33	60
≥30	40	65	83

The median maximum percent decreases from baseline in serum alkali were 25%, 41%, and 57%, and 25%, 47%, and 61% for the 15-mg, 45 response ≥50% decrease) for serum alkaline phosphatase was appro duration ranged from 1 to 372 days.

No statistically significant differences between treatment groups, or sta for the bone pain response, mobility, and global evaluation in the 45-r occurred in some patients in the 90-mg group.

Twenty-five patients who had Paget's disease were retreated with 90 r decrease in serum alkaline phosphatase from baseline after t hydroxyproline/creatinine ratio from baseline after treatment.

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions

Osteolytic bone metastases commonly occur in patients with multiple phenomenon known as osteotropism, meaning they possess an extrac bone metastases in these cancers is predominantly in the axial skeleto appendicular skeleton, although lesions in the proximal femur and hun the red bone marrow in which slow blood flow possibly assists attachi trabecular bone is much higher than cortical bone, and therefore disea bone than at sites of cortical tissue.

These bone changes can result in patients having evidence of osteolyti requires either radiation therapy or narcotic analgesics (or both) for sy fractures of bone in both the axial and appendicular skeleton. Axial ske cord compression or vertebral body collapse with significant neurologi episode(s) of hypercalcemia.

VED R_x only

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Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanism involved.

In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see **DOSAGE AND ADMINISTRATION**).

Clinical Trials

In one double-blind clinical trial, 52 patients who had hypercalcemia of malignancy were enrolled to receive 30 mg, 60 mg, or 90 mg of pamidronate disodium as a single 24-hour intravenous infusion if their corrected serum calcium levels were ≥12.0 mg/dL after 48 hours of saline hydration.

The mean baseline-corrected serum calcium for the 30-mg, 60, mg and 90-mg groups were 13.8 mg/dL, 13.8 mg/dL, and 13.3 mg/dL, respectively.

The majority of patients (64%) had decreases in albumin-corrected serum calcium levels by 24 hours after initiation of treatment. Mean-corrected serum calcium levels at days 2-7 after initiation of treatment with pamidronate disodium were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with pamidronate disodium, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of pamidronate disodium, respectively, had normal-corrected serum calcium levels. Many patients (33%-53%)in the 60-mg and 90-mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response (≥15% decrease of corrected serum calcium from baseline), at day 14.

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of ≥12.0 mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of pamidronate as a single 24-hour intravenous infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive pamidronate and 35 to receive etidronate.

The mean baseline-corrected serum calcium for the pamidronate disodium 60-mg and etidronate groups were 14.6 mg/dL and 13.8 mg/dL, respectively

By day 7, 70% of the patients in the pamidronate disodium group and 41% of the patients in the etidronate disodium group had normal-corrected serum calcium levels ($P<0.05$). When partial responders ≥15% decrease of serum calcium from baseline) were also included, the response rates were 97% for the pamidronate disodium group and 65% for the etidronate disodium group ($P<0.01$). Mean-corrected serum calcium for the pamidronate disodium and etidronate disodium groups decreased from baseline values to 10.4 and 11.2 mg/dL, respectively, on day 7. At day 14, 43% of patients in the pamidronate disodium group and 18% of patients in the etidronate disodium group still had normal-corrected serum calcium levels, or maintenance of a partial response. For responders in the pamidronate disodium and etidronate groups, the median duration of response was similar (7 and 5 days, respectively). The time course of effect on corrected serum calcium is summarized in the following table.

Change in Corrected Serum Calcium by Time from Initiation of Treatment

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)		
	Pamidronate disodium	Etidronate disodium	P-Value[1]
Baseline	14.6	13.8	
24	-0.3	-0.5	
48	-1.5	-1.1	
72	-2.6	-2.0	
96	-3.5	-2.0	<0.01
168	-4.1	-2.5	<0.01

[1]Comparison between treatment groups

In a third multicenter, randomized, parallel double-blind trial, a group of 69 cancer patients with hypercalcemia was enrolled to receive 60 mg of pamidronate disodium as a 4- or 24-hour infusion, which was compared to a saline treatment group. Patients who had a corrected serum calcium level of ≥12.0 mg/dL after 24 hours of saline hydration were eligible for this trial.

The mean baseline-corrected serum calcium levels for pamidronate disodium 60-mg 4-hour infusion, pamidronate disodium 60-mg 24-hour infusion, and saline infusion were 14.2 mg/dL, 13.7 mg/dL, and 13.7 mg/dL, respectively.

By day 7 after initiation of treatment, 78%, 61%, and 22% of the patients had normal-corrected serum calcium levels for the 60-mg 4-hour infusion, 60-mg 24-hour infusion, and saline infusion, respectively. At day 14, 39% of the patients in the pamidronate disodium 60-mg 4-hour infusion group and 26% of the patients in the pamidronate disodium 60-mg 24-hour infusion group had normal-corrected serum calcium levels or maintenance of a partial response.

For responders, the median duration of complete responses was 4 days and 6.5 days for pamidronate disodium 60-mg 4-hour infusion and pamidronate disodium 60-mg 24-hour infusion, respectively.

In all three trials, patients treated with pamidronate disodium had similar response rates in the presence or absence of bone metastases. Concomitant administration of furosemide did not affect response rates.

Thirty-two patients who had recurrent or refractory hypercalcemia of malignancy were given a second course of 60 mg of pamidronate disodium over a 4- or 24-hour period. Of these, 41% showed a complete response and 16% showed a partial response to the retreatment, and these responders had about a 3-mg/dL fall in mean-corrected serum calcium levels 7 days after retreatment.

Unlike pamidronate disodium 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90-mg dose infused over a 4-hour period.

Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic disease characterized by chronic, focal areas of bone destruction complicated by concurrent excessive bone repair, affecting one or more bones. These changes result in thickened but weakened bones that may fracture or bend under stress. Signs and symptoms may be bone pain, deformity, fractures, neurological disorders resulting from cranial and spinal nerve entrapment and from spinal cord and brain stem compression, increased cardiac output to the involved bone, increased serum alkaline phosphatase levels (reflecting increased bone formation) and/or urine hydroxyproline excretion (reflecting increased bone resorption).

Clinical Trials

In one double-blind clinical trial, 64 patients with moderate to severe Paget's disease of bone were enrolled to receive 5 mg, 15 mg, or 30 mg of pamidronate disodium as a single 4-hour infusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 mg of pamidronate disodium.

The mean baseline serum alkaline phosphatase levels were 1409 U/L, 983 U/L, and 1085 U/L, and the mean baseline urine

Clinical Trials

In a double-blind, randomized, placebo
pamidronate disodium or placebo in a
disodium on the occurrence of skeletal
therapy to bone, surgery to bone, and
placebo as a monthly 4-hour intraven
pamidronate disodium, 181 placebo). Th
disodium group (24% vs 41%, P<0.0
pamidronate disodium patients than fo
pathologic fracture, and radiation to bo
respectively). Moreover, fewer pamidron
radiation to bone (14% vs 22%, P=.049

In addition, decreases in pain scores fr
with pain at baseline (P=.026) but not in
the placebo group for the Spitzer quali
significant deterioration from baseline ir

After 21 months, the proportion of pati
disodium group than the placebo group
Pamidronate disodium patients vs place
disodium group compared to placebo
(16% vs 27%, P=.005). Survival of all p

Two double-blind, randomized, placebo
infused over 2 hours every 3 to 4 weel
osteolytic bone metastases who had one
treated with antineoplastic chemotherap
entry.

382 patients receiving chemotherapy we
hormonal therapy were randomized, 182
efficacy. Patients were followed for 24 m
in patients receiving chemotherapy and
the chemotherapy study and 37% of the
The efficacy results are shown in the tab

	Breast Cancer Receiving Che		
	Any SRE		Radiat
	A	P	A
N	185	195	185
Skeletal Morbidity Rate (#SRE/Year) Mean	2.5	3.7	0.8
P-Value	<.001		< .00
Proportion of Patients having an SRE	46%	65%	28%
P-Value	<.001		< .001
Median Time to SRE (months)	13.9	7.0	NR**
P-Value	< .001		< .001

Fractures and radiation to bone were tw
overestimated since numerous analyses
**NR = Not Reached

Bone lesion response was radiographicall
was 33% in pamidronate disodium patier
seen between pamidronate disodium and

Pain and analgesic scores, ECOG perform
during the trials. The changes from basel

	Mea		
	Brea		
	Rec		
	Pamidronate Disodium for Injection		Pl
	N	mean Δ	N
Pain Score	175	+0.93	183
Analgesic Score	175	+0.74	183
ECOG PS	178	+0.81	186
Spitzer QOL	177	-1.76	185

Decreases in pain, analgesic scores and E

*The statistical significance of analyses o
trials may be overestimated since numero

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Pamidronate disodium for injection, in co
hypercalcemia associated with malignanc
epidermoid tumors respond to treatment v
therapy, should be initiated promptly and
treatment. Mild or asymptomatic hypercal
loop diuretics). Patients should be hydrat
who have cardiac failure, must be avoided.
and efficacy of pamidronate disodium in t
tumor-related conditions has not been est

Paget's Disease

Pamidronate disodium for injection is indi
effectiveness of pamidronate disodium w
upper limit of normal. pamidronate disodiu
phosphatase and urinary hydroxyproline l
Pamidronate disodium therapy has also be
failed to respond, or no longer responded

Osteolytic Bone Metastases of Breast Ca

Pamidronate disodium for injection is indi

solvents. Its molecular formula is

yophilization).

ption. Although the mechanism of
o this action. Pamidronate disodium
olution of this mineral component of
oition of bone resorption. In animal
inhibits bone resorption apparently
alcemia of malignancy is the finding
last hyperactivity induced by various

ius infusion of 30, 60, or 90 mg of
ole 1).
of the dose over 120 hours.
.
and 90 mg of pamidronate disodium
urine within 120 hours. Cumulative
7 hours. Mean ± SD total and renal
ite of elimination from bone has not

pamidronate.

19) with normal and varying degrees
sed over 4 hours. The renal clearance
Figure 1). A trend toward a lower
Adverse experiences noted were not
dose, 90 mg infused over 4 hours,
dronate disodium is administered on

eatinine
nction.
intervals.

ium in patients who have hepatic

pamidronate disodium.

cer Patients

Renal Clearance (mL/min)
58
(27, 46.5%)
42
(28, 66.7%)
44
(16, 36.4%)
52
(42, 80.8%)

30% of the compound was rapidly
/kg bolus injections of radiolabeled
after administration and was then
ted with radiolabeled pamidronate
mainly by bones, liver, spleen, teeth,
as detectable in liver and spleen for
after dosing. Bone uptake occurred
was estimated to be approximately

disodium, presumably because of
normone levels, which are usually
herapy was administered in 30% of
eturned toward normal within 7-10

turn to within or below normal after
decreases in serum calcium levels,

corrected serum calcium levels. Many patients (33%-53%)in the 60-mg and 90-mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response (≥15% decrease of corrected serum calcium from baseline), at day 14.

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of ≥12.0 mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of pamidronate as a single 24-hour intravenous infusion or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive pamidronate and 35 to receive etidronate.

The mean baseline-corrected serum calcium for the pamidronate disodium 60-mg and etidronate groups were 14.6 mg/dL and 13.8 mg/dL, respectively

By day 7, 70% of the patients in the pamidronate disodium group and 41% of the patients in the etidronate disodium group had normal-corrected serum calcium levels ($P<0.05$). When partial responders ≥15% decrease of serum calcium from baseline) were also included, the response rates were 97% for the pamidronate disodium group and 65% for the etidronate disodium group ($P<0.01$). Mean-corrected serum calcium for the pamidronate disodium and etidronate disodium groups decreased from baseline values to 10.4 and 11.2 mg/dL, respectively, on day 7. At day 14, 43% of patients in the pamidronate disodium group and 18% of patients in the etidronate disodium group still had normal-corrected serum calcium levels, or maintenance of a partial response. For responders in the pamidronate disodium and etidronate groups, the median duration of response was similar (7 and 5 days, respectively). The time course of effect on corrected serum calcium is summarized in the following table.

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Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)		
	Pamidronate disodium	Etidronate disodium	P-Value[1]
Baseline	14.6	13.8	
24	-0.3	-0.5	
48	-1.5	-1.1	
72	-2.6	-2.0	
96	-3.5	-2.0	<0.01
168	-4.1	-2.5	<0.01

[1]Comparison between treatment groups

In a third multicenter, randomized, parallel double-blind trial, a group of 69 cancer patients with hypercalcemia was enrolled to receive 60 mg of pamidronate disodium as a 4- or 24-hour infusion, which was compared to a saline treatment group. Patients who had a corrected serum calcium level of ≥12.0 mg/dL after 24 hours of saline hydration were eligible for this trial.

The mean baseline-corrected serum calcium levels for pamidronate disodium 60-mg 4-hour infusion, pamidronate disodium 60-mg 24-hour infusion, and saline infusion were 14.2 mg/dL, 13.7 mg/dL, and 13.7 mg/dL, respectively.

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In all three trials, patients treated with pamidronate disodium had similar response rates in the presence or absence of bone metastases. Concomitant administration of furosemide did not affect response rates.

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Unlike pamidronate disodium 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90-mg dose infused over a 4-hour period.

Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic disease characterized by chronic, focal areas of bone destruction complicated by concurrent excessive bone repair, affecting one or more bones. These changes result in thickened but weakened bones that may fracture or bend under stress. Signs and symptoms may be bone pain, deformity, fractures, neurological disorders resulting from cranial and spinal nerve entrapment and from spinal cord and brain stem compression, increased cardiac output to the involved bone, increased serum alkaline phosphatase levels (reflecting increased bone formation) and/or urine hydroxyproline excretion (reflecting increased bone resorption).

Clinical Trials

In one double-blind clinical trial, 64 patients with moderate to severe Paget's disease of bone were enrolled to receive 5 mg, 15 mg, or 30 mg of pamidronate disodium as a single 4-hour infusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 mg of pamidronate disodium.

The mean baseline serum alkaline phosphatase levels were 1409 U/L, 983 U/L, and 1085 U/L, and the mean baseline urine hydroxyproline/creatinine ratios were 0.25, 0.19, and 0.19 for the 15-mg, 45- mg, and 90-mg groups, respectively.

The effects of pamidronate disodium on serum alkaline phosphatase (SAP) and urine hydroxy-proline/creatinine ratios (UOHP/C) are summarized in the following table:

Percent of Patients With Significant % Decreases in SAP and UOHP/C

	SAP			UOHP/C		
% Decrease	15 mg	45 mg	90 mg	15 mg	45 mg	90 mg
≥50	26	33	60	15	47	72
≥30	40	65	83	35	57	85

The median maximum percent decreases from baseline in serum alkaline phosphatase and urine hydroxyproline/creatinine ratios were 25%, 41%, and 57%, and 25%, 47%, and 61% for the 15-mg, 45-mg, and 90-mg groups, respectively. The median time to response ≥50% decrease) for serum alkaline phosphatase was approximately 1 month for the 90-mg group, and the response duration ranged from 1 to 372 days.

No statistically significant differences between treatment groups, or statistically significant changes from baseline were observed for the bone pain response, mobility, and global evaluation in the 45-mg and 90-mg groups. Improvement in radiologic lesions occurred in some patients in the 90-mg group.

Twenty-five patients who had Paget's disease were retreated with 90 mg of pamidronate disodium. Of these, 44% had a ≥50% decrease in serum alkaline phosphatase from baseline after treatment, and 39% had a ≥50% decrease in urine hydroxyproline/creatinine ratio from baseline after treatment.

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

Osteolytic bone metastases commonly occur in patients with multiple myeloma or breast cancer. These cancers demonstrate a phenomenon known as osteotropism, meaning they possess an extraordinary affinity for bone. The distribution of osteolytic bone metastases in these cancers is predominantly in the axial skeleton, particularly the spine, pelvis, and ribs, rather than the appendicular skeleton, although lesions in the proximal femur and humerus are not uncommon. This distribution is similar to the red bone marrow in which slow blood flow possibly assists attachment of metastatic cells. The surface-to volume ratio of trabecular bone is much higher than cortical bone, and therefore disease processes tend to occur more floridly in trabecular bone than at sites of cortical tissue.

These bone changes can result in patients having evidence of osteolytic skeletal destruction leading to severe bone pain that requires either radiation therapy or narcotic analgesics (or both) for symptomatic relief. These changes also cause pathologic fractures of bone in both the axial and appendicular skeleton. Axial skeletal fractures of the vertebral bodies may lead to spinal cord compression or vertebral body collapse with significant neurologic complications. Also, patients may experience episode(s) of hypercalcemia.

	A	P
N	185	19
Skeletal Morbidity Rate (#SRE/Year)		
Mean	2.5	3.
P-Value	<.001	
Proportion of Patients having an SRE	46%	6
P-Value	<.001	
Median Time to SRE (months)	13.9	7.
P-Value	< .001	

[1] Fractures and radiation to overestimated since numerc
**NR = Not Reached

Bone lesion response was r
was 33% in pamidronate di
seen between pamidronate

Pain and analgesic scores, I
during the trials. The chang

	Pamidrona Disodium for Inj	
	N	mean
Pain Score	175	+0.93
Analgesic Score	175	+0.74
ECOG PS	178	+0.81
Spitzer QOL	177	-1.76

Decreases in pain, analgesic
*The statistical significance
trials may be overestimated

INDICATIONS AND USAGE

Hypercalcemia of Malignan

Pamidronate disodium for ir
hypercalcemia associated w
epidermoid tumors respond
therapy, should be initiated
treatment. Mild or asympton
loop diuretics). Patients sho
who have cardiac failure, mu
and efficacy of pamidronate
tumor-related conditions has

Paget's Disease

Pamidronate disodium for in
effectiveness of pamidronat
upper limit of normal. pamid
phosphatase and urinary hy
Pamidronate disodium thera
failed to respond, or no long

Osteolytic Bone Metastases

Pamidronate disodium for inj
bone metastases of breast
appeared to be smaller in th
chemotherapy, however, ove
Bone Metastases of Breast

CONTRAINDICATIONS

Pamidronate disodium for i
disodium or other bisphosph

WARNINGS

In both rats and dogs, neph
disodium.

Two 7-day intravenous infusi
at doses of 1-20 mg/kg fo
recommended human dose
such as elevated BUN and cr
of ≥10 mg/kg. In the second
Additional findings included
≥1 mg/kg after each infusion

Pamidronate disodium for inj
as a 1-hour infusion, once a
≥6 mg/kg and included incr
present at 20 mg/kg at the e
kidney findings of elevated Bl
were partially reversible at 6
2 mg/kg (1.1 x HRHD for a s

Patients who receive an intra
parameters of renal function.

Studies conducted in young
administration of bisphosphc

PRECAUTIONS

General

Standard hypercalcemia-relat
should be carefully monit
hypophosphatemia (12%),
pamidronate disodium-treate
association with pamidronate

ɔrption is the underlying pathophysiologic derangement in metastatic
elease of calcium into the blood as bone is resorbed results in polyuria
ation and decreasing glomerularfiltration rate. This, in turn, results in
of worsening systemic hypercalcemia. Correction of excessive bone
t volume deficits are therefore essential to the management of

ccur in patients who have breast cancer; squamous-cell tumors of the
matologic malignancies, such as multiple myeloma and some types of
ncluding vasoactive intestinal-peptide-producing tumors and
nia as a metabolic complication. Patients who have hypercalcemia of
rding to the pathophysiologic mechanism involved.

ɔne resorption is stimulated by factors such as parathyroid-hormone-
late systemically. Humoral hypercalcemia usually occurs in squamous-
rinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal

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AGE AND ADMINISTRATION).

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calcium is summarized in the following table.

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ation of Treatment

Baseline in Corrected Serum Calcium (mg/dL)		
um	Etidronate disodium	P-Value[1]
13.8		
-0.5		
-1.1		
-2.0		
-2.0		<0.01
-2.5		<0.01

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infusion, which was compared to a saline treatment group. Patients
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line infusion, respectively. At day 14, 39% of the patients in the
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iptoms may be bone pain, deformity, fractures, neurological disorders
n spinal cord and brain stem compression, increased cardiac output
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nfusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and

e 1409 U/L, 983 U/L, and 1085 U/L, and the mean baseline urine

Clinical Trials

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myeloma were enrolled to receive pamidronate disodium or placebo in addition to their underlying antimyeloma therapy to determine the effect of pamidronate disodium 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 pamidronate disodium or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 pamidronate disodium, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the pamidronate disodium group (24% vs 41%, P<0.001), and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for pamidronate disodium patients than for placebo patients (mean: 1.1 vs 2.1, P<.02). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the pamidronate disodium group (P=.001, .006, and .046, respectively). Moreover, fewer pamidronate disodium patients suffered any pathologic fracture (17% vs 30%, P=.004) or needed radiation to bone (14% vs 22%, P=.049).

In addition, decreases in pain scores from baseline occurred at the last measurement for those pamidronate disodium patients with pain at baseline (P=.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<.001) and ECOG performance status (P<.011) while there was no significant deterioration from baseline in these parameters observed in pamidronate disodium-treated patients.*

After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the pamidronate disodium group than the placebo group (P=.015). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for Pamidronate disodium patients vs placebo patients (P=.008), and time to first SRE was significantly longer in the pamidronate disodium group compared to placebo (P=.016). Fewer pamidronate disodium patients suffered vertebral pathologic fractures (16% vs 27%, P=.005). Survival of all patients was not different between treatment groups.

Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of pamidronate disodium infused over 2 hours every 3 to 4 weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had one or more predominantly lytic metastases of at least 1 cm in diameter: one in patients being treated with antineoplastic chemotherapy and the second in patients being treated with hormonal antineoplastic therapy at trial entry.

382 patients receiving chemotherapy were randomized, 185 to pamidronate disodium and 197 to placebo. 372 patients receiving hormonal therapy were randomized, 182 to pamidronate disodium and 190 to placebo. All but three patients were evaluable for efficacy. Patients were followed for 24 months of therapy or until they went off study. Median duration of follow-up was 13 months in patients receiving chemotherapy and 17 months in patients receiving hormone therapy. Twenty five percent of the patients in the chemotherapy study and 37% of the patients in the hormone therapy study received pamidronate disodium for 24 months. The efficacy results are shown in the table below:

	Breast Cancer Patients Receiving Chemotherapy						Breast Cancer Patients Receiving Hormonal Therapy					
	Any SRE		Radiation		Fractures		Any SRE		Radiation		Fractures	
	A	P	A	P	A	P	A	P	A	P	A	P
N	185	195	185	195	185	195	182	189	182	189	182	189
Skeletal Morbidity Rate (#SRE/Year) Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-Value	<.001		<.001†		.018†		.021		.013†		.040†	
Proportion of Patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001†		.014†		.094		058†		054†	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3	10.9	7.4	NR**	23.4	20.6	12.8
P-Value	<.001		<.001†		009†		118		.016†		113†	

†Fractures and radiation to bone were two of several secondary endpoints. The statistical significance of these analyses may be overestimated since numerous analyses were performed.
**NR = Not Reached

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The complete + partial response rate was 33% in pamidronate disodium patients and 18% in placebo patients treated with chemotherapy (P=.001). No difference was seen between pamidronate disodium and placebo in hormonally-treated patients.

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index were measured at baseline and periodically during the trials. The changes from baseline to the last measurement carried forward are shown in the following table:

Mean Change (Δ) from Baseline at Last Measurement

	Breast Cancer Patients Receiving Chemotherapy					Breast Cancer Patients Receiving Hormonal Therapy				
	Pamidronate Disodium for Injection		Placebo		A vs P	Pamidronate Disodium for Injection		Placebo		A vs P
	N	mean Δ	N	Mean Δ	P-Value*	N	Mean Δ	N	Mean Δ	P-Value*
Pain Score	175	+0.93	183	+1.69	050	173	+0.50	179	+1.60	.007
Analgesic Score	175	+0.74	183	+1.55	.009	173	+0.90	179	+2.28	<.001
ECOG PS	178	+0.81	186	+1.19	.002	175	+0.95	182	+0.90	.773
Spitzer QOL	177	-1.76	185	-2.21	.103	173	-1.86	181	-2.05	.409

Decreases in pain, analgesic scores and ECOG PS, and increases in Spitzer QOL indicate an improvement from baseline.

*The statistical significance of analyses of these secondary endpoints of pain, quality of life, and performance status in all three trials may be overestimated since numerous analyses were performed.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Pamidronate disodium for injection, in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment with pamidronate disodium. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of pamidronate disodium in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

Paget's Disease

Pamidronate disodium for injection is indicated for the treatment of patients with moderate to severe Paget's disease of bone. The effectiveness of pamidronate disodium was demonstrated primarily in patients with serum alkaline phosphatase ≥3 times the upper limit of normal. pamidronate disodium therapy in patients with Paget's disease has been effective in reducing serum alkaline phosphatase and urinary hydroxyproline levels by ≥50% in at least 50% of patients, and by ≥30% in at least 80% of patients. Pamidronate disodium therapy has also been effective in reducing these biochemical markers in patients with Paget's disease who failed to respond, or no longer responded to other treatments.

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

Pamidronate disodium for injection is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The pamidronate disodium treatment effect

	A	P	A	P	A	P	A	P	A	P	A	P
N	185	195	185	195	185	195	182	189	182	189	182	189
Skeletal Morbidity Rate (#SRE/Year) Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-Value	<.001		<.001†		.018†		.021		.013†		.040†	
Proportion of Patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001†		.014†		.094		058†		054†	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3	10.9	7.4	NR**	23.4	20.6	12.8
P-Value	<.001		<.001†		009†		118		.016†		113†	

†Fractures and radiation to bone were two of several secondary endpoints. The statistical significance of these analyses may be overestimated since numerous analyses were performed.
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Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The complete + partial response rate was 33% in pamidronate disodium patients and 18% in placebo patients treated with chemotherapy (P=.001). No difference was seen between pamidronate disodium and placebo in hormonally-treated patients.

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index were measured at baseline and periodically during the trials. The changes from baseline to the last measurement carried forward are shown in the following table:

Mean Change (Δ) from Baseline at Last Measurement

	Breast Cancer Patients Receiving Chemotherapy					Breast Cancer Patients Receiving Hormonal Therapy				
	Pamidronate Disodium for Injection		Placebo		A vs P	Pamidronate Disodium for Injection		Placebo		A vs P
	N	mean Δ	N	Mean Δ	P-Value*	N	Mean Δ	N	Mean Δ	P-Value*
Pain Score	175	+0.93	183	+1.69	050	173	+0.50	179	+1.60	.007
Analgesic Score	175	+0.74	183	+1.55	.009	173	+0.90	179	+2.28	<.001
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INDICATIONS AND USAGE

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Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

Pamidronate disodium for injection is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The pamidronate disodium treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated (see **CLINICAL PHARMACOLOGY, Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma, *Clinical Trials*** section.)

CONTRAINDICATIONS

Pamidronate disodium for injection is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates.

WARNINGS

In both rats and dogs, nephropathy has been associated with intravenous (bolus and infusion) administration of pamidronate disodium.

Two 7-day intravenous infusion studies were conducted in the dog wherein pamidronate disodium was given for 1, 4, or 24 hours at doses of 1-20 mg/kg for up to 7 days. In the first study, the compound was well tolerated at 3 mg/kg (1.7 x highest recommended human dose [HRHD] for a single intravenous infusion) when administered for 4 or 24 hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occurred when 3 mg/kg was infused for 1 hour and at doses of ≥10 mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 hours. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at ≥1 mg/kg after each infusion time.

Pamidronate disodium for injection was given to rats at doses of 2, 6, and 20 mg/kg and to dogs at doses of 2, 4, 6, and 20 mg/kg as a 1-hour infusion, once a week, for 3 months followed by a 1-month recovery period. In rats, nephrotoxicity was observed at ≥6 mg/kg and included increased BUN and creatinine levels and tubular degeneration and necrosis. These findings were still present at 20 mg/kg at the end of the recovery period. In dogs, moribundity/death and renal toxicity occurred at 20 mg/kg as did kidney findings of elevated BUN and creatinine levels at ≥6 mg/kg and renal tubular degeneration at ≥4 mg/kg. The kidney changes were partially reversible at 6 mg/kg. In both studies, the dose level that produced no adverse renal effects was considered to be 2 mg/kg (1.1 x HRHD for a single intravenous infusion).

Patients who receive an intravenous infusion of pamidronate should have periodic evaluations of standard laboratory and clinical parameters of renal function.

Studies conducted in young rats have reported the disruption of dental dentine formation following single- and multi-dose administration of bisphosphonates. The clinical significance of these findings is unknown.

PRECAUTIONS

General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, and potassium, should be carefully monitored following initiation of therapy with pamidronate disodium. Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5%-12%), were reported in pamidronate disodium-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with pamidronate disodium therapy. If hypocalcemia occurs, short-term calcium therapy may be necessary. In Paget's

disease of bone, 17% of patients treated with 90 mg of pamidronate disodium showed serum calcium levels below 8 mg/dL.

Pamidronate disodium for injection has not been tested in patients who have class Dc renal impairment (creatinine >5.0 mg/dL), and in few multiple myeloma patients with serum creatinine ≥3.0 mg/dL. (See also **CLINICAL PHARMACOLOGY, Pharmacokinetics.**) Clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

Laboratory Tests

Serum calcium, electrolytes, phosphate, magnesium and creatinine, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with pamidronate disodium. Patients who have preexisting anemia, leukopenia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment.

Drug Interactions

Concomitant administration of a loop diuretic had no effect on the calcium-lowering action of pamidronate disodium.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study (daily oral administration) in rats, there was a positive dose response relationship for benign adrenal pheochromocytoma in males (P <0.00001). Although this condition was also observed in females, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited oral bioavailability of pamidronate disodium in rats, the lowest daily dose associated with adrenal pheochromocytoma was similar to the intended clinical dose. Adrenal pheochromocytoma was also observed in low numbers in the control animals and is considered a relatively common spontaneous neoplasm in the rat. Pamidronate disodium (daily oral administration) was not carcinogenic in an 80-week study in mice.

Pamidronate disodium for injection was nonmutagenic in six mutagenicity assays: Ames test, *Salmonella* and *Escherichia*/liver-microsome test, nucleus-anomaly test, sister-chromatid-exchange study, point-mutation test, and micronucleus test in the rat.

In rats, decreased fertility occurred in first-generation offspring of parents who had received 150 mg/kg of pamidronate disodium orally; however, this occurred only when animals were mated with members of the same dose group. Pamidronate disodium has not been administered intravenously in such a study.

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

Bolus intravenous studies conducted in rats and rabbits determined that pamidronate disodium 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 disodium can cross the placenta in rats and has produced marked maternal and nonteratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

Nursing Mothers

It is not known whether pamidronate disodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pamidronate disodium is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of pamidronate disodium in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Studies

Hypercalcemia of Malignancy

Transient mild elevation of temperature by at least 1°C was noted 24 to 48 hours after administration of pamidronate disodium in 34% of patients in clinical trials. In the saline trial, 18% of patients had a temperature elevation of at least 1°C 24 to 48 hours after treatment.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (18%) in patients treated with 90 mg of pamidronate disodium. When all on-therapy events are considered, that rate rises to 41%. Symptomatic treatment resulted in rapid resolution in all patients.

Rare cases of uveitis, iritis, scleritis, and episcleritis have been reported, including one case of scleritis, and one case of uveitis upon separate rechallenges.

Four of 128 patients (3%) who received pamidronate disodium during the three U.S. controlled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure.

At least 15% of patients treated with pamidronate disodium for hypercalcemia of malignancy also experienced the following adverse events during a clinical trial:

General: Fluid overload, generalized pain

Cardiovascular: Hypertension

Gastrointestinal: Abdominal pain, anorexia, constipation, nausea, vomiting

Genitourinary: Urinary tract infection

Musculoskeletal: Bone pain

Laboratory abnormality: Anemia, hypokalemia, hypomagnesemia, hypophosphatemia

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

The following table lists the adverse experiences considered to be treatment-related during comparative, controlled U.S. trials.

Treatment-Related Adverse Experiences Reported in Three U.S. Controlled Clinical Trials

	Percent of Patients				
	Pamidronate Disodium			Etidronate	Saline
	60 mg over 4 hr	60 mg over 24 hr	90 mg over 24 hr	7.5mg/kg x 3 days	
	n=23	n=73	n=17	n=35	n=23
General					
Edema	0	1	0	0	0
Fatigue	0	0	12	0	0
Fever	26	19	18	9	0
Fluid overload	0	0	0	6	0
Infusion-site reaction	0	4	18	0	0
Moniliasis	0	0	6	0	0
Rigors	0	0	0	0	4
Gastrointestinal					
Abdominal pain	0	1	0	0	0
Anorexia	4	1	12	0	0
Constipation	4	0	6	3	0
Diarrhea	0	1	0	0	0
Dyspepsia	4	0	0	0	0
Gastrointestinal hemorrhage	0	0	6	0	0
Nausea	4	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	0	0	0	0
Respiratory					
Dyspnea	0	0	0	3	0
Rales	0	0	6	0	0
Rhinitis	0	0	6	0	0
Upper respiratory infection	0	0	0	0	0

Paget's Disease

Transient mild elevation of temperature >1°C above pretreatment in 21% of the patients treated with 90 mg of pamidronate disodi

Drug-related musculoskeletal pain and nervous system sympto more common in patients with Paget's disease treated with 90 r of malignancy treated with the same dose.

Adverse experiences considered to be related to trial drug, whic with 90 mg of pamidronate disodium in two U.S. clinical trials,

At least 10% of all pamidronate disodium-treated patients with P during clinical trials:

Cardiovascular: Hypertension

Musculoskeletal: Arthrosis, bone pain

Nervous system: Headache

Most of these adverse experiences may have been related to the

Osteolytic Bone Metastases of Breast Cancer and Osteolytic L

The most commonly reported (>15%) adverse experiences occ placebo treatment groups, and most of these adverse experience therapy.

Commonly Reported Adverse Experience

	Pamidronate Disodium for Injection 90 mg over 4 hours N=205	Placebo N=187	Pamidro Disodium fo 90 mg over 2 h N=367
	%	%	%
General			
Asthenia	16.1	17.1	25.6
Fatigue	31.7	28.3	40.3
Fever	38.5	38.0	38.1
Metastases	1.0	3.0	31.3
Pain	13.2	11.8	15.0
DigestiveSystem			
Anorexia	17.1	17.1	31.1
Constipation	28.3	31.7	36.0
Diarrhea	26.8	26.8	29.4
Dyspepsia	17.6	13.4	18.3
Nausea	35.6	37.4	63.5
Pain Abdominal	19.5	16.0	24.3
Vomiting	16.6	19.8	46.3
Hemic and Lymphatic			
Anemia	47.8	41.7	39.5
Granulocytopenia	20.5	15.5	19.3
Thrombocytopenia	16.6	17.1	12.5
MusculoskeletalSystem			
Arthralgias	10.7	7.0	15.3
Myalgia	25.4	15.0	26.4
Skeletal Pain	61.0	71.7	70.0
CNS			
Anxiety	7.8	9.1	18.0
Headache	24.4	19.8	27.2
Insomnia	17.1	7.2	25.1
Respiratory System			
Coughing	26.3	22.5	25.3
Dyspnea	22.0	21.4	35.1
Pleural Effusion	2.9	4.3	15.0
Sinusitis	14.6	16.6	16.1
Upper Respiroatory Tract Infection	32.2	28.3	19.6
Urogenital System			
Urinary tract Infection	15.6	9.1	20.2

Of the toxicities commonly associated with chemotherapy, the f common in the pamidronate disodium patients whereas stomatiti patients. In the breast cancer trials, mild elevations of serum cre 12.3% of placebo patients. Mineral and electrolyte disturbance percentages of pamidronate disodium-treated patients compare hypocalcemia, hypokalemia, hypophosphatemia, and hypomagn 10.5% 1.7%, and 4.4%, respectively, and for placebo-treated pat hypercalcemia of malignancy trials, patients treated with pamidro abnormalities more frequently (see **ADVERSE REACTIONS**, Hype

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Post-Marketing Experience

Rare instances of allergic manifestations have been reported, in anaphylactic shock. Pamidronate disodium is contraindicated in p disodium or other bisphosphonates (see **CONTRAINDICATIONS**).

OVERDOSAGE

There have been several cases of drug maladministration of intr total doses of 225 mg to 300 mg given over 2 1/2 to 4 days. All that required intravenous and/or oral administration of calcium.

In addition, one obese woman (95 kg) who was treated with 28

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Fatigue	0	0	12	0	0
Fever	26	19	18	9	0
Fluid overload	0	0	0	6	0
Infusion-site reaction	0	4	18	0	0
Moniliasis	0	0	6	0	0
Rigors	0	0	0	0	4
Gastrointestinal					
Abdominal pain	0	1	0	0	0
Anorexia	4	1	12	0	0
Constipation	4	0	6	3	0
Diarrhea	0	1	0	0	0
Dyspepsia	4	0	0	0	0
Gastrointestinal hemorrhage	0	0	6	0	0
Nausea	4	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	0	0	0	0
Respiratory					
Dyspnea	0	0	0	3	0
Rales	0	0	6	0	0
Rhinitis	0	0	6	0	0
Upper respiratory infection	0	3	0	0	0
CNS					
Anxiety	0	0	0	0	4
Convulsions	0	0	0	3	0
Insomnia	0	1	0	0	0
Nervousness	0	0	0	0	4
Psychosis	4	0	0	0	0
Somnolence	0	1	6	0	0
Taste perversion	0	0	0	3	0
Cardiovascular					
Atrial fibrillation	0	0	6	0	4
Atrial flutter	0	1	0	0	0
Cardiac failure	0	1	0	0	0
Hypertension	0	0	6	0	4
Syncope	0	0	6	0	0
Tachycardia	0	0	6	0	4
Endocrine					
Hypothyroidism	0	0	6	0	0
Hemic and Lymphatic					
Anemia	0	0	6	0	0
Leukopenia	4	0	0	0	0
Neutropenia	0	1	0	0	0
Thrombocytopenia	0	1	0	0	0
Musculoskeletal					
Myalgia	0	1	0	0	0
Urogenital					
Uremia	4	0	0	0	0
Laboratory Abnormalities					
Hypocalcemia	0	1	12	0	0
Hypokalemia	4	4	18	0	0
Hypomagnesemia	4	10	12	3	4
Hypophosphatemia	0	9	18	3	0
Abnormal liver function	0	0	0	3	0
Anorexia	17.1	17.1	31.1		
Constipation	28.3	31.7	36.0		
Diarrhea	26.8	26.8	29.4		
Dyspepsia	17.6	13.4	18.3		
Nausea	35.6	37.4	63.5		
Pain Abdominal	19.5	16.0	24.3		
Vomiting	16.6	19.8	46.3		
Hemic and Lymphatic					
Anemia	47.8	41.7	39.5		
Granulocytopenia	20.5	15.5	19.3		
Thrombocytopenia	16.6	17.1	12.5		
MusculoskeletalSystem					
Arthralgias	10.7	7.0	15.3		
Myalgia	25.4	15.0	26.4		
Skeletal Pain	61.0	71.7	70.0		
CNS					
Anxiety	7.8	9.1	18.0		
Headache	24.4	19.8	27.2		
Insomnia	17.1	7.2	25.1		
Respiratory System					
Coughing	26.3	22.5	25.3		
Dyspnea	22.0	21.4	35.1		
Pleural Effusion	2.9	4.3	15.0		
Sinusitis	14.6	16.6	16.1		
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Urogenital System					
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In addition, one obese woman (95 kg) who was treated with 285 m fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), first infusion. The fever and hypotension were rapidly corrected with

If overdosage occurs, symptomatic hypocalcemia could also result; calcium.

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

Consideration should be given to the severity of as well as the symp be sufficient for treating mild, asymptomatic hypercalcemia. Overhy cardiac failure. In hypercalcemia associated with hematologic malign

Moderate Hypercalcemia

The recommended dose of pamidronate disodium in moderate hy 12-13.5 mg/dL) is 60 to 90 mg. The 60-mg dose is given as an i hours. The 90-mg dose must be given by an initial, SINGLE-DOSE

Severe Hypercalcemia

The recommended dose of pamidronate disodium in severe hyperc The 90-mg dose must be given by an initial, SINGLE-DOSE, intrav

*Albumin-corrected serum calcium (CCa,mg/dL) = serum calcium, n

Retreatment

A limited number of patients have received more than one treatment with pamidronate disodium, in patients who show complete or partia not return to normal or remain normal after initial treatment. **It is retreatment, to allow for full response to the initial dose.** The dos therapy.

Paget's Disease

The recommended dose of pamidronate disodium in patients with r administered as a 4-hour infusion on 3 consecutive days for a tota

Retreatment

A limited number of patients with Paget's disease have received more When clinically indicated, patients should be retreated at the dose of

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of pamidronate disodium in patients wit administered as a 4-hour infusion given on a monthly basis.

um calcium levels below 8 mg/dL.

al impairment (creatinine >5.0 mg/dL), also **CLINICAL PHARMACOLOGY**, ighs the potential risk in such patients.

, and hematocrit/hemoglobin must be e preexisting anemia, leukopenia, or

of pamidronate disodium.

dose response relationship for benign rved in females, the incidence was not ted oral bioavailability of pamidronate similar to the intended clinical dose. nd is considered a relatively common ot carcinogenic in an 80-week study in

test, *Salmonella* and *Escherichia*/liver- st, and micronucleus test in the rat.

d 150 mg/kg of pamidronate disodium ose group. Pamidronate disodium has

odium produces maternal toxicity and ghest recommended human dose for a the placenta in rats and has produced be given to women during pregnancy.

ny drugs are excreted in human milk, nan.

olished.

inistration of pamidronate disodium in ion of at least 1°C 24 to 48 hours after

ation) at the site of catheter insertion all on-therapy events are considered,

se of scleritis, and one case of uveitis

led hypercalcemia clinical studies were seizures were considered to be drug- ccurrence of seizures cannot be ruled

nancy also experienced the following

comparative, controlled U.S. trials.
e U.S.

Etidronate 7.5mg/kg x 3 days n=35	Saline n=23
0	0
0	0
9	0
6	0
0	0
0	0
0	4
0	0
0	0
3	0
0	0
0	0
0	0
6	0
3	0
0	0
3	0
0	0
0	0

Paget's Disease

Transient mild elevation of temperature >1°C above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of pamidronate disodium in clinical trials.

Drug-related musculoskeletal pain and nervous system symptoms (dizziness, headache, paresthesia, increased sweating) were more common in patients with Paget's disease treated with 90 mg of pamidronate disodium than in patients with hypercalcemia of malignancy treated with the same dose.

Adverse experiences considered to be related to trial drug, which occurred in at least 5% of patients with Paget's disease treated with 90 mg of pamidronate disodium in two U.S. clinical trials, were fever, nausea, back pain, and bone pain.

At least 10% of all pamidronate disodium-treated patients with Paget's disease also experienced the following adverse experiences during clinical trials:

Cardiovascular: Hypertension

Musculoskeletal: Arthrosis, bone pain

Nervous system: Headache

Most of these adverse experiences may have been related to the underlying disease state.

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

The most commonly reported (>15%) adverse experiences occurred with similar frequencies in the pamidronate disodium and placebo treatment groups, and most of these adverse experiences may have been related to the underlying disease state or cancer therapy.

Commonly Reported Adverse Experiences in Three U.S. Controlled Clinical Trials

	Pamidronate Disodium for Injection 90 mg over 4 hours N=205	Placebo N=187	Pamidronate Disodium for Injection 90 mg over 2 hours N=367	All Pamidronate Disodium for Injection Placebo N=386	90 mg N=572	Placebo N=573
	%	%	%	%	%	%
General						
Asthenia	16.1	17.1	25.6	19.2	22.2	18.5
Fatigue	31.7	28.3	40.3	28.8	37.2	29.0
Fever	38.5	38.0	38.1	32.1	38.5	34.0
Metastases	1.0	3.0	31.3	24.4	20.5	17.5
Pain	13.2	11.8	15.0	18.1	14.3	16.1
DigestiveSystem						
Anorexia	17.1	17.1	31.1	24.9	26.0	22.3
Constipation	28.3	31.7	36.0	38.6	33.2	35.1
Diarrhea	26.8	26.8	29.4	30.6	28.5	29.7
Dyspepsia	17.6	13.4	18.3	15.0	22.6	17.5
Nausea	35.6	37.4	63.5	59.1	53.5	51.8
Pain Abdominal	19.5	16.0	24.3	18.1	22.6	17.5
Vomiting	16.6	19.8	46.3	39.1	35.7	32.8
Hemic and Lymphatic						
Anemia	47.8	41.7	39.5	36.8	42.5	38.4
Granulocytopenia	20.5	15.5	19.3	20.5	19.8	18.8
Thrombocytopenia	16.6	17.1	12.5	14.0	14.0	15.0
MusculoskeletalSystem						
Arthralgias	10.7	7.0	15.3	12.7	13.6	10.8
Myalgia	25.4	15.0	26.4	22.5	26.0	20.1
Skeletal Pain	61.0	71.7	70.0	75.4	66.8	74.0
CNS						
Anxiety	7.8	9.1	18.0	16.8	14.3	14.3
Headache	24.4	19.8	27.2	23.6	26.2	22.3
Insomnia	17.1	7.2	25.1	19.4	22.2	19.0
Respiratory System						
Coughing	26.3	22.5	25.3	19.7	25.7	20.6
Dyspnea	22.0	21.4	35.1	24.4	30.4	23.4
Pleural Effusion	2.9	4.3	15.0	9.1	10.7	7.5
Sinusitis	14.6	16.6	16.1	10.4	15.6	12.0
Upper Respiroatory Tract Infection	32.2	28.3	19.6	20.2	24.1	22.9
Urogenital System						
Urinary tract Infection	15.6	9.1	20.2	17.6	18.5	15.6

Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia, and anemia were slightly more common in the pamidronate disodium patients whereas stomatitis and alopecia occurred at a frequency similar to that in placebo patients. In the breast cancer trials, mild elevations of serum creatinine occurred in 18.5% of pamidronate disodium patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of pamidronate disodium-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for pamidronate disodium-treated patients were 3.3%, 10.5% 1.7%, and 4.4%, respectively, and for placebo-treated patients were 1.2%, 12%, 1.7%, and 4.5% respectively. In previous hypercalcemia of malignancy trials, patients treated with pamidronate disodium (60 or 90 mg over 24 hours) developed electrolyte abnormalities more frequently (see **ADVERSE REACTIONS**, Hypercalcemia of Malignancy).

Arthralgias and myalgias were reported slightly more frequently in the pamidronate disodium group than in the placebo group (13.6% and 26% vs 10.8% and 20.1%, respectively).

In multiple myeloma patients, there were five pamidronate disodium-related serious and unexpected adverse experiences. Four of these were reported during the 12-month extension of the multiple myeloma trial. Three of the reports were of worsening renal function developing in patients with progressive multiple myeloma or multiple myeloma-associated amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a patient recovering from pneumonia and acute gangrenous cholecystitis. One pamidronate disodium-treated patient experienced an allergic reaction characterized by swollen and itchy eyes, runny nose, and scratchy throat within 24 hours after the sixth infusion.

In the breast cancer trials, there were four pamidronate disodium-related adverse experiences, all moderate in severity, that caused a patient to discontinue participation in the trial. One was due to interstitial pneumonitis, another to malaise and dyspnea. One pamidronate disodium patient discontinued the trial due to a symptomatic hypocalcemia. Another pamidronate disodium patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

Post-Marketing Experience

Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and, very rarely, anaphylactic shock. Pamidronate disodium is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates (see **CONTRAINDICATIONS**).

OVERDOSAGE

There have been several cases of drug maladministration of intravenous pamidronate disodium in hypercalcemia patients with total doses of 225 mg to 300 mg given over 2 1/2 to 4 days. All of these patients survived, but they experienced hypocalcemia that required intravenous and/or oral administration of calcium.

In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium/day for 3 days experienced high fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), and transient taste perversion, noted about 6 hours after the

Patients with marked Bence infusion.

Limited information is avai ≥3.0 mg/dL.

The optimal duration of the demonstrated overall benefi

Osteolytic Bone Metastase

The recommended dose of 2-hour infusion given ever

Pamidronate disodium for i mitoxantrone, vinblastine, d frequently with etoposide, c however, in two breast can **CLINICAL TRIALS** section).

Preparation of Solution

Reconstitution

Pamidronate disodium for i a solution of 30 mg/10 mL dissolved before the solutio

Hypercalcemia of Maligna

The daily dose must be adn the 90-mg dose. The recon Dextrose Injection, USP. Thi

Paget's Disease

The recommended daily dc Dextrose Injection, USP, an

Osteolytic Bone Metastase

The recommended dose of injection, USP, and adminis

Osteolytic Bone Lesions o

The recommended dose of Injection, USP, and adminis

Pamidronate disodium for and should be given in a s

***Note*: Parenteral drug prod whenever solution and con**

Pamidronate disodium for i 46°F) for up to 24 hours.

HOW SUPPLIED

Pamidronate Disodium for

NDC	
0703-**4375-01**	
0703-**4375-09**	
0703-**4385-01**	

Do not store above 30°C (8

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Irvine CA 92618

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U.S.

Etidronate 7.5mg/kg x 3 days n=35	Saline n=23
0	0
0	0
9	0
6	0
0	0
0	0
0	4
0	0
0	0
3	0
0	0
0	0
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6	0
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3	4
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3	0

Constipation	28.3	31.7	36.0	38.6	33.2	35.1
Diarrhea	26.8	26.8	29.4	30.6	28.5	29.7
Dyspepsia	17.6	13.4	18.3	15.0	22.6	17.5
Nausea	35.6	37.4	63.5	59.1	53.5	51.8
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MusculoskeletalSystem						
Arthralgias	10.7	7.0	15.3	12.7	13.6	10.8
Myalgia	25.4	15.0	26.4	22.5	26.0	20.1
Skeletal Pain	61.0	71.7	70.0	75.4	66.8	74.0
CNS						
Anxiety	7.8	9.1	18.0	16.8	14.3	14.3
Headache	24.4	19.8	27.2	23.6	26.2	22.3
Insomnia	17.1	7.2	25.1	19.4	22.2	19.0
Respiratory System						
Coughing	26.3	22.5	25.3	19.7	25.7	20.6
Dyspnea	22.0	21.4	35.1	24.4	30.4	23.4
Pleural Effusion	2.9	4.3	15.0	9.1	10.7	7.5
Sinusitis	14.6	16.6	16.1	10.4	15.6	12.0
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Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia, and anemia were slightly more common in the pamidronate disodium patients whereas stomatitis and alopecia occurred at a frequency similar to that in placebo patients. In the breast cancer trials, mild elevations of serum creatinine occurred in 18.5% of pamidronate disodium patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of pamidronate disodium-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for pamidronate disodium-treated patients were 3.3%, 10.5% 1.7%, and 4.4%, respectively, and for placebo-treated patients were 1.2%, 12%, 1.7%, and 4.5% respectively. In previous hypercalcemia of malignancy trials, patients treated with pamidronate disodium (60 or 90 mg over 24 hours) developed electrolyte abnormalities more frequently (see **ADVERSE REACTIONS**, Hypercalcemia of Malignancy).

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In multiple myeloma patients, there were five pamidronate disodium-related serious and unexpected adverse experiences. Four of these were reported during the 12-month extension of the multiple myeloma trial. Three of the reports were of worsening renal function developing in patients with progressive multiple myeloma or multiple myeloma-associated amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a patient recovering from pneumonia and acute gangrenous cholecystitis. One pamidronate disodium-treated patient experienced an allergic reaction characterized by swollen and itchy eyes, runny nose, and scratchy throat within 24 hours after the sixth infusion.

In the breast cancer trials, there were four pamidronate disodium-related adverse experiences, all moderate in severity, that caused a patient to discontinue participation in the trial. One was due to interstitial pneumonitis, another to malaise and dyspnea. One pamidronate disodium patient discontinued the trial due to a symptomatic hypocalcemia. Another pamidronate disodium patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

Post-Marketing Experience

Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and, very rarely, anaphylactic shock. Pamidronate disodium is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates (see **CONTRAINDICATIONS**).

OVERDOSAGE

There have been several cases of drug maladministration of intravenous pamidronate disodium in hypercalcemia patients with total doses of 225 mg to 300 mg given over 2 1/2 to 4 days. All of these patients survived, but they experienced hypocalcemia that required intravenous and/or oral administration of calcium.

In addition, one obese woman (95 kg) who was treated with 285 mg of pamidronate disodium/day for 3 days experienced high fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), and transient taste perversion, noted about 6 hours after the first infusion. The fever and hypotension were rapidly corrected with steroids.

If overdosage occurs, symptomatic hypocalcemia could also result; such patients should be treated with short-term intravenous calcium.

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. Vigorous saline hydration alone may be sufficient for treating mild, asymptomatic hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. In hypercalcemia associated with hematologic malignancies, the use of glucocorticoid therapy may be helpful.

Moderate Hypercalcemia

The recommended dose of pamidronate disodium in moderate hypercalcemia (corrected serum calcium* of approximately 12-13.5 mg/dL) is 60 to 90 mg. The 60-mg dose is given as an initial, SINGLE-DOSE, intravenous infusion over at least 4 hours. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

Severe Hypercalcemia

The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum calcium*>13.5 mg/dL) is 90 mg. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

*Albumin-corrected serum calcium (CCa,mg/dL) = serum calcium, mg/dL + 0.8 (4.0-serum albumin, g/dL).

Retreatment

A limited number of patients have received more than one treatment with pamidronate disodium for hypercalcemia. Retreatment with pamidronate disodium, in patients who show complete or partial response initially, may be carried out if serum calcium does not return to normal or remain normal after initial treatment. **It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.** The dose and manner of retreatment is identical to that of the initial therapy.

Paget's Disease

The recommended dose of pamidronate disodium in patients with moderate to severe Paget's disease of bone is 30 mg daily, administered as a 4-hour infusion on 3 consecutive days for a total dose of 90 mg.

Retreatment

A limited number of patients with Paget's disease have received more than one treatment of pamidronate disodium in clinical trials. When clinically indicated, patients should be retreated at the dose of initial therapy.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of pamidronate disodium in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4-hour infusion given on a monthly basis.

and should be given in a sing

***Note*: Parenteral drug produc**
whenever solution and contai

Pamidronate disodium for inje
46°F) for up to 24 hours.

HOW SUPPLIED

Pamidronate Disodium for Inj

NDC	STI
0703-**4375-01**	30
0703-**4375-09**	30
0703-**4385-01**	90

Do not store above 30°C (86°

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in Three U.S. Controlled Clinical Trials

ɪte
ɲjection

rs	All Pamidronate Disodium for Injection		
	Placebo N=386 %	90 mg N=572 %	Placebo N=573 %
	19.2	22.2	18.5
	28.8	37.2	29.0
	32.1	38.5	34.0
	24.4	20.5	17.5
	18.1	14.3	16.1
	24.9	26.0	22.3
	38.6	33.2	35.1
	30.6	28.5	29.7
	15.0	22.6	17.5
	59.1	53.5	51.8
	18.1	22.6	17.5
	39.1	35.7	32.8
	36.8	42.5	38.4
	20.5	19.8	18.8
	14.0	14.0	15.0
	12.7	13.6	10.8
	22.5	26.0	20.1
	75.4	66.8	74.0
	16.8	14.3	14.3
	23.6	26.2	22.3
	19.4	22.2	19.0
	19.7	25.7	20.6
	24.4	30.4	23.4
	9.1	10.7	7.5
	10.4	15.6	12.0
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and transient taste perversion, noted about 6 hours after the

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to pamidronate disodium infusion.

Limited information is available on the use of pamidronate disodium in multiple myeloma patients with a serum creatinine ≥3.0 mg/dL.

The optimal duration of therapy is not yet known, however, in a study of patients with myeloma, final analysis after 21 months demonstrated overall benefit (see **CLINICAL TRIALS** section).

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of pamidronate disodium in patients with osteolytic bone metastases is 90 mg administered over a 2-hour infusion given every 3-4 weeks.

Pamidronate disodium for injection has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotrexate, mitoxantrone, vinblastine, dexamethasone, prednisone, melphalan, vincristine, megesterol, and tamoxifen. It has been given less frequently with etoposide, cisplatin, cytarabine, paclitaxel, and aminoglutethimide. The optimal duration of therapy is not known, however, in two breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefit (see **CLINICAL TRIALS** section).

Preparation of Solution

Reconstitution

Pamidronate disodium for injection is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each vial, resulting in a solution of 30 mg/10 mL or 90 mg/10 mL. The pH of the reconstituted solution is 6.0 -7.4. The drug should be completely dissolved before the solution is withdrawn.

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 4 hours for the 60-mg dose, and over 24 hours for the 90-mg dose. The recommended dose should be diluted in 1000 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. This infusion solution is stable for up to 24 hours at room temperature.

Paget's Disease

The recommended daily dose of 30 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, and administered over a 4-hour period for 3 consecutive days.

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of 90 mg should be diluted in 250 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose injection, USP, and administered over a 2-hour period every 3-4 weeks.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, and administered over a 4-hour period on a monthly basis.

Pamidronate disodium for injection must not be mixed with calcium-containing infusion solutions, such as Ringer's solution, and should be given in a single intravenous solution and line separate from all other drugs.

***Note*: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

Pamidronate disodium for injection reconstituted with Sterile Water for Injection may be stored under refrigeration at 2°-8°C (36°-46°F) for up to 24 hours.

HOW SUPPLIED

Pamidronate Disodium for Injection is available as follows:

NDC	STRENGTH	SIZE
0703-**4375-01**	30 mg per vial	10 mL - individually packaged.
0703-**4375-09**	30 mg per vial	10 mL - in 4 vials per package.
0703-**4385-01**	90 mg per vial	10 mL - individually packaged.

Do not store above 30°C (86°F).

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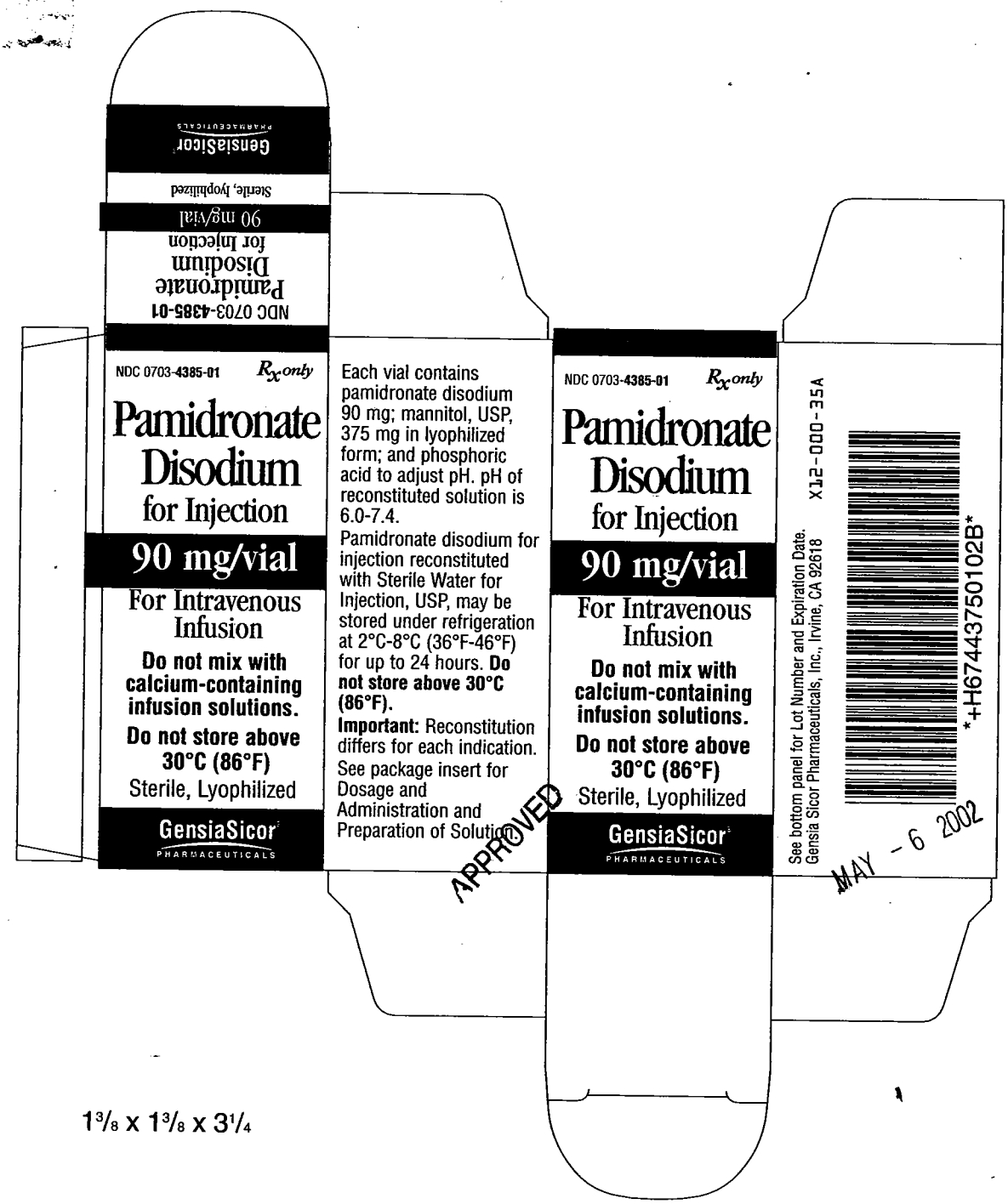
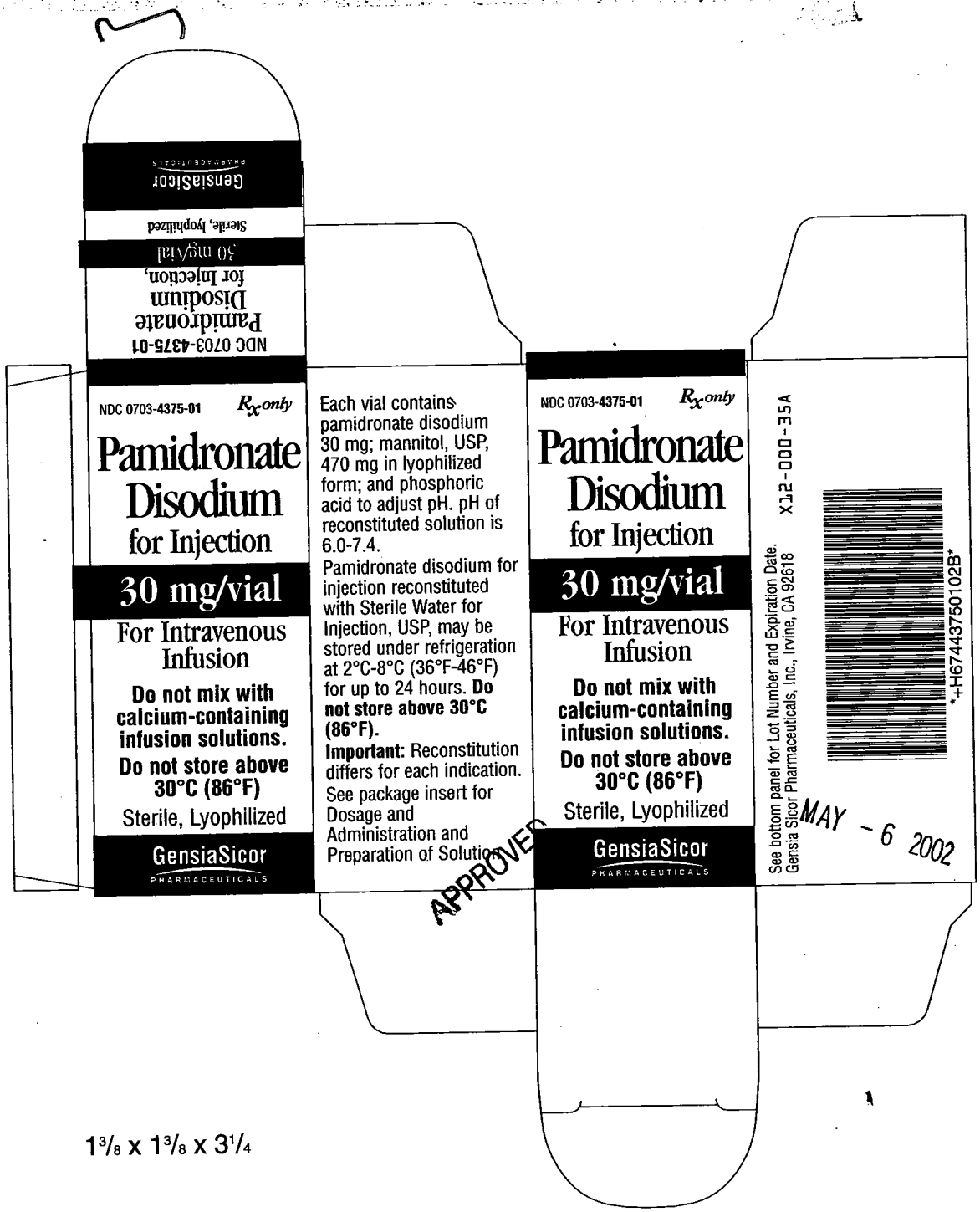
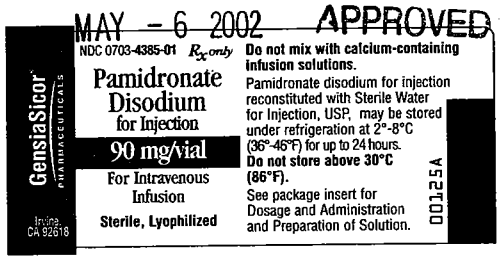
Irvine CA 92618
Issued: November 2000


GensiaSicor PHARMACEUTICALS
Sterile, lyophilized
90 mg/vial
for Injection
Pamidronate Disodium
NDC 0703-4385-01
NDC 0703-4385-01 Rx only
Pamidronate Disodium
for Injection
90 mg/vial
For Intravenous Infusion
Do not mix with calcium-containing infusion solutions.
Do not store above 30°C (86°F)
Sterile, Lyophilized
GensiaSicor PHARMACEUTICALS
Each vial contains pamidronate disodium 90 mg; mannitol, USP, 375 mg in lyophilized form; and phosphoric acid to adjust pH. pH of reconstituted solution is 6.0-7.4.
Pamidronate disodium for injection reconstituted with Sterile Water for Injection, USP, may be stored under refrigeration at 2°C-8°C (36°F-46°F) for up to 24 hours. Do not store above 30°C (86°F).
Important: Reconstitution differs for each indication. See package insert for Dosage and Administration and Preparation of Solution.
APPROVED
MAY - 6 2002
NDC 0703-4385-01 Rx only
Pamidronate Disodium
for Injection
90 mg/vial
For Intravenous Infusion
Do not mix with calcium-containing infusion solutions.
Do not store above 30°C (86°F)
Sterile, Lyophilized
GensiaSicor PHARMACEUTICALS
X12-000-35A
See bottom panel for Lot Number and Expiration Date.
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618
+H67443750102B
1 3/8 x 1 3/8 x 3 1/4



$1\frac{3}{8}$ x $1\frac{3}{8}$ x $3\frac{1}{4}$

Container Label
90 mg/vial
(Part No. 00125A)



100040

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-594

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
2 Research Way
Third Level East
Princeton, NJ 08540

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that U.S. Patent No. 4,711,880 will not Be infringed by the manufacture, use, or sale of Aesgen, Inc. Pamidronate Disodium for injection, 30 mg/vial, for which this ANDA is submitted under paragraph IV certification.

5. SUPPLEMENT(s)

Original 2/17/99
Accepted 4/5/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 4/1/99
Amendment 4/21/99

10. PHARMACOLOGICAL CATEGORY

Treatment of moderate or severe hypercalcemia associated with malignancy.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

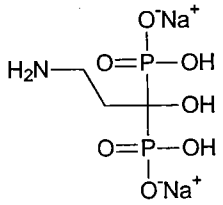
Lyophilized cake for suspension

14. POTENCY

30 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. $C_3H_9NNa_2O_7P_2$. 109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS

The firm will be asked to submit certificate of analysis for the including methods and limits.

The firm will be asked to revise their specifications for finished drug product to include limits for individual impurities and tight the limit for total related compounds.

The firm will be asked to revise their specifications for finished drug product to include limits for

The firm will be asked to revise their stability specifications to include limits for individual impurities and tight total limit

The firm will be asked to revise their stability specifications to include limit for

The firm will be asked to clarify the difference in related substance p. 451 and p.558 for the finished product release and stability.

The DMF is deficient. The DMF holder has been notified. Please do not respond to this amendment until you have been notified by the DMF holder that the DMF deficiencies have been addressed.

The firm will be asked to provide complete method validation for nd its related compounds in the drug substance and the finished drug product.

The firm will be asked to provide information regarding the reference standard and submit certificate of analysis.

The firm will be asked to provide limits for Bacterial Endotoxin for the finished drug product and stability.

The firm will be asked to provide 24 hour data for reconstituted drug product.

The firm will be asked to revise their stability commitment to indicate that extending the expiration date requires full

term data on 3 production batches.

The firm will be asked to submit their stability data in one table.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 9/10/99

Supervisor: Paul Schwartz, Ph.D./10/4/99

V:\FIRMSAM\AESGEN\LTRS&REV\75-594.1.DOC

Redacted 11

pages of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-594

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
2 Research Way
Third Level East
Princeton, NJ 08540

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that U.S. Patent No. 4,711,880 will not Be infringed by the manufacture, use, or sale of Aesgen, Inc. Pamidronate Disodium for injection, 30 mg/vial, for which this ANDA is submitted under paragraph IV certification.

5. SUPPLEMENT(s)

Original 2/17/99
Accepted 4/5/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 4/1/99
Amendment 4/21/99
Amendment 1/19/00
Amendment 4/17/00 - Microbiology

10. PHARMACOLOGICAL CATEGORY

Treatment of moderate or severe hypercalcemia associated with malignancy.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

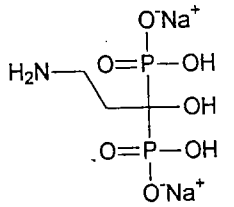
Lyophilized cake for suspension

14. POTENCY

30 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. $C_3H_9NNa_2O_7P_2$. [redacted]. 109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS

We do not agree, [redacted] should be tested in the drug product and stability.

The firm will be asked to provide methods for determination of the [redacted]

The firm will be asked to provide current stability data including tests result for [redacted]

The firm will be asked to revise their specifications for [redacted] to include limits for unknown and total impurities, heavy metals, pH, OVI'S or statement not used in the synthesis, and microbial limits.

The firm will be asked to revise their in-process controls specifications to include limit for [redacted]

The firm will be asked to provide method validation for the drug substance and related impurities.

The firm will be asked to provide all available room temperature stability data including test results for [redacted]

The firm will be asked to provide admixture study.

The firm will be asked to revise their stability specifications regarding the assay to tighten the limits to [redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 6/12/00

Supervisor: Paul Schwartz, Ph.D. 6/20/00

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pages of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-594

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
2 Research Way
Third Level East
Princeton, NJ 08540

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that U.S. Patent No. 4,711,880 will not Be infringed by the manufacture, use, or sale of Aesgen, Inc. Pamidronate Disodium for injection, 30 mg/vial, for which this ANDA is submitted under paragraph IV certification. They need to certify for the 90 mg/vial.

5. SUPPLEMENT(s)

Original 2/17/99
Accepted 4/5/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 4/1/99
Amendment 4/21/99
Amendment 1/19/00
Amendment 4/17/00 - Microbiology
Amendment 12/22/00, 3/30/01-new site, new strength

10. PHARMACOLOGICAL CATEGORY

Treatment of moderate or severe hypercalcemia associated with malignancy.

11. Rx or OTC

Rx

13. DOSAGE FORM

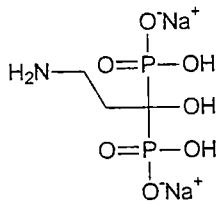
Lyophilized cake for suspension

14. POTENCY

30 mg/vial and
90 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. $C_3H_9NNa_2O_7P_2$. 109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS

An additional product strength of 90 mg/Vial is being submitted to the current pending application.

The microbiology portion is satisfactory 5/16/01

The firm will be asked to provide a components and composition statement.

You do not indicate that [redacted] yet your batch records show that it was used to [redacted] This is unacceptable.
Please revise your manufacturing records to delete the steps that call for [redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 5/29/01

Supervisor: Paul Schwartz, Ph.D. 6/5/01

cc: ANDA 75-594
Dup
Division File
Field Copy
Endorsements:
HFD-623/NNashed/
HFD-623/PSchwartz/
V:\FIRMSAM\AESGEN\LTRS&REV\75-594.3.DOC
F/T by: DJ 6/8/01

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1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-594

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
2 Research Way
Third Level East
Princeton, NJ 08540

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that U.S. Patent No. 4,711,880 will not Be infringed by the manufacture, use, or sale of Aesgen, Inc. Pamidronate Disodium for injection, 30 mg/vial, for which this ANDA is submitted under paragraph IV certification.

5. SUPPLEMENT(s)

Original 2/17/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

*denotes subjects covered in the review
Amendment 4/1/99
Amendment 4/21/99
Amendment 1/19/00
Amendment 4/17/00 - Microbiology
Amendment 12/22/00, 3/30/01-new site, new strength
*Amendment 6/21/01
*Amendment 7/10/01 - Patent
*Amendment 8/1/01 - Telephone
*Amendment 8/13/01 - Patent
*Amendment 8/16/01 - Telephone
*Amendment 8/22/01 - Telephone
*Amendment 8/23/01 - Telephone
*Amendment 9/27/01 - Exclusivity statement

10. PHARMACOLOGICAL CATEGORY

Treatment of moderate or severe hypercalcemia associated with malignancy.

11. Rx or OTC

Rx

13. DOSAGE FORM

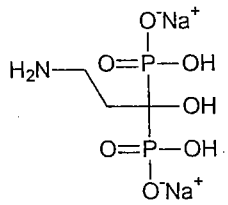
Lyophilized cake for suspension

14. POTENCY

30 mg/vial and
90 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. $C_3H_9NNa_2O_7P_2$. 109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS

The firm's response to the deficiencies cited in the NA letter of 06/18/01 was reviewed. Subsequently, four telephone amendments (CMC) were requested, and reviewed. All CMC issues have been resolved.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable Pending acceptable method validation.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 11/20/01 10/3/01

Supervisor: James M. Fan 10/5/01

cc: ANDA 75-594
Division File

Endorsements:
HFD-600/N.Nashed/ 11/20/01
HFD-625/J.Fan/ 11/20/01

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1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-594

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
2 Research Way
Third Level East
Princeton, NJ 08540

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that U.S. Patent No. 4,711,880 will not Be infringed by the manufacture, use, or sale of Aesgen, Inc. Pamidronate Disodium for injection, 30 mg/vial, for which this ANDA is submitted under paragraph IV certification.

5. SUPPLEMENT(s)

Original 2/17/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

*denotes subjects covered in the review
Amendment 4/1/99
Amendment 4/21/99
Amendment 1/19/00
Amendment 4/17/00 - Microbiology
Amendment 12/22/00, 3/30/01-new site, new strength
Amendment 6/21/01
Amendment 7/10/01 - Patent
Amendment 8/1/01 - Telephone
Amendment 8/13/01 - Patent
Amendment 8/16/01 - Telephone
Amendment 8/22/01 - Telephone
Amendment 8/23/01 - Telephone
Amendment 9/27/01 - Exclusivity statement
*Amendment 2/26/02 - Request for Final Approval
Correspondence 4/1/02 - MV commitment

10. PHARMACOLOGICAL CATEGORY

Treatment of moderate or severe hypercalcemia associated with malignancy.

11. Rx or OTC

Rx

13. DOSAGE FORM

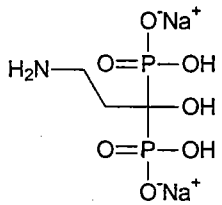
Lyophilized cake for suspension

14. POTENCY

30 mg/vial and
90 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. $C_3H_9NNa_2O_7P_2$. 109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS

[redacted]

No other changes have been made since the tentative approval (11/28/01).

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable Pending acceptable method validation.

19. REVIEWER: /S/ DATE COMPLETED: 4/5/02

Nashed E. Nashed, Ph.D. 3/12/02

/S/ 4/2/02

Supervisor: James M. Fan 3/17/02

cc: ANDA 40-414
Dup
Division File
Field Copy

Endorsements:
HFD-627/NNashed 4/5/02
HFD-627/JFan/ 4/2/02

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F/T by: DJ 4/4/02

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
June 27, 2000

A. 1. ANDA 75-594

APPLICANT Aesgen Inc.

2. PRODUCT NAME: Pamidronate Disodium for Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 30-mg/vial as Lyophilized powder for I/V use

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

B. 1. DATE OF INITIAL SUBMISSION: February 17, 1999 > Refusal to file
Subject of this Review (Received March 4, 1999)
Resubmitted amendment April 1, 1999 (Received 4/5/99) /S/ 4/14/00

2. DATE OF AMENDMENT: Gratuitous amendment April 17, 2000.
Subject of this Review (Received April 18, 2000)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: June 19, 2000

C. REMARKS: The subject drug product was manufactured by [redacted] for Aesgen Inc. The subject drug was [redacted]

Gratuitous amendment April 17, 2000 was reviewed for the [redacted] validation.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant" found at the end of this review. The deficiencies represent minor amendment.

/S/
Nrapendra Nath, Ph. D.

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75594.doc
Initialed by A. High

AH 7/10/00

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DO NOT PROCESS

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Preliminary Review #1
April 19, 2000

A. 1. ANDA: **75-594**

APPLICANT: Aesgen, Inc
Attention: Chris L. French
2 Research Way, Third Level East
Princeton, NJ 08540

2. PRODUCT NAMES: **Pamidronate Disodium for Inj 30mg/vial**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile lyophilized cake for intravenous infusion

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Bone-resorption inhibitor

B. 1. DATE OF INITIAL SUBMISSION: ~~June, 1999~~ Feb 17, 1999
Subject of this Review (Received June 24, 1999)

2. DATE OF AMENDMENT: April 21, 1999
3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW:

C. REMARKS: The application was filed (i.e., received) without data is an essential component of the sterility assurance review.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Failure to provide these data is grounds for a **major** action. The sponsor has been notified.

/S/

4-19-00
Joseph Buccine, Project Manager

CSO 4/19/00

cc: Original ANDA
Duplicate ANDA
Initialed by A. High

v:microrev\75594pr1

Microbiology Comments to be Provided to the Applicant

ANDA #: 75-594 **APPLICANT: Aesgen, Inc**

DRUG PRODUCT: Pamidronate Disodium for Inj 30 mg/vial

Microbiology Deficiency:

Please refer to the *Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Products, November 1994* and provide the following:

[redacted]

used for the subject [redacted]

Please clearly identify your amendment as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

Nashed

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #2
May 1, 2001

A. 1. **ANDA** 75-594

APPLICANT Aesgen Inc.
(Gensia Sicor Pharmaceuticals)

2. PRODUCT NAME: Pamidronate Disodium for Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 30-mg/vial and 90-mg/vial as Lyophilized powder for I/V use

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: February 17, 1999

2. DATE OF AMENDMENT: December 22, 2000.
Subject of this Review (Received December 26, 2000)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: April 30, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated July 18, 2000. The applicant stated that the subject drug product shall be manufactured by Gensia Sicor at Irvine, Ca. replacing [redacted] as the primary [redacted] The subject amendment describes sterility assurance issues in regard to Gensia Sicor facility.

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

/S/

Nrapendra Nath, Ph. D.

CR 5/16/01

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75594a2.doc
Initialed by A. High

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

BIOEQUIVALENCE REVIEW

4.1
NEN

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-594 (Amendment) SPONSOR : Aesgen, Inc.

DRUG AND DOSAGE FORM : Pamidronate Disodium for Injection

STRENGTH(S) : 30 mg/vial and 90 mg/vial

TYPES OF STUDIES : SD SDF MULT OTHER X

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY: N/A

Formulation is acceptable, waiver is granted

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
other ____		

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : /S/ DATE : 8/9/01

TEAM LEADER : Barbara M. Davit BRANCH : 3

Or INITIAL : /S/ DATE : 8/9/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

Jr INITIAL : /S/ DATE : 8/9/01

Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA #75-594
Reviewer: Carol Y. Kim
v:\firmsam\aesgen\ltrs&rev\75594sta.601

Aesgen, Inc.
Princeton, New Jersey
Submission Date:
June 21, 2001

REVIEW OF AN AMENDMENT

I. Background

1. The firm submitted this amendment to request a wavier of *in vivo* bioequivalence study requirements to add an additional strength, 90 mg/vial, to pending ANDA #75-594.

2. In the original submission dated April 1, 1999, the firm submitted a request for a waiver of *in vivo* bioequivalence study requirements for Pamidronate Disodium for Injection, 30 mg/vial. Subsequently, the DBE granted a waiver for the 30 mg strength vial on May 26, 1999.

3. The reference listed product is Aredia^{R} (Pamidronate Disodium) Injection, 90 mg/vial of lyophilized powder, manufactured for Novartis Pharmaceuticals Corporation. Both the RLD and the proposed product are lyophilized powder to be reconstituted with 10 ml of Sterile Water for Injection, USP, to each vial, resulting in a solution of 90 mg Pamidronate per 10ml.

5. The test and the reference listed product are both administered intravenously.

II. Formulation Comparison

The test and reference formulations are compared as shown below:

Ingredient	Test Product (per vial) (90 mg/vial)	Aredia^{R} (per vial) (90 mg/vial)
Pamidronate Disodium	**90 mg***	**90 mg**
Mannitol, USP	375 mg	375 mg
		NA
Phosphoric Acid, NF	pH adjustment	pH adjustment
Water for Injection, USP	QS	QS

III. Comments

1. The test product, Pamidronate Disodium for Injection, 90 mg/vial, contains the same active and inactive ingredients in the same concentrations as the reference product, Aredia^{R} (Pamidronate Disodium) Injection, 90 mg/vial.

2. A waiver is granted under 21 CFR 320.22 (b) (1), which states that the drug product is (i) a parenteral solution intended solely for administration by injection; and (ii) contains the same active and inactive ingredients in the same concentrations as a drug product that is the subject of an approved full NDA.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Aesgen Inc. on its drug product, Pamidronate Disodium for Injection, 90 mg/vial, falls under 21 CFR section 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Pamidronate Disodium for Injection, 90 mg/vial, bioequivalent to the reference product, Aredia^{R} (Pamidronate Disodium) Injection, 90 mg/vial, manufactured for Norvatis.

The firm should be informed of the recommendation.

/S/

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

/S/

for RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT

Date: 8/9/01

/S/

Concur:
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 8/9/01

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-594 APPLICANT: Aesgen, Inc.

DRUG PRODUCT: Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-594
ANDA DUPLICATE
DIVISION FILE
HFD-651/Bio Drug File
HFD-658/C. Kim

Endorsements: (Draft and final with dates)
HFD-658/Reviewer C. Kim /S/ 8/9/01 /S/
for HFD-658/Bio Team Leader B. Davit
HFD-617/Project Manager
for HFD-650/D. Conner /S/ 8/9/01

v:\firmsam\aesgen\ltrs&rev\75594sta.601

BIOEQUIVALENCY-ACCEPTABLE Submission date: 6/21/01

OK 1. WAIVER (WAI) **Strength: 30 mg/vial and 90 mg/vial**
Outcome: AC

Outcome decisions: AC-Acceptable

WinBio Comments: A waiver is granted

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

(2)

ANDA # : 75-594 SPONSOR : Aesgen, Inc.

DRUG AND DOSAGE FORM : Pamidronate Disodium for Injection

STRENGTH(S) : 30 mg/vial

TYPES OF STUDIES : SD SDF MULT OTHER X

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY: N/A

Formulation is acceptable, waiver is granted

DISSOLUTION : N/A

BMD 5/14/99

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL /S/ DATE : 5/10/99

TEAM LEADER : Barbara M. Davit BRANCH : 3

INITIAL : /S/ DATE : 5/10/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 5/12/99

Pamidronate Disodium for Injection
30 mg/vial
ANDA #75-594
Reviewer: Carol Y. Kim
v:\firmsam\aesgen\ltrs&rev\75594w.499

Aesgen, Inc.
Princeton, New Jersey
Submission Date:
April 1, 1999

REVIEW OF A WAIVER REQUEST

I. Background

1. The firm has requested a waiver of an in vivo bioequivalence study requirement for its proposed product, Pamidronate Disodium for Injection, 30 mg/vial. The reference listed product is Aredia^{R} (Pamidronate Disodium) Injection, 30 mg/vial of lyophilized powder, manufactured for Novartis Pharmaceuticals Corporation. Both RLD and proposed product are lyophilized powder to be reconstituted with 10 ml of Sterile Water for Injection, USP, to each vial, resulting in a solution of 30 mg Pamidronate per 10ml.

2 [redacted]

[redacted]

4. Pamidronate Disodium for injection is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, the treatment of patients with moderate to severe Paget's disease of bone, and treatment of patients with osteolytic bone lesions of multiple myeloma.

5. The test and the reference listed product are both administered intravenously.

II. Formulation Comparison

The test and reference formulations are compared as shown below:

Ingredient	Test Product (30 mg/vial)	Aredia® (30 mg/vial)
Pamidronate Disodium	**30 mg***	**30 mg**
Mannitol, USP	470 mg/ml	470 mg/ml
Phosphoric Acid, NF	pH adjustment to 6.5	pH adjustment to 6.5
Water for Injection, USP	QS	QS

Unit Composition of Proposed Product

Ingredient	Test Product (mg/ml)
Pamidronic Acid	
Mannitol, USP	
Phosphoric Acid, NF	QS
Water for Injection, USP	QS

III. Comments

1. The test product, Pamidronate Disodium for Injection, 30 mg/vial, contains the same active ( ) and inactive ingredients in the same concentrations as the reference product, Aredia® (Pamidronate Disodium) Injection, 30 mg/vial.

2. The amount of was verified by analyses of the two product solutions, Aesgen formulation, 30 mg/vial, and RLD, Aredia®, 30 mg/vial, using . The analysis result indicates that equivalent amounts of were found in both solutions. (see attachment, continental file no. 5359)

3. A waiver is granted under 21 CFR 320.22 (b) (1), which states that the drug product is

(i) a parenteral solution intended solely for administration by injection; and (ii) contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Aesgen Inc. on its drug product, Pamidronate Disodium for Injection, 30 mg/vial, falls under 21 CFR section 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Pamidronate Disodium for Injection, 30 mg/vial, bioequivalent to the reference product, Aredia^{R} (Pamidronate Disodium) Injection, 30 mg/vial, manufactured for Norvatis.

The firm should be informed of the recommendation.

/S/

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

/S/ 5/7/99

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT /S/ Date: 5/10/99

Concur: /S/ Date: 5/26/99

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-594 APPLICANT: Aesgen, Inc.

DRUG PRODUCT: Pamidronate Disodium for Injection, 30 mg/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-594
ANDA DUPLICATE
DIVISION FILE
HFD-651/Bio Drug File
HFD-658/C. Kim

Endorsements: (Draft and final with dates)
HFD-658/Reviewer C. Kim /S/ 5/4/99
HFD-658/Bio Team Leader P. Davit /S/ 5/10/99
HFD-617/Project Mana /S/ 5/21/99
HFD-650/D. Conner /S/ 5/26/99

v:\firmsam\aesgen\ltrs&rev\75594w.499

BIOEQUIVALENCY-ACCEPTABLE Submission date: 4/1/99

1. WAIVER (WAI) **Strength: 30 mg/vial**
Outcome: AC

Outcome decisions: AC-Acceptable

WinBio Comments: A waiver is granted

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-594 **Date of Submission: January 19, 2000 and February 4, 2000**
Applicant's Name: Aesgen, Inc.
Established Name: Pamidronate Disodium for Injection, 30 mg/vial

Labeling Deficiencies:

1. CONTAINER (30 mg) – Satisfactory in draft.
2. CARTON (4 vials per carton)

   a. Delete "
   b. Delete the , which appear around "Rx only".
   c. Revise " to read "calcium-containing" in the penultimate line on the principle display panel.
   d. Revise " to read "expiration date" in the last line on the back panel.

3. INSERT

   i. TITLE – Revise " to read "Pamidronate Disodium for Injection".
   ii. DESCRIPTION-

   Although you start with The ultimate active ingredient is pamidronate disodium in the lyophilized product. You must accurately describe the finished product. Therefore, revise this section to be the same as the reference listed drug. We refer you to the reference listed drug labeling which was sent to you previously for guidance.

   iii. CLINICAL PHARMACOLOGY
      a. Distribution- Revise " to read "54 ± 16%".
      b. Excretion – Revise this section to read as follows:

      After administration of 30, 60, and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate over 24 hours, an overall mean ± SD of 46 ± 16% of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean ± SD elimination half-life is 28 ± 7 hours. Mean ± SD total and renal clearance of pamidronate were 107 ± 50 mL/min and 49 ± 28 mL/min, respectively. The rate of elimination from bone has not been determined.

      c. Renal Insufficiency (Figure 1) – Only the line indicating Upper 95% CI, there is a dot at coordinate (and one at coordinate) which do not belong in this figure. Delete these dots. We refer you to the reference listed drug labeling which was sent to you previously for guidance.
      d. Pharmacodynamics

         1. Revise the first sentence of the first paragraph of this subsection to read as follows:

            ...because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal.

         2. Revise the second paragraph of this subsection to read as follows:

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

e. Hypercalcemia of Malignancy – Revise the sentence of the last paragraph of this subsection to read as follows:

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present.

f. Hypercalcemia of Malignancy (Clinical Trials)

1. Revise the fourth paragraph of this subsection to read as follows:

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of ≥12.0 mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of pamidronate as a single 24 hour intravenous infusion or 7.5 mg/kg of etidronate disodium as a 2 hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive pamidronate and 35 to receive etidronate.

2. Revise ——— to read "etidronate" in the fifth paragraph of this subsection and throughout the text as necessary.

g. Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma (Clinical Trials)

1. Revise ——— to read "longer" in sentence two of paragraph three of this subsection.
2. Delete the last paragraph as the same information is contained as a footnote in the table above it.

iv. INDICATIONS AND USAGE (Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma) – Revise the first sentence of this subsection to read as follows:

——— is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma.

v. WARNINGS – Include the following to appear as the penultimate paragraph of this section:

Patients who receive an intravenous infusion of pamidronate should have periodic evaluations of standard laboratory and clinical parameters of renal function.

vi. ADVERSE REACTIONS (Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma) – Revise the first sentence of this subsection to read as follows:

...may have been related to the underlying disease state or cancer therapy.

vii. PREPARATION OF THE SOLUTION (Osteolytic Bone Metastases of Breast Cancer) – Revise ——— to read "250 mL" in this subsection.

Please revise your carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes: http//www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FINAL APPROVAL PACAGE SUMMARY FOR 75-594

ANDA: 75-594

FIRM: Aesgen, Inc.

DRUG: Pamidronate Disodium

DOSAGE: Lyophilized cake for suspension for injection

STRENGTH: 30 mg/vial and 90 mg/vial

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 7/23/01

BIO STUDY/BIOEQUIVALENCE: Bio waiver was granted 5/26/99 (for 30 mg/vial). Bio waiver was granted 8/9/01 (for 90 mg/vial).

METHOD VALIDATION: Method validation is Pending.

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C±2°C/75%±5%RH and 3 months room temperature at 25°±2°C/60%±5%RH. The drug product also exhibited excellent stability when reconstituted in sterile WFI for 24 hours and then analyzed.

LABELING REVIEW STATUS: Labeling is acceptable 4/6/01

STERILIZATION VALIDATION: Microbiology portion is satisfactory 5/16/01

BATCH SIZES: The manufacturing process for 90 mg/vial is similar for 30 mg/vial.
The firm has submitted blank batch record for 30 mg/vial (——— and blank batch record for 90 mg/vial (——— .
The firm has provided copies of the exhibit batch records lot #X00N206 ——— for (30 mg/vial) and lot #X00N213 ——— for (90 mg/vial). The maximum production batch will be ——— for the 30 mg/vial product strength, and ——— for the90 mg/vial. The firm will be using the same drug substance manufacture, same equipment and same process.

COMMENTS: The application is approvable - (acceptable method validation pending).

/S/

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 3/12/02

4/5/02

/S/

Supervisor: James M. Fan DATE: 3/17/02

4/2/02

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

ANDA # 75-594

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aesgen, Inc.	August 7, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
609-419-1090	609-419-1092
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Aesgen, Inc. Two Research Way Third Level East Princeton, NJ 08540	NONE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* N/A

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Pamidronate Disodium for Injection	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Phosphonic acid (3-amino, 1-hydroxypropylidene) bis-, disodium salt, pentahydrate

CODE NAME *(If any)* N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Lyohilized cake for suspension	30 mg/vial	Intravenous Infusion

(PROPOSED) INDICATION(S) FOR USE:
Pamidronate Disodium for Injection is indicated for the treatment of: (1) moderate or severe hypercalcemia associated with malignancy; (2) moderate to severe Paget's Disease of bone; (3) osteolytic bone lesions of multiple myeloma

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
AREDIA	Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION General correspondence - transfer of duties and responsibilities of regulatory agent to GensiaSicor

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to original ANDA application

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Please refer to original ANDA application

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* General correspondence - transfer of duties and responsibilities of regulatory agent to GensiaSicor

CERTIFICATION

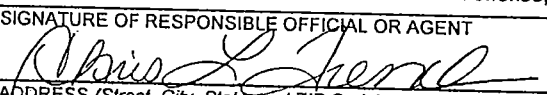
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Chris L. French	8/7/2000

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
Two Research Way, Third Level East, Princeton, NJ 08540	609-419-1090 x103

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
ood and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

RECORD OF TELEPHONE CONVERSATION

On this date we contacted the firm and made reference their ANDA 75-594 and their amendment dated June 21, 2001.

We requested that the firm reduce the limits for the individual and total impurities, and the ——— for the stability.

Elvia Gustavson acknowledged the request and will contact us with the response. She also informed us that Aesgen may request a T-con to discuss these issues and the previous issue from the August 9, 2001 T-con.

DATE:
8/13/01

ANDA NUMBER
75-594

TELECON INITIATED BY FDA

PRODUCT NAME:
Pamidronate Disodium

FIRM NAME:
U.S. Agent for Aesgen

FIRM REPRESENTATIVES:
Elvia Gustavson, U.S. Agent for Aesgen

TELEPHONE NUMBER:
(949)455-4724

FDA REPRESENTATIVES
Gil Kang
Nashed Nashed
Sarah Ho

SIGNATURES:
G. Kang 8/13/01
N. Nashed 8/13/01
S. Ho 8/13/01

Orig: ANDA 75-594
Cc: Division File
Chem. I Telecon Binder
V:\FIRMSAM\AESGEN\TELECON\75594.13aug01.doc

RECORD OF TELEPHONE CONVERSATION

On this date we contacted the firm and made reference to our letter dated June 18, 2001 and their amendment dated June 21, 2001.

Paul Schwartz made reference to their response to Deficiency #2. According to their response (as stated in their manufacturing record),

Elvia Gustavson responded by stating that

She stated that the statement could be changed from

Paul Schwartz also added that we also need to know the

revised when the above mentioned statement is corrected.

Elvia Gustavson acknowledged the comments and will submit the changes as a Telephone amendment.

DATE:
8/1/01

ANDA NUMBER
75-594

TELECON INITIATED BY AGENT

PRODUCT NAME:
Pamidronate Disodium

FIRM NAME:
U.S. Agent for Aesgen

FIRM REPRESENTATIVES:
Elvia Gustavson, U.S. Agent for Aesgen
John Havlett, Regulatory Affair Specialist

TELEPHONE NUMBER:
(949)455-4724

FDA REPRESENTATIVES
Paul Schwartz
Kathy Woodland
Nashed Nashed
Sarah Ho

SIGNATURES:
P. Schwartz PS 8/1/01
K. Woodland KPW 8/1/01
N. Nashed NN 8/2/01
S. Ho SHO 8/1/01

Orig: ANDA
Cc: Division File
Chem. I Telecon Binder
V:\FIRMSAM\AESGEN\TELECON\75594.1aug01.doc

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pages of trade secret and /or confidential commercial information

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-594 Date of Submission: April 1, 1999
Applicant's Name: Aesgen, Inc.

Established Name: Pamidronate Disodium for Injection, 30 mg/vial

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Revise your storage recommendation to read as follows on all labels and labeling:

      Pamidronate Disodium for injection reconstituted with Sterile water for injection may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 24 hours. Do not store above 30°C (86°F).

2. CONTAINER (30 mg)

   a. Include "Rx only" on the principal display panel.

   b. See comment (a) under GENERAL COMMENTS.

3. CARTON (4 vials per carton)

   a. See comment (a) under GENERAL COMMENTS.

   b. Revise [redacted] to read "Rx only".

   c. See comment (a) CONTAINER.

4. INSERT

   a. GENERAL COMMENT:

      Due to changes in the insert labeling for the reference listed drug, Aredia® (approved September 22, 1998), please revise your insert labeling to be in accord with the enclosed copy of this labeling.

b. TITLE

We encourage the inclusion of "Rx only" in this section.

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes: http//www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-594

CORRESPONDENCE

GensiaSicor™
PHARMACEUTICALS
A sicor Company

February 26, 2002

ORIG AMENDMENT
N/Am

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, dated on March 3, 1999, and amended with the 90 mg/vial on December 22, 2000. Reference is also made to the Agency's letter dated November 28, 2001.

In accordance with the tentative approval granted for this application, we are amending the application approximately 90 days prior to the date we believe we will be eligible for final approval, May 6, 2002.

A change has been made to the [redacted] specifications to tighten the bioburden limits as follows:

Bioburden, CFU/g	Previous Specification	Revised Specification
Total [redacted]	Not More Than [redacted]	Not More Than [redacted]
Total [redacted]	Not More Than [redacted]	Not More Than [redacted]

A copy of the current Raw Material Specifications and Data Sheet for [redacted] immediately follows this letter. No other changes have been made.

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact me at (949) 455-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

S:\Pamidronate Iyo75594\Amends\Amend17.doc
Attachment

cc: Mr. Alonza Cruse, District Director
FDA, Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Edward Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

GensiaSicor™
PHARMACEUTICALS
A sicor Inc. Company

August 23, 2001

NC to FAX

NEW CORRESP

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, dated on March 3, 1999, and amended with the 90 mg/vial on December 22, 2000. Reference is also made to the telephone conversation with Ms. Sarah Ho on August 22, 2001.

In accordance with Section 314.96 of the *Code of Federal Regulations, Title 21*, we amend this application to provide the requested clarification regarding [redacted] %, for the 30 mg/vial and 90 mg/vial sizes.

After reviewing the [redacted] %, stability data of the 90 mg/vial, we have elected to harmonize the specification with the 30 mg/vial [redacted] %, specification. The revised specification is presented in the table below:

Specification	Pamidronate Disodium Injection, 90 mg/vial	
	Previous Limit	Revised Limit
[redacted]	Shelf Life: NMT [redacted]	Shelf Life: NMT [redacted]
	Release: NMT [redacted]	Release: NMT [redacted]

Attached please find the revised Finished Product Specifications and Data Sheet for the 90 mg/vial size.

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Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact me at (949) 455-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

H:\DATA\IRG\Pamidronate lyo75594\Amends\Amend 14.doc

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Edward Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

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N/AM

ORIG AMENDMENT

Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, California 92618-1902

REGULATORY AFFAIRS
FAX COVER SHEET

DATE: August 23, 2001

TO: Sarah Ho, Project Manager
OGD, FDA
PHONE: 301-827-5754
FAX: 301-594-0180

Documentation Control Room
FAX: 301-827-4337

FROM: Elvia O. Gustavson, EOG
U.S. Agent for Aesgen, Inc.
PHONE: 949-455-4724
FAX: 949- 583-7351

CC: Edward Shinal, Aesgen, Inc.

RE: Telephone Amendment: ANDA 75-594 Pamidronate Disodium for Injection

Number of pages including cover sheet: 8

Message-

Per your request, we are providing you and the Documentation Control Room a copy of our Telephone Amendment dated August 23, 2001, for subject ANDA, via facsimile. Original and one copy will be sent to Mr. Gary Buehler's attention via Federal Express today.

GensiaSicor™
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A sicor Inc. Company

August 22, 2001

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC to Fax

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, dated on March 3, 1999, and amended with the 90 mg/vial on December 22, 2000. Reference is also made to the telephone conversation with Ms. Sarah Ho on August 22, 2001.

In accordance with Section 314.96 of the *Code of Federal Regulations, Title 21*, we amend this application to provide the requested clarification regarding the release and shelf specifications for Related Compounds, including [redacted], for the drug product.

The specifications presented in the following table represent the revised release specifications for the [redacted]

Specification	[redacted]	
	Previous Limit	Revised Limit
[redacted]	[redacted]	[redacted]
Related Compounds:		
Single Largest Other	[redacted]	[redacted]
Total	[redacted]	[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 23 2001
OGD

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

The specifications presented in the following table represent both the release and shelf specifications for the Pamidronate Disodium drug product:

Specification	30 mg/Vial Drug Product		90 mg/Vial Drug Product	
	Previous Limit	Revised Limit	Previous Limit	Revised Limit
Related Compounds:				
Single Largest Other				
Total				

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact me at (949) 455-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

H:\DATA\IRG\Pamidronate lyo75594\Amends\Amend 14.doc

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Edward Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

GensiaSicor™
PHARMACEUTICALS
A sicor Company

N/AM

August 16, 2001

ORIG AMENDMENT

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 17 2001
OGD

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, dated on March 3, 1999, and amended with the 90 mg/vial on December 22, 2000. Reference is also made to the telephone conversations with Ms. Sarah Ho on August 9 and 13, 2001.

In accordance with Section 314.96 of the *Code of Federal Regulations, Title 21*, we amend this application to provide the revised documentation.

The Related Compounds specification, including the specification for ——, has been revised for both ——— and the 30 mg/vial and 90 mg/vial drug products. The specifications have been revised as follows:

Specification	Pamidronic Acid		30 mg/Vial Drug Product		90 mg/Vial Drug Product	
	Previous Limit	Revised Limit	Previous Limit	Revised Limit	Previous Limit	Revised Limit
—	—	—	—	—	—	—
Related Compounds:						
Single Largest Other	—	—	—	—	—	—
Total	—	—	—	—	—	—

000003

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

The revised specifications for Related Compounds and [redacted] are reflected on the revised **Raw Material Specifications and Data Sheet** for [redacted], and **Finished Product Specifications and Data Sheet** for the 30 mg/vial and 90 mg/vial drug products, provided in **Attachment 1**.

In addition, we are providing the revised method, QCP-1357, for determination of [redacted] and other Related Compounds in the drug product. The method was revised to clarify interpretation to account for the revised limits. The revised method is provided in **Attachment 2**.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact me at (949) 455-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

H:\DATA\IRG\Pamidronate lyo75594\Amends\Amend 13.doc

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Edward Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

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Acknowledged NAT 8/23/01

Copy NAT 8/17/01

Not sued on 1880 on 90mg/V

August 13, 2001

NC

NEW CORRESP

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999, and amended with the 90 mg/vial, submitted on December 22, 2000. Reference is also made to the patent amendment dated July 10, 2001.

As required under CFR 314.107(f)(2) in regard to Patent No 4,711,800, we wish to inform the Agency that neither Aesgen, Inc. nor its legal representatives have been served with a legal complaint as a result of the Notice of Certification received by Novartis Pharmaceuticals Corporation. To the best of our knowledge, we are not aware of any legal action taken within the requisite 45 days that expired on August 5, 2001.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. I can also be contacted by facsimile at (949) 583-7351.

Sincerely,

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 14 2001
OGD

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

H:\DATA\IRG\Pamidronate lyo75594\Amends\Pat Amend 12.doc

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Edward C. Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

GensiaSicor™
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August 1, 2001

ORIG AMENDMENT
N/AM

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999, and amended with the 90 mg/vial, submitted on December 22, 2000. Reference is also made to the telephone conversation with Ms. Sarah Ho on August 1, 2001.

In accordance with Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby submit an amendment to provide the revised manufacturing batch records.

The batch record – Compounding, has been revised for each strength to reflect the proper function of [redacted] in the formulation. Specifically, the function of [redacted] is to [redacted] The amounts of [redacted] for the 30 mg/vial product strength, and [redacted], for the 90 mg/vial product strength. The [redacted]. However, [redacted] This step is reflected in step 10 of the attached compounding procedures for the 30 mg/vial and 90 mg/vial product strengths.

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Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact the undersigned at (949) 455-4724.

Sincerely,

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

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cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Edward Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

GensiaSicor™
PHARMACEUTICALS
A sicor Company

July 10, 2001

NEW CORRESP
NC.

/S/
7/10/01

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999, and amended with the 90 mg/vial, submitted on December 22, 2000. Reference is also made to the Paragraph IV Patent Certification Statement for the 90 mg/vial size for U.S. Patent No. 4,711,800 contained in the patent amendment dated June 18, 2001.

In accordance with the provisions of Section 314.95(e) of the *Code of Federal Regulations*, *Title 21*, we hereby amend this application to document receipt of the notice required under Section 314.95(a) for the person provided the notice. On June 21, 2001, Novartis Pharmaceuticals Corporation received notice of certification. A copy of the return receipt is included in this amendment. In addition, we wish to inform the Agency that Novartis Pharmaceuticals Corporation has 45 days from the receipt date of June 21, 2001, in which to file a patent infringement lawsuit. We estimate this period to expire on August 5, 2001.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

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RECD
JUL 11 2001
OGD

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cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Ed Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

GensiaSicor™
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June 21, 2001

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773

N/APM
ORIG AMENDMENT

RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

MINOR AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999, and amended with the 90 mg/vial, submitted on December 22, 2000. Reference is also made to our patent amendment dated June 18, 2001. Further reference is made to the Agency's facsimile dated June 18, 2001.

In accordance with Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby submit an amendment to provide the additional **chemistry** information requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact the undersigned at (949) 455-4724.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
U.S. Agent for Aesgen, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 22 2001
OGD

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cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Ed Shinal, Ph.D.
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

Aesgen INC.

PATENT AMENDMENT

June 23, 1999

NAF
[S]
Civil Action
Notice of Lawsuit
[S] 25/99
NEW CORRESP
NC

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs, FDA
7500 Standish Place, Room 150
Rockville, Maryland 20857

Re: PATENT AMENDMENT
Aesgen Inc. ANDA 75-594
Pamidronate Disodium for Injection

Dear Mr. West:

This letter is sent in accordance with the instructions in your April 20, 1999 letter.

- Notice of Paragraph IV Certification

  On April 26, 1999, in accordance with the notice requirements of 21 C.F.R. § 314.95 and 21 U.S.C. § 355(j)(2)(B)(ii), Aesgen provided notice of its ANDA 75-594 to Novartis Corporation. Novartis is the holder of record of the approved application under 21 U.S.C. § 355(b) for the listed drug and the owner of U.S. Patent No. 4,711,880 ("the '880 patent") which has been listed as relating to the product. Therefore, an amendment to ANDA 75-594 with the certification required by 21 C.F.R. § 314.95(a) and a copy of the return receipt establishing such notice per 21 C.F.R. § 314.95(e) was submitted to ANDA 75-594 on May 14, 1999.

- Expiration of 45-Day Litigation Period

  Pursuant to section 505(j)(4)(B)(iii) of the Act, the holder of record of the approved application and patent owner have 45 days to commence litigation against the applicant seeking approval. Aesgen's notification was received by Novartis on April 29, 1999 as confirmed by return receipt. Based upon the date on which the notification was received, the 45-day period to file a patent infringement suit expired on June 14, 1999. To date, Aesgen does not have notice or any knowledge of legal action that has been taken by Novartis against Aesgen.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 2 1999
OGD

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

- Status of 180-Day Exclusivity Provision

  As was mentioned in our patent amendment dated May 14, 1999, Aesgen is aware through publicly available documents filed in the Federal District Court in New Jersey that Ben Venue Laboratories, Inc. has also filed an ANDA (i.e., ANDA 75-290) seeking approval from the FDA to sell Pamidronate Disodium for injection.

  Documents from the Court indicate that Novartis filed a patent infringement suit against Ben Venue alleging infringement of the '880 patent. In this suit, Ben Venue admitted that it's paragraph IV certification was incomplete, since it did not make a certification as to the manufacture of the product. Specifically, Novartis publicly stated on the record that Ben Venue did not make a complete paragraph IV certification (Exhibit A) and in response, Ben Venue admitted that its certification was incomplete (Exhibit B). Assuming no other ANDAs were filed, Aesgen's ANDA 75-594 is therefore the first complete paragraph IV certification, and as such, Aesgen should be accorded "first filer" status under 21 U.S.C. § 355(j)(5)(B)(iv) and the 180-day exclusivity it provides.

  The FDA's "Guidance For Industry: 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act," June 1988, Section IV, indicates that the first applicant to submit an ANDA with a paragraph IV certification, but who was not sued by the patent owner or NDA sponsor, as well as an applicant whose final approval would be affected by another's 180-day exclusivity, would generally receive a letter from the Office of Generic Drugs regarding this issue. To date, Aesgen has not received any correspondence addressing the 180-day exclusivity.

Given the information presented in this amendment and the June 1998 Guidance, would you please provide the status of Aesgen's claim to first to file provision for 180-day exclusivity on the product.

Sincerely,

Chris L. French
Director of Scientific and Regulatory Affairs

Attachments

Please file in latest op archival volume 75-594

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

GensiaSicor Pharmaceuticals
19 Hughes
Irvine, California 92618-1902

NEW CORRESP
NC

REGULATORY AFFAIRS FAX COVER SHEET

DATE: June 4, 2001

TO: Lt. Gregg Davis
Office of Generic Drugs, FDA
PHONE: 301-827-5862
FAX: 301-594-1174

FROM: Ms. Elvia O. Gustavson, EVG
U.S. Agent for Aesgen, Inc.
PHONE: 949-455-4724
FAX: 949-583-7351

RE: ANDA 75-594 Pamidronate Disodium for Injection

CC: Ed Shinal, Aesgen, Inc.

OK to use FedEx for overseas notifi
/S/ 05-JUN-20
/S/

Number of pages including cover sheet: 1

Message

Securing a return receipt for patent notices sent to Europe via the United States Postal Service can be problematic. Aesgen, Inc., is preparing to notify _____, co-owner of U.S. Patent No. 4,711,880, located in _____, of the Paragraph IV Patent Certification listed in Aesgen's ANDA 75-594 for Pamidronate Disodium for Injection, 90 mg/vial size. Therefore, Aesgen intends to send the initial patent notice to _____ via Federal Express to assure traceability of the correspondence. The Federal Express confirmation of delivery will serve as adequate documentation of receipt of notice in accordance with 21 CFR 314.95(e). Your confirmation of this agreement would be greatly appreciated.

Thank you for your assistance in this matter.

GensiaSicor™
PHARMACEUTICALS
A sicor Inc. Company

March 30, 2001

ORIG AMENDMENT AC

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Pamidronate Disodium for Injection
ANDA 75-594

AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application, ANDA 75-594, for Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999 by Aesgen Incorporated. Reference is also made to the amendment, submitted December 22, 2000, requesting a change in manufacturing site to Gensia Sicor Pharmaceuticals, Inc., for both the 30 mg/vial and 90 mg/vial product strength.

Reference is made to Gensia Sicor's commitment in the above referenced amendment, to further amend the application with additional **stability data**. We hereby submit this amendment, presenting the stability report for Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial, with data generated through 3 months under both accelerated and labeled storage conditions.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Agent for Aesgen Incorporated

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 02 2001
OGD

H:\DATA\IRG\Pam75594\Amends\Amend6.doc

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Ed Shinal, PhD
Aesgen, Inc.
2 Research Way
Princeton, NJ 08540

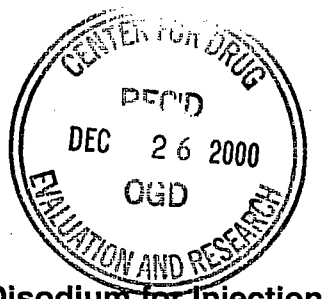
000003

GensiaSicor™
PHARMACEUTICALS
A sicor Company

ORIG AMENDMENT
N/A C

December 22, 2000

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Documentation Control Room150
Metro Park North II,
7500 Standish Place
Rockville, MD 20855-2773



RE: Pamidronate Disodium for Injection
30 mg/vial and 90 mg/vial
ANDA 75-594

AMENDMENT

Dear Mr. Buehler:

Reference is made to the abbreviated new drug application for Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999 by Aesgen Incorporated, ANDA 75-594.

Reference is made to the Agency's facsimile dated July 17, 2000. Reference is also made to the telephone conference held on August 8, 2000 with Ms. Elaine Hu and Dr. Paul Schwartz of the Office of Generic Drugs, FDA. During our telephone conversation, we informed the agency of the desire to withdraw the [redacted] We also advised the agency that Gensia Sicor would not be formally responding to the deficiency letter dated July, 17, 2000. However, information regarding every noted deficiency would be incorporated, if appropriate, within the text of the amendment relative to the alternate manufacturing site. The microbiology deficiencies noted in the Agency's deficiency letter dated July 18, 2000, have been evaluated and every attempt was made to address the issues that pertain to Gensia Sicor's facility and processes in **Volume 3** of this amendment. It was also discussed and agreed upon that Gensia Sicor would submit the amendment with one (1) month of stability data and will further amend the application with data through three (3) months once the data becomes available.

In accordance with Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby submit an amendment to provide for an alternate manufacturing site for Pamidronate Disodium for Injection supplied as:

100003

Strength	How Supplied
30 mg/Vial	10 mL Glass Vial
90 mg/Vial	10 mL Glass Vial

We wish to amend this application to provide for the manufacture of the product at an alternate site, Gensia Sicor Pharmaceuticals, Inc., Irvine, CA.

This amendment is identical to the original ANDA 75-594, submitted by Aesgen Incorporated, with respect to the following:

Basis for ANDA (Section II) – 30 mg/vial
Patent Certification and Exclusivity Statement (Section III)
Bioavailability/Bioequivalence (Section VI)
Environmental Impact Analysis Statement (Section XX)

Changes from the original application are presented in the table below.

An additional product strength of 90 mg/vial is included in this amendment. **Section 1** provides the basis of the ANDA and comparison statement to the Reference Listed Drug for this new strength.

One stability lot of each product strength was manufactured to support this amendment. Documentation supporting the manufacture of the stability lots is provided in the sections listed in the following table. Any differences from the original application are noted in the appropriate section.

Change from Original Application	Supporting Documents	Section
Addition of a 90 mg/vial product strength	Basis for ANDA	1.1
	Comparison Statement	1.2
The proposed labeling incorporates changes necessitated by identifying the manufacturer and manufacturing site.	Comparison Between Gensia Sicor's proposed labeling and the innovator's labeling.	2.1
	Labeling (12 copies of final printed labeling)	2.2
The manufacturing and processing instructions have been revised to reflect the manufacturer of the product at the alternate manufacturing site.	Manufacturing and Processing Instructions	3
	Description of the Manufacturing Process	3.1
	Blank Batch Records for Intended Production Runs with Equipment Specified	3.2

Item	Title	Section
Outside Firms Including Contract Testing Laboratories	Full Address	4.1
	Functions	4.2
	cGMP Certification/ GLP	4.3
Raw Material Controls	Active Ingredient: Testing specifications and data from drug product manufacturer and drug substance manufacturer	5.1
	Inactive Ingredients: Testing specifications and data from drug product manufacturer and drug substance manufacturer	5.2
Container Closure System	Summary of Container/Closure System	6.1
	Components Specification and Test Data	6.2
	Packaging Configuration and Sizes	6.3
	Container/Closure Testing	6.4
In-Process Controls	Copy of Executed Batch Record with Equipment Specified, Including Packaging Records, Batch Reconciliation and Label Reconciliation	7.1
	In-Process Controls, Sampling Record and Test Procedures	7.2
Controls for Finished Dosage Form	Sampling Records and Test Procedures	8.1
	Testing Specifications and Data	8.2
Analytical Methods	Methods for Drug Substance	9.1
	Methods for Drug Product	9.2
Stability of Finished Dosage Form	Developmental Stability Protocol	10.1
	Post Approval Stability Commitments	10.2
	Expiration Dating Period	10.3
	Stability Data Submitted	10.4
Sample Availability and Identification of:	Drug Substance and Finished Dosage Form	11
The sterility assurance validation data associated with change of manufacturing site.	Validation	12 (Vol. 3)

The amendment consists of three (3) volumes. Since the stability indicating methods are non-compendial, three (3) additional methods validation packages have been included in this amendment and are marked "Analytical Methods". These three additional copies are identical to **Section 9** as presented in the archival and review copies, and have been separately bound in Gray Jackets.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please contact the undersigned at (949) 455-4724.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Agent for Aesgen Incorporated

S:\DOX64140\GSPISITE\S003.WPD

cc: Mr. Alonza Cruse
District Director
Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

GensiaSicor™
PHARMACEUTICALS
A sicor Company

August 23, 2000

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC
NAT IC
8/24/00

RE: Pamidronate Disodium for Injection
ANDA 75-594

AMENDMENT

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 75-584, for Pamidronate Disodium for Injection, 30 mg/vial, submitted on March 3, 1999. Reference is also made to the Agency's facsimile dated July 18, 2000.

As a result of the extent of additional Research & Development studies required to respond to the deficiencies, we intend to reply to the Agency's facsimile dated July 18, 2000 by December 29, 2000.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724 or by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Associate Director, Regulatory Affairs

H:\DATA\IRG\Pam75594\Amends\Amend4.doc

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 24 2000
OGD

cc: Ms. Elizabeth Kezille
Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

S 8-28-00

Aesgen INC.

August 7, 2000

NEW CORRESP
NC

NAI
8/10/15

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA AIRBORNE EXPRESS

Re: ANDA #75-594
Pamidronate Disodium for Injection, 30 mg/vial
General Correspondence

Dear Mr. Buehler:

On June 21, 2000, Aesgen submitted a formal communication to the FDA requesting that the duties and responsibilities of regulatory agent remain with Aesgen as opposed to being transferred to GensiaSicor. This action seemed premature, as GensiaSicor was not involved with any of the information currently under review in pending ANDA #75-594 (letter attached for your reference).

However, recent developments necessitate the involvement of GensiaSicor immediately:
(a) the original [redacted]) filed in ANDA #75-594 has closed and Aesgen has selected GensiaSicor as the new manufacturing site for this application; the application will be amended to reflect the manufacturing site change; and
(b) a Major Amendment has been received for chemistry, and the micro and labeling comments, of which many comments are related to manufacturing and to the specific site. Since the original manufacturing site is closed, we need to discuss with the Agency how best to respond to the Major Amendment and at the same time amend the application with the manufacturing site change.

1
1 a 0-491

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

I therefore ask that you please accept this communication as formal notice that Aesgen, Inc., Princeton, NJ has transferred the duties and responsibilities of Regulatory Agent for ANDA #75-594, Pamidronate Disodium for Injection, 30 mg/vial, to GensiaSicor. This transfer is effective immediately, therefore we request that all future regulatory communications and correspondence relating to ANDA #75-594 be directed to the attention of:

Armand Le Blanc
Sr. V.P. Corporate Scientific Affairs
GensiaSicor
19 Hughes
Irvine, CA 92618-1902
949- 455-4724(t)
949- 583-7351(f)
OR

Elvia O. Gustavson
Associate Director Regulatory Affairs
GensiaSicor
19 Hughes
Irvine, CA 92618-1902
949- 455-4716(t)
949- 583-7351(f)

This information is being provided to the Office of Generic Drugs in duplicate. Please incorporate this information into the application. I can be reached at 609-419-1090 x103 or by fax at 609-419-1092.

Thank you for your assistance and I apologize for the inconvenience and confusion.

Sincerely,

Chris L. French
Director, Scientific and Regulatory Affairs

Cc Elaine Hu Project Manager, Chemistry I

Aesgen INC.

August 7, 2000

Elaine Hu
Project Manager
Division of Chemistry 1
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA AIRBORNE EXPRESS

Re: ANDA #75-594
Pamidronate Disodium for Injection, 30 mg/vial
General Correspondence

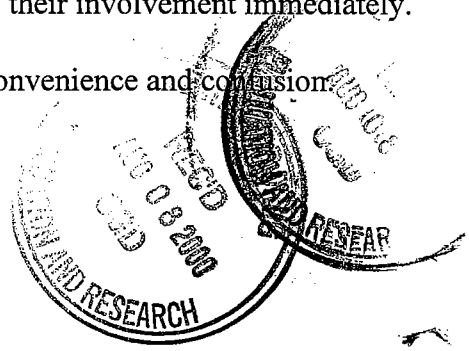
Dear Ms. Hu:

Please see the attached letter to Gary Buehler regarding our need to transfer the duties and responsibilities of Regulatory Agent to GensiaSicor. I know that we just did this recently and then revoked it as they were not involved with the ANDA that is under active review. However, recent development necessitates their involvement immediately.

Thank you for your assistance and I apologize for the inconvenience and confusion.

Sincerely,

Chris L. French
Director, Scientific and Regulatory Affairs



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This information is being provided to the Office of Generic Drugs in duplicate. Please incorporate this information into the application. I can be reached at 609-419-1090 x103 or by fax at 609-419-1092.

Thank you for your assistance and I apologize for the inconvenience and confusion.

Sincerely,

Chris L. French
Director, Scientific and Regulatory Affairs

Cc Elaine Hu Project Manager, Chemistry I

APPEARS THIS WAY
ON ORIGINAL

Aesgen INC.

June 21, 2000

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA AIRBORNE EXPRESS

Re: ANDA #75-594
Pamidronate Disodium for Injection, 30 mg/vial
General Correspondence

Dear Mr. Buehler:

On May 26, 2000, Aesgen submitted a formal communication to the FDA to notify the Agency that the duties and responsibilities of Regulatory Agent for ANDA #75-594 had been transferred to Gensia Sicor (letter attached for your reference). In hindsight, this transfer was premature.

Gensia Sicor has recently become a contractor to Aesgen on this ANDA and should be considered an authorized official entitled to submit regulatory correspondence and supplements to the above referenced ANDA. However, Gensia Sicor was not involved with any part of the filing currently under active review with the agency; I therefore ask that you continue to keep me as Regulatory Agent and the primary contact on the file and that you please send all communications to my attention:

Chris L. French
Director, Scientific and Regulatory Affairs
Aesgen, Inc.
2 Research Way
Third Level East
Princeton, NJ 08540
609-419-1090 x103 (t)
609-419-1092 (f)

This information is being provided to the Office of Generic Drugs in duplicate. Please incorporate this information into the application. I can be reached at 609-419-1090 x103 or by fax at 609-419-1092.

Thank you for your assistance and I apologize for the inconvenience and confusion.

Sincerely,

Chris L. French
Director, Scientific and Regulatory Affairs

Cc Elaine Hu Project Manager, Chemistry I

APPEARS THIS WAY
ON ORIGINAL

2.1

Aesgen INC.

May 26, 2000

Gary Buehler,
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

NEW CORRESP
NC

VIA AIRBORNE EXPRESS

Re: ANDA #75-594
Pamidronate Disodium for Injection, 30 mg/vial
General Correspondence

Dear Mr. Rickman:

Please accept this communication as formal notice that Aesgen, Inc., Princeton, NJ has transferred the duties and responsibilities of Regulatory Agent for ANDA #75-594, Pamidronate Disodium for Injection, 30 mg/vial, to GensiaSicor. This transfer is effective immediately, therefore we request that all future regulatory communications and correspondence relating to ANDA #75-594 be directed to the attention of:

Armand Le Blanc
Sr. V.P. Corporate Scientific Affairs
GensiaSicor
19 Hughes
Irvine, CA 92618-1902
949- 455-4716(t)
949- 583-7351(f)

OR

Elvia O. Gustavson
Associate Director Regulatory Affairs
GensiaSicor
19 Hughes
Irvine, CA 92618-1902
949- 455-4724(t)
949- 583-7351(f)

This information is being provided to the Office of Generic Drugs in duplicate. Please incorporate this information into the application. I can be reached at 609-419-1090 x103 or by fax at 609-419-1092.

Sincerely,

Chris L. French
Director, Scientific and Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 30 2000
OGD

cc Elaine Hu, Project Manager, Chemistry I

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

/S/ 5-30-00

Aesgen INC.

April 17, 2000

NDA ORIG AMENDMENT
N/As

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Microbiology Review

RE: Abbreviated New Drug Application: 75-594
Pamidronate Disodium for Injection
30 mg/vial

GRATUTITOUS AMENDMENT FOR MICROBIOLOGY REVIEW

Dear Madam or Sir:

Pursuant to a telephone conversation on April 14, 2000 with Joseph Buccine, OGD Division of Microbiology, Aesgen, Inc. is providing the validation report for ANDA 75-594 to the Agency. This information is submitted to the ANDA as a Gratuitous Amendment for Microbiology Review as requested by Mr. Buccine. Please incorporate this information into the application.

Copies of this Gratuitous Amendment for Microbiology Review for ANDA 75-594, Pamidronate Disodium for Injection, 30 mg/vial, have been provided to FDA's New Jersey, San Francisco and Kansas City District Offices.

If more information is needed, please contact me at (609) 419-1090 Ext. 103 or fax (609) 419-1092.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 18 2000
OGD

Sincerely,

Chris L French
Director, Scientific and Regulatory Affairs

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

Aesgen INC.

March 2, 2000

NEW CORRESP

Director
Office of Generic Drugs
Center of Drug Evaluation and Research, CDER, FDA
Metro Park North II
Standish Place Room 150
Rockville, MD 20855

Re: ANDA 75-594
Pamidronate Disodium for Injection, 30 mg/vial

Correspondence to the File

Dear Director:

Reference is made to pending Abbreviated New Drug Application for Pamidronate Disodium for Injection, ANDA 75-594 submitted to the Agency on April 5, 1999. On October 19, 1999, Aesgen, Inc. received the first amendment on ANDA 75-594, which was quite comprehensive as it addressed chemistry (noting that microbiology was under review), labeling, and bioequivalence (attached for your information). After reviewing the deficiencies, we were surprised to see that this amendment was designated as a "Major Amendment".

This correspondence is therefore a formal request to the Agency to reconsider the designation of this Amendment from a "Major" to that of a "Minor Amendment". We are familiar with the Agency's policy on categorizing deficiencies as "Major" or "Minor" deficiencies and believe that the response submitted on January 19, 1999 could be reviewed in less than one hour given the following observations on the Chemistry comments:

- Items 2 and 3 were linked and therefore responded to together.
- Items 4 and 5 were linked and therefore responded to together.
- Further clarification was required on the items 3 and 5 from the Agency. We were not aware that the product reacts with glass.
- Item 7 was responded to by the DMF holder on October 19, 1999.

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 0 3 2000 OGD

/S/

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax [illegible]092

- Item 12 required a simple revision of the stability statement.
- Item 13 was a simple change in format.

For the above reasons, we believe that the number of deficiencies could have been decreased and that the response submitted on January 19, 2000 could be reviewed in less than an hour and would therefore qualify for a "Minor" designation.

Thank you for your consideration of this request. I can be reached at 609-419-1090 x103.

Sincerely,

Chris L. French
Director of Scientific and Regulatory Affairs

Cc Elaine Hu, Project Manager, Division of Chemistry I, Team 3

APPEARS THIS WAY
ON ORIGINAL

Aesgen INC.

January 19, 2000

ORIG AMENDMENT
N/A C

Douglas Sporn
Director
Office of Generic Drugs
Center of Drug Evaluation and Research, CDER, FDA
Metro Park North II
Standish Place Room 150
Rockville, MD 20855

Re: ANDA 75-594
Pamidronate Disodium for Injection, 30 mg/vial
Response to Minor Amendment

MAJOR AMENDMENT
(Response to chemistry and labeling deficiencies)

Dear Mr. Sporn:

Aesgen, Inc. is submitting an amendment to the pending Abbreviated New Drug Application for Pamidronate Disodium for Injection, 30 mg/vial (ANDA 75-594). This amendment is being submitted in response to the FDA's MAJOR deficiency letter dated October 19, 1999. A copy of this communication is provided for your convenience. Aesgen, Inc. submitted a letter to the Agency on November 3, 1999, requesting further clarification on items 1., 3., 5., and 7. of the chemistry deficiencies. These clarifications were conveyed via voicemail by Joseph Buccini, FDA Project Manager, on November 12, 1999.

Pursuant to 21 CFR 314.120, Aesgen wishes to amend the application by restating the Agency's deficiencies (in bold type) followed by our responses with corresponding exhibits where appropriate.

This amendment is being provided to the Office of Generic Drugs in duplicate: one Archival copy and one Review copy. Please incorporate this information into the application.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 24 2000
OGD

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

A. Deficiencies

1. **Please provide your certificate of analysis for** [redacted]

   The Certificates of Analysis for three lots of the raw material [redacted] (lot numbers P1778, P1779, and P1780) are enclosed in Exhibit 1.

2. **Please revise your specifications for finished drug product to include limits for individual impurities and tighten the limit for total related compound based on your data.**

3. **Please revise your specifications for finished drug product to include limits for** [redacted]

   Response to Deficiencies 2. and 3.

   The following specifications for the finished drug product were established:

   - [redacted] Not more than [redacted]
   - [redacted] Not more than [redacted]
   - Other Related Substances (except Phosphate and [redacted]):
     Not more than [redacted] Label Claim each
     Not more than [redacted] Label Claim total
   - [redacted] Not more than [redacted]
   - [redacted] Not more than [redacted]

   Since [redacted] can only be formed during the synthesis process, its content is included in the Certificates of Analysis for three lots of [redacted] (see Exhibit 1). [redacted] is not considered a related substance or impurity in the finished drug product and therefore a specification is not set.

   The revised specifications for finished drug product are enclosed in Exhibit 2.

4. **Please revise your stability specifications to include limits for individual impurities and tighten your total limit based on your data.**

5. **Please revise your stability specifications to include limits for** [redacted]

   Response to Deficiencies 4. and 5.

   The revised stability specifications are enclosed in Exhibit 3.

Redacted 1

pages of trade secret and /or confidential commercial information

Preparation Date: August 18, 1998, Revision Date: January 14, 2000) is also included in Exhibit 8.

11. Please provide 24 hour stability data for reconstituted drug product.

The stability of the reconstituted Pamidronate Disodium for Injection, 30 mg/vial was investigated by —— Vials of lyophilized drug product from the exhibit batch, lot J57B003.00, stored at ambient room conditions, were used for the study. The reconstituted vials were stored in the inverted position at 5 °C conditions under ambient relative humidity (RH) and also at 30 °C conditions under 60% RH. The content of the vials was analyzed initially, at 24-hour, 48-hour, and 1-week time points.

Testing was performed for the following specified methods:

- Assay for pamidronate disodium and related substances on reconstituted vials at the initial and subsequent time points.
- Appearance and pH on reconstituted vials at the initial and subsequent time points.
- Particulate matter testing on reconstituted vials stored at 5 °C for 24 hours.
- ——— analysis on reconstituted vials stored at 5 °C for 24 hours.

All specifications outlined in the stability protocol OLI-PE530-9911-TNN-1, Revision 1, (Original Preparation Date: November 24, 1999, Revision Date: January 12. 2000) "Protocol for Reconstituted Pamidronate Disodium for Injection, 30 mg/Vial" (see Exhibit 9) are met. The stability report OLI-RE530-0001-TNN-1 "Stability for Reconstituted Pamidronate Disodium for Injection, 30 mg/Vial" (Original Preparation Date: January 14, 2000) is included in Exhibit 9.

12. Please revise your stability commitment to indicate that extending the expiration date requires full term data on 3 production batches.

Aesgen revised the stability commitment indicating that extending the expiration date requires full term data on three production batches. The revised stability statement is included in Exhibit 10.

13. Please submit your stability data in one table.

See Exhibit 11 for the revised stability data in one table.

B. Acknowledgements

Aesgen, Inc. notes and acknowledges the following comments:

1. The firms referenced in ANDA 75-594 will be in compliance with cGMP at the time of approval.

2. The Microbiology portion of ANDA 75-594 is under review. Comments if any, will be transmitted at a later date.

3. Aesgen's methods validation will be submitted for validation by FDA district laboratories.

This concludes our response to all of the Agency's comments listed in the Agency's letter of October 19, 1999.

We look forward to the Agency's review of this amendment response. I can be reached at 609-419-1090 x103. Thank you.

Sincerely,

Chris L. French
Director of Scientific and Regulatory Affairs

Aesgen INC.

PATENT AMENDMENT

May 14, 1999

NEW CORRESP
NC

Denise Huie
Project Manager
Division of Labeling and Program Support
Office of Generic Drugs
Department of Health and Human Resources
Food and Drug Administration
Rockville, Maryland 20857

Re: PATENT AMENDMENT
Aesgen, Inc. ANDA 75-594
Pamidronate Disodium for Injection 30 mg/vial

Dear Ms. Huie:

Aesgen has received the FDA's letter dated April 20, 1999 which acknowledges receipt of the abbreviated new drug application filed by Aesgen, Inc. for Pamidronate Disodium for Injection, 30mg/vial ("ANDA 75-594").

On April 26, 1999, in accordance with the instruction in the FDA's letter and the notice requirements of 21 C.F.R. § 314.95 and 21 U.S.C. § 355(j)(2)(B)(ii), Aesgen provided notice of its ANDA 75-594 to Novartis Corporation. Novartis is the holder of record of the approved application under 21 U.S.C. § 355(b) for the listed drug and the owner of U.S. Patent No. 4,711,880 ("the '880 patent") which has been listed as relating to the product. Therefore, an amendment to ANDA 75-594 with the certification required by 21 C.F.R. § 314.95(a) and a copy of the return receipt establishing such notice per 21 C.F.R. § 314.95(e) are attached hereto.

Please note that based on publicly available documents filed in the Federal District Court in New Jersey, Aesgen has become aware that Ben Venue Laboratories, Inc. has also filed an ANDA (i.e., ANDA 75-290) seeking approval from the FDA to sell Pamidronate Disodium for injection in 30 mg/vial, 60 mg/vial, and 90 mg/vial dosages. The documents from the New Jersey Court indicate that Novartis filed a patent infringement suit against Ben Venue alleging infringement of the '880 patent.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 17 1999
OGD

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

I have been informed that in the suit between Ben Venue and Novartis, Novartis alleged and Ben Venue admitted that Ben Venue's paragraph IV certification filed under 21 U.S.C § 355(j)(2)(A)(vii) with respect to the Novartis '880 patent was incomplete, having no certification as to the manufacture of Ben Venue's product. Specifically, Ben Venue "admit[ted] that the certification did not specifically mention the 'manufacture' of the accused product...." This certification as to manufacture is required by 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (the ANDA filer must certify that the patent listed in conjunction with the brand name drug "will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." (emphasis added)).

Based upon this information, it appears that Ben Venue has failed to certify that the manufacture of its product would not infringe Novartis' patent, rendering its paragraph IV certification incomplete. Thus, Ben Venue's certification fails to meet the statutory requirements of § 355(j)(2)(A)(vii)(IV). Accordingly, to Aesgen's knowledge, Aesgen's ANDA 75-594 is the first complete paragraph IV certification, and Aesgen should be accorded "first filer" status under 21 U.S.C. § 355(j)(5)(B)(iv) and the 180 day exclusivity it provides.

Sincerely,

Chris L. French
Director of Scientific and Regulatory Affairs

Enclosures

Aesgen INC.

April 21, 1999

NDA ORIG AMENDMENT
N/AC

Saundra T. Middleton
Project Manager
Office of Generic Drugs
Center of Drug Evaluation and Research, CDER, FDA
Metro Park North II
Standish Place Room 150
Rockville, MD 20855

Re: ANDA 75-594
Pamidronate Disodium for Injection, 30 mg/vial
Response to Refusal to File Letter

Dear Ms. Middleton:

During our telephone conversation on April 14, 1999 regarding the "Refusal to File" letter issued by the OGD on March 26, 1999 for ANDA 75-594, (Pamidronate Disodium for Injection 30 mg/vial); I was informed that the Agency has accepted Aesgen's "proposed response" (faxed to the Agency on April 1, 1999) to the "Refusal to File" letter as sufficiently complete to merit a critical technical review of this ANDA. In addition, the Agency has granted an official filing date of April 1, 1999 for this ANDA.

Reference is make to the Agency's "Refusal to File" letter dated March 26, 1999, a copy of which is provided here for your reference. Pursuant to 21 CFR 314.120, Aesgen wishes to amend the application by restating the Agency's reasons for the refusal to file (in bold type) followed by our responses with corresponding exhibits where appropriate.

- **Certificate of analysis (COA), test specifications and data for the active ingredient Pamidronate are required from the applicant.**

  This information is provided in Section XV (Finished Product Controls) of the submission. The information is included in that section because it is the final drug product that is tested for Pamidronate Disodium.

RECEIVED
APR 26 1999
GENERIC DRUGS

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

The information was not included in Section VIII (Controls) of the submission because the , and that is used to produce the final product is rather than the . The The specifications, testing and release of the final drug product is based on the analysis of the Pamidronate Disodium, the active agent. The COA, test specifications, and data for Pamidronate Disodium are found in Section XV.

The above mentioned Certificate of analysis (COA), test specifications, and data for the ultimate active ingredient Pamidronate Disodium are included again in **Exhibit 1.**

Please provide for the reference standards and test samples.

are included in the submission for the reference standard (which is also the drug substance) in Section XVI, pp. 529, 541, 543-545 (Analytical Methods). A representative for finished product is included in Section XVI, p. 511. for finished product are not included since the assay was performed with conductivity detection. The COA for the exhibit batch is in Section XV, p. 453-454.

The above mentioned are included again in **Exhibit 2.**

According to the Approved Drug Products with Therapeutic Evaluations, 18th Edition, there is an exclusivity period for the reference listed drug. Please provide an exclusivity state ment.

The Original Exclusivity Statement for Aesgen, Inc. is provided in **Exhibit 3**.

You have failed to provide an original signature for the Debarment Certification and Convictions Statement. Please resubmit the certification with original signature.

The Original Debarment Certification and Convictions Statements for Aesgen, Inc. and for are included in **Exhibit 4**.

In addition, you have failed to provide three separately bound copies of your methods validation package. Please submit three copies in separate binders.

> Based on the Guidance Document "Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application, April 1997", *two* additional copies of the methods validation package were included with the Archival Copy of the submission. During the telephone conversation of April14, 1999, I was informed that it was not necessary to send additional packages since we had included 2 copies of the method validation package in accordance with the guidance and that a note would make to the Chemistry Reviewer as to where to find these copies.

This concludes our response to all of the Agency's comments listed in the Agency's letter of March 26, 1999.

I would also like to request that the Agency provide us with a notice of acceptance to file letter confirming the filing date of April 1, 1999 for ANDA 75-594. Since this is a Paragraph IV filing, pursuant to 21 U.S.C. § 314.95(3)(b), we will send notice to the innovator as required by paragraph (a) of this section when we receive an acknowledgement letter from the FDA stating that the ANDA is sufficiently complete to permit a substantive review.

We look forward to the Agency's review of this ANDA. I can be reached at 609-419-1090 x103. Thank you.

Sincerely,

Chris L. French
Director of Scientific and Regulatory Affairs

ANDA 75-594

Aesgen, Inc.
Attention: Chris French
2 Research Way
3rd Level East
Princeton, NJ 08540

APR 20 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated March 26, 1999 and your amendment dated April 1, 1999.

NAME OF DRUG: Pamidronate Disodium for Injection, 30 mg/vial

DATE OF APPLICATION: February 17, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 5, 1999

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Harvey Greenberg, Acting Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-594
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-330
HFD-610/R.West
HFD-615/MBennett

/S/ 4/19/99

Endorsements: HFD-615/HGreenberg, Chief, RSB date
HFD-615/SMiddleton, CSO /S/ date 4/16/99
HFD-625/MSmela, Sup. Chemistry date
Word Document
V:\FIRMSAM\AESGEN\LTRS&REV\75594.ACK
F/T by mjl/4/15/99
ANDA Acknowledgment Letter!

ANDA 75-594

Aesgen, Inc.
Attention: Chris French
2 Research Way
3rd Level East
Princeton NJ 08540

MAR 26 1999

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 17, 1999 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pamidronate Disodium for Injection, 30 mg/vial.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

Certificate of analysis (COA), test specifications and data for the active ingredient Pamidronate, are required from the applicant.

Please provide Spectra and Chromatograms for the reference standards and test samples.

According to the Approved Drug Products with Therapeutic Evalutions, 18th Edition, there is an exclusivity period for the reference listed drug. Please provide an exclusivity statement.

You have failed to provide an original signature for the Debarment Certification and Convictions Statement. Please resubmit the certification with original signature.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, you have failed to provide three separately bound copies of your methods validation package. Please submit three copies in separate binders.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call.

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

/S/

for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RTF 3/16/99 /S/

Aesgen INC.

February 17, 1999

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application including Sterility Assurance Data
Pamidronate Disodium for Injection
30 mg/vial

Dear Madam or Sir:

In accordance with 21 C.F.R. § 314.92 (a)(1), Aesgen, Inc. hereby submits this Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection, 30 mg/vial, an injectable drug indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, the treatment of patients with moderate to severe Paget's disease of bone, and the treatment of patients with osteolytic bone lesions of multiple myeloma. The innovator drug is AREDIA®, NDA 20-036, held by Novartis and approved on October 31, 1991. The suitability of the ANDA is documented in the submission.

Pursuant to 21 C.F.R. § 314.94 (a)(12), paragraph IV patent certification is provided. The [redacted] in accordance with their DMF # [redacted] Aesgen's Pamidronate Disodium for Injection, 30 mg/vial will be manufactured and sold as a sterile product. The subject product is [redacted] for Aesgen by [redacted]. Appropriate current GLP and GMP certifications are provided within this application for both facilities.

In support of this submission, Aesgen commissioned [redacted] to produce a [redacted] exhibit batch, lot #1680451 which is within the [redacted] scaling factor of our proposed [redacted] commercial batch size. Three months of stability data generated for lot #1680451 stored under accelerated conditions (40° ± 2°C, 75% ± 5% RH) and controlled room temperature conditions (25° ± 2°C, 60% ± 5% RH) is included in this submission for Agency review. An expiration dating period of twenty-four months is requested based on three months acceptable stability data for the exhibit batch #1680451 stored at accelerated stability conditions.

RECEIVED
MAR 0 4 1999
GENERIC DRUGS

2 Research Way • Third Level East • Princeton, New Jersey 08540 • Telephone (609) 419-1090 • Fax (609) 419-1092

Side-by-side comparisons of the Aesgen-proposed labeling and the reference listed drug labeling are provided in this submission. In addition, 4 copies of draft labels, cartons and inserts are also provided for Agency review.

This ANDA is contained in two volumes and is organized in the manner recommended by the Office of Generic Drugs in its Policy & Procedure Guide 30-91. The [redacted]validation (Sterility Assurance) information for the [redacted] manufacturing facility is provided in Section XI of this submission. A FDA archival copy (blue folder) and a technical review copy (red folder) are provided in this submission. Field copies (maroon folder) have been sent to the FDA New Jersey District Office in Parsippany, NJ, the field office for the applicant; the FDA San Francisco District Office in Alameda, CA, the field office for [redacted]and the FDA Kansas City District Office in Lenexa, KS, the field office for [redacted] Appropriate certifications attesting to the accuracy of each copy have been provided with the field copies. Two extra copies of the method validation package for non-compendial methods are provided in black binders. Pursuant to 21 C.F.R. § 314.94 (a)(10), samples of the drug substance, finished product, applicable data and documentation, and applicable reference standards with appropriate identification will be made available upon request.

In accordance with 21 CFR § 314.94 (d)(5), Aesgen, Inc. certifies that true copies of this Abbreviated New Drug Application for Pamidronate Disodium for Injection, 30 mg/vial, have been provided to FDA's New Jersey, San Francisco and Kansas City District Offices. Copies of the accompanying certifications with original signatures are provided with this application.

If more information is needed, please contact me at (609) 419-1090 Ext. 103 or fax (609) 419-1092.

Sincerely,

Chris L French
Director, Scientific and Regulatory Affairs