

**CENTER FOR DRUG EVALUATION  
AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**75-773**

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

***Sponsor:*** American Pharmaceutical Partners, Inc.

***Approval Date:*** May 6, 2002

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:  
75-773**

## CONTENTS

---

### Reviews / Information Included in this ANDA Review.

---

|  |   |
|--|---|
| Approval Letter                                  | X |
| Tentative Approval Letter                        | X |
| ANDAs  |   |
| Approvable Letter                                |   |
| Final Printed Labeling                           | X |
| Medical Review(s)                                |   |
| Chemistry Review(s)                              | X |
| EA/FONSI   |   |
| Pharmacology Review(s)                           |   |
| Statistical Review(s)                            |   |
| Microbiology Review(s)                           | X |
| Clinical Pharmacology & Biopharmaceutics Reviews |   |
| Bioequivalence Review(s)                         | X |
| Administrative Document(s)                       | X |
| Correspondence                                   | X |

---

**CENTER FOR DRUG  
EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

*75-773*

**APPROVAL LETTER**

ANDA 75-773

MAY 6 2002

American Pharmaceutical Partners, Inc.  
Attention: Krisztina Nemenyi, Ph.D.  
2045 North Cornell Avenue  
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 29, 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 August 24, 2001, and to your amendments dated November 8, 2001; and January 25, and April 1, 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).

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. This certification states that the '880 patent will not be infringed by your manufacture, use, or sale of this drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effectively immediately, unless an action is brought against American Pharmaceutical Partners, Inc. (APP) for infringement of the patent that is the subject of the certification (the '880

patent). You have notified the agency the APP has complied with the requirements of Section 505 (j) (2) (B) of the Act. As a result, APP was sued in the United States District Court for the Northern District of Illinois involving a challenge to the '880 patent (Novartis Corporation v. American Pharmaceutical Partners, Inc., Civil Action No. 00C 2313). You have informed the agency of a Consent Order entered by the district court on November 6, 2001, stating that the drug product provided for in this ANDA does not infringe the '880 patent held by Novartis Corporation. Furthermore, the 180-day generic drug exclusivity granted by the agency to Bedford Laboratories (Bedford) for this drug product under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j) (5) (B) (iv) of the Act expired on May 5, 2002.

Under Section 506(A) 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 ANDA 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 that 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 final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Ytansmittal 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 that may be identified.

Sincerely yours,

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

APPEARS THIS WAY  
ON ORIGINAL

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

***75-773***

**TENTATIVE APPROVAL  
LETTER**

ANDA 75-773

AUG 24 2001

American Pharmaceutical Partners, Inc.  
Attention: Lincy Michael  
2045 North Cornell Avenue  
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application dated December 29, 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 March 13, June 18, and July 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. This certification states that the '880 patent will not be infringed by your manufacture, use, or sale of this drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effectively immediately, unless an action is brought against American Pharmaceutical Partners, Inc. (APP) for infringement of

the patent that is the subject of the certification (the '880 patent). You have notified the agency the APP has complied with the requirements of Section 505 (j) (2) (B) of the Act. As a result, litigation is currently underway in the United States District Court for the Northern District of Illinois involving a challenge to the '880 patent (Novartis Corporation v. American Pharmaceutical Partners, Inc., Civil Action No. 00C 2313).

Furthermore, please note that ANDA 75-290 submitted by Bedford Laboratories (Bedford) for this drug product and also containing a Paragraph IV Certification was accepted for filing by this office prior to the filing of your application. This application was granted final approval on April 30, 2001. Consequently, Bedford is deemed eligible for 180-days of generic drug market exclusivity as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j) (5) (B) (iv) of the Act. Bedford's exclusivity will begin to run either from the date Bedford begins commercial marketing of the drug product under its ANDA, or in the absence of marketing from the date of a decision of a court finding that Bedford did not infringe the '880 patent, whichever event occurs earlier (Section 505(j) (5) (B) (iv)). We refer you to the Agency's issued guidance document "180 Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

We believe that your application for this drug product will be eligible for final approval upon your successful resolution of your court case with Novartis or expiration of the 30-month statutory period, and upon the expiration of Bedford's 180-day generic drug exclusivity.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED approximately 90 days prior to the date you believe your application should be considered eligible for final approval. Your amendment should provide:

1. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
2. a statement that no such changes have been made to the application since the date of tentative approval, and

3. a summary of the legal and/or regulatory events which have occurred and which you believe provide for final approval of this application.

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

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

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.

The amendment should be designated as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED in your cover letter. Before you submit the amendment or if you have questions about the status of this application, please contact Sarah Ho, R.Ph., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,

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

*For 8/24/2001*

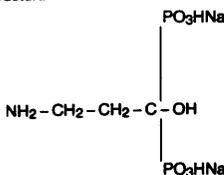
**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

*75-773*

Final Printed Labeling

**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 for Injection, 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, and its structural formula is:



$\text{C}_3\text{H}_9\text{NO}_7\text{P}_2\text{Na}_2$  M.W. 279.03

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.

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

**CLINICAL PHARMACOLOGY:**  
The principle 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  $\pm$  SD body retention of pamidronate was calculated to be  $54 \pm 16\%$  of the dose over 120 hours.

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

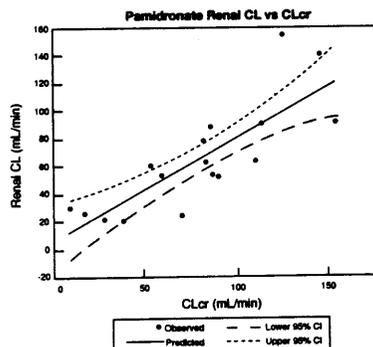
**Excretion**  
After administration of 30, 60, and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate disodium over 24 hours, an overall mean  $\pm$  SD of  $46 \pm 16\%$  of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean  $\pm$  SD elimination half-life is  $28 \pm 7$  hours. Mean  $\pm$  SD total and renal clearances of pamidronate were  $107 \pm 50$  mL/min and  $49 \pm 28$  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.

**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 (4 hrs)        | 0.73 (0.14, 19.1%)             | 43.9 (14.0, 31.9%)                | 136 (44, 32.4%)          | 58 (27, 46.5%)           |
| 60 mg (4 hrs)        | 1.44 (0.57, 39.6%)             | 47.4 (47.4, 54.4%)                | 88 (56, 63.6%)           | 42 (28, 66.7%)           |
| 90 mg (4 hrs)        | 2.61 (0.74, 28.3%)             | 45.3 (25.8, 56.9%)                | 103 (37, 35.9%)          | 44 (16, 36.4%)           |
| 90 mg (24 hrs)       | 1.38 (1.97, 142.7%)            | 47.5 (10.2, 21.5%)                | 101 (58, 57.4%)          | 52 (42, 80.8%)           |

After intravenous administration of radiolabeled pamidronate in rats, approximately 50% to 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 to 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 to 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 20% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7 to 10 days.

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

**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 prograde dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal reabsorption 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 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. Tumor products 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 calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several algorithms are in use for this type of calculation (see DOSE AND ADMINISTRATION).

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

The mean baseline-corrected serum calcium levels 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 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 64% of the patients receiving 30 mg, 60 mg, and 90 mg of pamidronate disodium, respectively, had normal-corrected serum calcium levels. Many patients (33% to 53%) in the 30-mg and 90-mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response (21.5% 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

**APP AMERICAN PHARMACEUTICAL PARTNERS, INC.**



45885/issued: August 2000

**PAMIDRONATE DISODIUM FOR INJECTION**

Rx only

**APPROVED**

MAY - 6 2002

≥ 12.0 mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of pamidronate disodium 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 disodium and 35 to receive etidronate disodium.

The mean baseline-corrected serum calcium for the pamidronate disodium 60-mg and etidronate disodium 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 ( $\geq 15\%$  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 disodium 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:

**Table 2**  
Change in Corrected Serum Calcium by Time from Initiation of Treatment

| Time (hr) | Mean Change from Baseline in Corrected Serum Calcium (mg/dL) |                     |  | P-Value <sup>1</sup> |
|-----------|--|---------------------|--|----------------------|
|           | Pamidronate Disodium   | Etidronate Disodium |  |                      |
| 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                |

<sup>1</sup>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  $\geq 12.0$  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 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 hydroxyproline/creatinine ratios (UOHP/C) are summarized in the following table:

**Table 3**  
Percent of Patients With Significant % Decreases in SAP and UOHP/C

| % Decrease | SAP   |       |       | UOHP/C |       |       |
|------------|-------|-------|-------|--------|-------|-------|
|            | 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 decrease 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 ( $\geq 50\%$  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  $\geq 50\%$  decrease in serum alkaline phosphatase from baseline after treatment, and 39% had a  $\geq 50\%$  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 can 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.

#### 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 antineoplastic 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 than 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 ( $P < .01$ ) 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 Table 4 below.

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 Table 5 below.

#### 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 for Injection. 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 for Injection 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 for Injection was demonstrated primarily in patients with serum alkaline phosphatase  $\geq 3$  times the upper limit of normal. Pamidronate Disodium for Injection therapy in patients with Paget's disease has been effective in reducing serum alkaline phosphatase and urinary hydroxyproline levels by  $\geq 50\%$  in at least 50% of patients, and by  $\geq 30\%$  in at least 80% of patients. Pamidronate Disodium for Injection 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 for Injection 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).

**Table 4**

|                                      | Breast Cancer Patients Receiving Chemotherapy |     |                    |     |                    |     | Breast Cancer Patients Receiving Hormonal Therapy |     |                   |     |                   |     |
|--------------------------------------|---|-----|--------------------|-----|--------------------|-----|---|-----|-------------------|-----|-------------------|-----|
|                                      | Any SRE                                       |     | Radiation          |     | Fractures          |     | Any SRE   |     | Radiation         |     | Fractures         |     |
|                                      | PD  | P   | PD                 | P   | PD                 | P   | PD  | P   | PD                | P   | PD                | 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 <sup>1</sup> |     | <.018 <sup>1</sup> |     | .021  |     | .013 <sup>1</sup> |     | .040 <sup>1</sup> |     |
| Proportion of patients having an SRE |   |     |                    |     |                    |     |   |     |                   |     |                   |     |
| P-Value                              | .46%  |     | .65%               |     | .28%               |     | .45%  |     | .36%              |     | .49%              |     |
| P-Value                              | <.001   |     | <.001 <sup>1</sup> |     | <.014 <sup>1</sup> |     | .094  |     | .058 <sup>1</sup> |     | .054 <sup>1</sup> |     |
| Median Time to SRE (months)          |   |     |                    |     |                    |     |   |     |                   |     |                   |     |
| P-Value                              | 13.9  |     | 7.0                |     | NR**               |     | 14.2  |     | 25.8              |     | 13.3              |     |
| P-Value                              | <.001   |     | <.001 <sup>1</sup> |     | <.009 <sup>1</sup> |     | .118  |     | .016 <sup>1</sup> |     | .113 <sup>1</sup> |     |

<sup>1</sup>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.

**Table 5**  
Mean Change ( $\Delta$ ) from Baseline at Last Measurement

|                 | Breast Cancer Patients Receiving Chemotherapy |               |         |               | Breast Cancer Patients Receiving Hormonal Therapy |               |         |               |
|-----------------|---|---------------|---------|---------------|---|---------------|---------|---------------|
|                 | Pamidronate Disodium                          |               | Placebo |               | Pamidronate Disodium                              |               | Placebo |               |
|                 | N   | Mean $\Delta$ | N       | Mean $\Delta$ | N   | Mean $\Delta$ | N       | Mean $\Delta$ |
| Pain Score      | 175   | +0.93         | 183     | +1.69         | 173   | +0.50         | 179     | +1.60         |
| Analgesic Score | 175   | +0.74         | 183     | +1.55         | 173   | +0.90         | 179     | +2.28         |
| ECOG PS         | 178   | +0.81         | 186     | +1.19         | 175   | +0.95         | 182     | +0.90         |
| Spitzer QOL     | 177   | -1.76         | 185     | -2.21         | 173   | -1.86         | 181     | -2.05         |

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.

• PD = Pamidronate Disodium

**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 for Injection.

Two 7-day intravenous infusion studies were conducted in the dog wherein Pamidronate Disodium for Injection was given for 1, 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  $\geq 10$  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  $\geq 1$  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  $\geq 6$  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, morbidity/death and renal toxicity occurred at 20 mg/kg and kidney findings of elevated BUN and creatinine levels at  $\geq 6$  mg/kg and renal tubular degeneration at  $\geq 4$  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 Disodium for Injection 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 for Injection. Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (1%), and hypocalcemia (5%-12%), were reported in Pamidronate Disodium for Injection-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with Pamidronate Disodium for Injection 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 for Injection showed serum calcium levels below 8 mg/dL.

Pamidronate Disodium for Injection has not been tested in patients who have class D or renal impairment (creatinine  $\geq 5.0$  mg/dL), and in few multiple myeloma patients with serum creatinine  $\geq 3.0$  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 for Injection. Patients who have pre-existing 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 for Injection.

**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 ( $P < 0.0001$ ). 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 for Injection 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 for Injection (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 coli*-microsome test, nucleus-anomaly test, sister-chromatid-exchange study, point-mutation test, and micronucleus test in the rat.

In rats, decreased fertility occurred in the first-generation offspring of parents who had received 150 mg/kg of Pamidronate Disodium for Injection orally; however, this occurred only when animals were mated with members of the same dose group. Pamidronate Disodium for Injection 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 for Injection 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 for Injection can cross the placenta in rats and has produced marked maternal and nonreproductive 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 for Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Pamidronate Disodium for Injection is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of Pamidronate Disodium for Injection 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 for Injection 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 for Injection. 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 has been reported, including one case of scleritis, and one case of uveitis upon separate rechallenges.

Four of 128 patients (3%) who received Pamidronate Disodium for Injection 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 Injection 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
- Neurological: 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 the comparative, controlled U.S. trials.

**Table 6**  
Treatment-Related Adverse Experiences Reported in Three U.S. Controlled Clinical Trials

|                                 | Percent of Patients           |                           |                           |  |        |
|---------------------------------|-------------------------------|---------------------------|---------------------------|--|--------|
|                                 | Pamidronate Disodium for Inj. |                           |                           |  | Saline |
|                                 | 60 mg over 4 hrs<br>n=23      | 60 mg over 24 hrs<br>n=73 | 90 mg over 24 hrs<br>n=17 | 7.5 mg/kg over 24 hrs x3 doses<br>n=35 |        |
| <b>General</b>                  |                               |                           |                           |  |        |
| 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      |
| <b>Gastrointestinal</b>         |                               |                           |                           |  |        |
| Abdominal pain                  | 0                             | 1                         | 0                         | 0                                      | 0      |
| Anorexia                        | 4                             | 1                         | 12                        | 0                                      | 0      |
| Constipation                    | 4                             | 0                         | 0                         | 0                                      | 0      |
| Diarrhea                        | 0                             | 1                         | 0                         | 3                                      | 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      |
| <b>Respiratory</b>              |                               |                           |                           |  |        |
| 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      |
| <b>CNS</b>                      |                               |                           |                           |  |        |
| 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      |
| <b>Cardiovascular</b>           |                               |                           |                           |  |        |
| 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      |
| <b>Endocrine</b>                |                               |                           |                           |  |        |
| Hypothyroidism                  | 0                             | 0                         | 6                         | 0                                      | 0      |
| <b>Hemic and Lymphatic</b>      |                               |                           |                           |  |        |
| Anemia                          | 0                             | 0                         | 6                         | 0                                      | 0      |
| Leukopenia                      | 4                             | 0                         | 0                         | 0                                      | 0      |
| Neutropenia                     | 0                             | 1                         | 0                         | 0                                      | 0      |
| Thrombocytopenia                | 0                             | 1                         | 0                         | 0                                      | 0      |
| <b>Musculoskeletal</b>          |                               |                           |                           |  |        |
| Myalgia                         | 0                             | 1                         | 0                         | 0                                      | 0      |
| <b>Urogenital</b>               |                               |                           |                           |  |        |
| Uremia                          | 4                             | 0                         | 0                         | 0                                      | 0      |
| <b>Laboratory Abnormalities</b> |                               |                           |                           |  |        |
| 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      |

**Paget's Disease**

Transient mild elevation of temperature  $> 1^\circ\text{C}$  above pre-treatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of Pamidronate Disodium for Injection 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 for Injection 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 for Injection in two U.S. clinical trials, were fever, nausea, back pain, and bone pain.

At least 10% of all Pamidronate Disodium for Injection-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 for Injection and placebo treatment groups, and most of these adverse experiences may have been related to the underlying disease state or cancer therapy. (See Table 7 below).

Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia, and anemia were slightly more common in the Pamidronate Disodium for Injection 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 for Injection patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of Pamidronate Disodium for Injection-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for Pamidronate Disodium for Injection-treated patients were 3.3%, 10.5%, 1.7% and 4.4%, respectively, and for placebo-treated patients were 1.2%, 1.2%, 1.7%, and 4.5%, respectively. In previous hypercalcemia of malignancy trials, patients treated with Pamidronate Disodium for Injection (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 for Injection 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 for Injection-related serious and unexpected

other bisphosphonates

**OVERDOSAGE:**

There have been several of intravenous Pamidronate Disodium for Injection patients with severe hypocalcemia. In addition, one case with 285 mg of Pamidronate Disodium for Injection experienced hypocalcemia noted about 6 hours and hypotension were also reported; such patient received intravenous calcium.

**DOSE AND ADMINISTRATION**

**Hypercalcemia of Malignancy**  
Consideration should be given to the symptoms of hypercalcemia. Overhydration may be sufficient to relieve hypercalcemia. Overhydration may have potential for associated with hemolysis and acute renal failure.

**Moderate Hypercalcemia**  
The recommended dose of Pamidronate Disodium for Injection in moderate hypercalcemia\* of approximately 60 mg over 24 hours. The 60-mg dose is given as a 1-hour intravenous infusion over 24 hours.

**Severe Hypercalcemia**  
The recommended dose of Pamidronate Disodium for Injection in severe hypercalcemia\* is 90 mg over 24 hours.

\*Albumin-corrected calcium, mg/dL  $\pm 0.8$

**Table 7**

|                                   | Commonly Reported Adverse Experiences in Three U.S. Controlled Trials |                       |  |                     |
|-----------------------------------|---|-----------------------|--|---------------------|
|                                   | Pamidronate Disodium for Injection 90 mg over 4 hrs<br>N=205<br>%     | Placebo<br>N=187<br>% | Pamidronate Disodium for Injection 90 mg over 24 hrs<br>N=367<br>% | Placebo<br>N=3<br>% |
| <b>General</b>                    |   |                       |  |                     |
| Asthenia                          | 16.1  | 17.1                  | 25.6   | 19.0                |
| Fatigue                           | 31.7  | 28.3                  | 40.3   | 28.0                |
| Fever                             | 38.5  | 38.0                  | 38.1   | 32.0                |
| Metastases                        | 0   | 3.0                   | 31.3   | 24.0                |
| Pain                              | 13.2  | 11.8                  | 15.0   | 18.0                |
| <b>Digestive System</b>           |   |                       |  |                     |
| Anorexia                          | 17.1  | 17.1                  | 31.1   | 24.0                |
| Constipation                      | 28.3  | 31.7                  | 36.0   | 38.0                |
| Diarrhea                          | 26.8  | 26.8                  | 29.4   | 30.0                |
| Dyspepsia                         | 17.6  | 13.4                  | 18.3   | 15.0                |
| Nausea                            | 35.6  | 37.4                  | 63.5   | 59.0                |
| Pain Abdominal                    | 19.5  | 16.0                  | 24.3   | 18.0                |
| Vomiting                          | 16.6  | 19.8                  | 46.3   | 39.0                |
| <b>Hemic and Lymphatic</b>        |   |                       |  |                     |
| Anemia                            | 47.8  | 41.7                  | 39.5   | 36.0                |
| Granulocytopenia                  | 20.5  | 15.5                  | 19.3   | 20.0                |
| Thrombocytopenia                  | 16.6  | 17.1                  | 12.5   | 14.0                |
| <b>Musculoskeletal System</b>     |   |                       |  |                     |
| Arthralgias                       | 10.7  | 7.0                   | 15.3   | 12.0                |
| Myalgia                           | 25.4  | 15.0                  | 26.4   | 22.0                |
| Skeletal pain                     | 61.0  | 71.7                  | 70.0   | 75.0                |
| <b>CNS</b>                        |   |                       |  |                     |
| Anxiety                           | 7.8   | 9.1                   | 18.0   | 16.0                |
| Headache                          | 24.4  | 19.8                  | 27.2   | 23.0                |
| Insomnia                          | 17.1  | 17.2                  | 25.1   | 19.0                |
| <b>Respiratory System</b>         |   |                       |  |                     |
| Coughing                          | 26.3  | 22.5                  | 25.3   | 19.0                |
| Dyspnea                           | 22.0  | 21.4                  | 35.1   | 24.0                |
| Pleural Effusion                  | 2.9   | 4.3                   | 15.0   | 9.0                 |
| Sinusitis                         | 14.6  | 16.6                  | 16.1   | 10.0                |
| Upper Respiratory Tract Infection | 32.2  | 28.3                  | 19.6   | 20.0                |
| <b>Urogenital System</b>          |   |                       |  |                     |
| Urinary Tract Infection           | 15.6  | 9.1                   | 20.2   | 17.0                |

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 for Injection-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 for Injection-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 for Injection patient discontinued the trial due to a symptomatic hypocalcemia. Another Pamidronate Disodium for Injection 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 for Injection is contraindicated in patients with clinically significant hypersensitivity to Pamidronate Disodium for Injection or

**Retreatment**

A limited number of patients with moderate hypercalcemia. Retreatment, in patients who have received a normal or remain normal, is not recommended, to allow the dose and manner of the initial therapy.

**Paget's Disease**

The recommended dose of Pamidronate Disodium for Injection in patients with severe hypercalcemia is 90 mg over 24 hours.

**Retreatment**

A limited number of patients with moderate hypercalcemia. Retreatment, in patients who have received a normal or remain normal, is not recommended, to allow the dose and manner of the initial therapy.

**Osteolytic Bone Lesions**

The recommended dose of Pamidronate Disodium for Injection in patients with severe hypercalcemia is 90 mg over 24 hours.

curred in at least 5% of patients with Paget's with 90 mg of Pamidronate Disodium for Injection trials, were fever, nausea, back pain,

of all Pamidronate Disodium for Injection with Paget's disease also experienced the adverse experiences during clinical trials:  
**Adverse Experiences:**  
 Arthrosis, bone pain  
 Headache  
 Adverse experiences may have been related to disease state.  
**Osteolytic Bone Metastases of Breast Cancer and Lesions of Multiple Myeloma:**  
 Adverse experiences similar to those reported in the Pamidronate Disodium and placebo treatment groups, and most adverse experiences may have been related to the disease state or cancer therapy. (See Table 7)

Adverse experiences commonly associated with chemotherapy of vomiting, anorexia, and anemia were common in the Pamidronate Disodium for Injection trials whereas stomatitis and alopecia occurred infrequently in the Pamidronate Disodium for Injection trials. In the breast cancer trials, elevations of serum creatinine occurred infrequently in Pamidronate Disodium for Injection patients and placebo patients. Mineral and electrolyte disturbances were reported rarely in Pamidronate Disodium for Injection patients compared with those in the placebo group. Reported frequencies of hypocalcemia, hypophosphatemia, and hypomagnesemia for Pamidronate Disodium for Injection-treated patients were 7% and 4.4%, respectively, and for placebo patients were 1.2%, 1.2%, 1.7%, and 4.5%, respectively. In malignancy trials, patients receiving Pamidronate Disodium for Injection (every 24 hours) developed electrolyte abnormalities infrequently (see ADVERSE REACTIONS, Laboratory Tests). In malignancy trials, patients receiving Pamidronate Disodium for Injection (every 24 hours) were reported slightly more frequently than placebo patients (13.6% and 26% vs 10.8% and 20.1%, respectively).

In malignancy trials, there were five Pamidronate Disodium for Injection-related serious and unexpected

other bisphosphonates (see CONTRAINDICATIONS).

**OVERDOSAGE:**

There have been several cases of drug maladministration of intravenous Pamidronate Disodium for Injection 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 for Injection/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.

**DOSE 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 for Injection 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 for Injection 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).

Table 7

| Commonly Reported Adverse Experiences in Three U.S. Controlled Clinical Trials |   |                 |   |                 |  |                 |
|--|---|-----------------|---|-----------------|--|-----------------|
|  | Pamidronate Disodium for Injection 90 mg over 4 hrs N=205 % | Placebo N=187 % | Pamidronate Disodium for Injection 90 mg over 2 hrs N=367 % | Placebo N=386 % | All Pamidronate Disodium for Injection 90 mg N=572 % | Placebo N=573 % |
| fever  | 16.1  | 17.1            | 25.6  | 19.2            | 22.2   | 18.5            |
|  | 31.7  | 28.3            | 40.3  | 28.8            | 37.2   | 29.0            |
|  | 38.5  | 38.0            | 38.1  | 32.1            | 38.5   | 34.0            |
|  | 1.0   | 3.0             | 31.3  | 24.4            | 20.5   | 17.5            |
|  | 13.2  | 11.8            | 15.0  | 18.1            | 14.3   | 16.1            |
| nausea   | 17.1  | 17.1            | 31.1  | 24.9            | 26.0   | 22.3            |
|  | 28.3  | 31.7            | 36.0  | 38.6            | 33.2   | 35.1            |
|  | 26.8  | 26.8            | 29.4  | 30.6            | 28.5   | 29.7            |
|  | 17.6  | 13.4            | 18.3  | 15.0            | 22.6   | 17.5            |
|  | 35.6  | 37.4            | 63.5  | 59.1            | 53.5   | 51.8            |
|  | 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            |
|  | 47.8  | 41.7            | 39.5  | 36.8            | 42.5   | 38.4            |
| diarrhea   | 20.5  | 15.5            | 19.3  | 20.5            | 19.8   | 18.8            |
|  | 16.6  | 17.1            | 12.5  | 14.0            | 14.0   | 15.0            |
| GI System  | 10.7  | 7.0             | 15.3  | 12.7            | 13.6   | 10.8            |
|  | 25.4  | 15.0            | 26.4  | 22.5            | 26.0   | 20.1            |
|  | 61.0  | 71.7            | 70.0  | 75.4            | 66.8   | 74.0            |
| headache   | 7.8   | 9.1             | 18.0  | 16.8            | 14.3   | 14.3            |
|  | 24.4  | 19.8            | 27.2  | 23.6            | 26.2   | 22.3            |
|  | 17.1  | 17.2            | 25.1  | 19.4            | 22.2   | 19.0            |
| fatigue  | 26.3  | 22.5            | 25.3  | 19.7            | 25.7   | 20.6            |
|  | 22.0  | 21.4            | 35.1  | 24.4            | 30.4   | 23.4            |
|  | 2.9   | 4.3             | 15.0  | 9.1             | 10.7   | 7.5             |
|  | 14.6  | 16.6            | 16.1  | 10.4            | 15.6   | 12.0            |
| dyspnea  | 32.2  | 28.3            | 19.6  | 20.2            | 24.1   | 22.9            |
|  | 15.6  | 9.1             | 20.2  | 17.6            | 18.5   | 15.6            |

cases. Four of these were reported during the course of the multiple myeloma trial. Three of these were of worsening renal function developing in aggressive multiple myeloma or multiple myeloma with amyloidosis. The fourth report was of respiratory distress syndrome developing in a patient with pneumonia and acute gangrenous necrotizing colitis. Pamidronate Disodium for Injection-related allergic reaction characterized by itchy eyes, runny nose, and scratchy throat after the sixth infusion. In the breast cancer trials, there were four Pamidronate Disodium for Injection-related adverse experiences, all moderate to severe, that caused a patient to discontinue Pamidronate Disodium for Injection. One was due to interstitial pneumonitis and dyspnea. One Pamidronate Disodium for Injection patient discontinued the trial due to hypocalcemia. Another Pamidronate Disodium for Injection patient discontinued therapy due to hypocalcemia after each infusion, which the investigator-related.

**Experience:** Allergic manifestations have been reported, including anaphylaxis, angioedema, and, very rarely, shock. Pamidronate Disodium for Injection-related adverse experiences with clinically significant hypocalcemia were reported in Pamidronate Disodium for Injection

**Retreatment**

A limited number of patients have received more than one treatment with Pamidronate Disodium for Injection for hypercalcemia. Retreatment with Pamidronate Disodium for Injection, 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 for Injection 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 for Injection 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 for Injection in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4-hour infusion given on a monthly basis.

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to Pamidronate Disodium for Injection infusion.

Limited information is available on the use of Pamidronate Disodium for Injection 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 benefits (see Clinical Trials).

**Osteolytic Bone Metastases of Breast Cancer**

The recommended dose of Pamidronate Disodium for Injection 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, megestrol, 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 benefits (see Clinical Trials).

**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 to 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:**

| Product No. | NDC No.      | Description  |
|-------------|--------------|--|
| 730610      | 63323-736-10 | Pamidronate Disodium for Injection, 30 mg/vial, in a 10 mL vial, packaged in trays of 4. |
| 730710      | 63323-737-10 | Pamidronate Disodium for Injection, 90 mg/vial, in a 10 mL vial, individually packaged.  |

Vial stoppers do not contain natural rubber latex.

Do not store above 86°F (30°C).

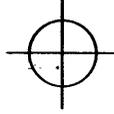


Los Angeles, CA 90024

45885  
 Issued: August 2000

7B

7B



**PAMIDRONATE  
DISODIUM  
FOR INJECTION  
90 mg/vial**

Each vial contains:  
pamidronate disodium  
90 mg; mannitol, USP,  
375 mg in lyophilized  
form; and phosphoric  
acid to adjust pH. The  
pH of the reconstituted  
solution is 6.0 to 7.4.

Vial stoppers do  
not contain natural  
rubber latex.

**Important:  
Reconstitution differs  
for each indication.**

Usual Dosage: See  
insert for Dosage and  
Administration and  
Preparation of Solution.

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

**Do not store above  
30°C (86°F).**

**APP** AMERICAN  
PHARMACEUTICAL  
PARTNERS, INC.  
Los Angeles, CA 90024

**APP** AMERICAN  
PHARMACEUTICAL  
PARTNERS, INC.

NDC 63323-737-10 730710  
Sterile, Lyophilized

**PAMIDRONATE  
DISODIUM**

**FOR INJECTION**

**90 mg/vial**

For Intravenous  
Infusion

Do not mix with calcium-  
containing infusion  
solutions.

Rx only

**APP** AMERICAN  
PHARMACEUTICAL  
PARTNERS, INC.

MAY - 6 2002



3 63323-737-10 8

**APPROVED**

62715

**BLACK 339C**

75-778

AP 5/6/02

NDC 63323-737-10 730710  
Sterile, Lyophilized

**PAMIDRONATE  
DISODIUM**

FOR INJECTION  
**90 mg/vial**

For Intravenous Infusion  
Do not mix with calcium-  
containing infusion solutions.  
Rx only

Each vial contains pamidronate disodium 90 mg, mannitol USP, 37.5 mg in lyophilized form, and phosphoric acid to adjust pH. The pH of the reconstituted solution is 6.0 to 7.4.

**MAY - 6 2002**

Important: Reconstitution differs for each indication. See insert for Dosage, Administration and Preparation of Solution.

Pamidronate disodium reconstituted with water for injection, USP, may be stored under refrigeration (2°-8°C (35°-46°F)) for up to 24 hours. Do not store above 30°C (86°F). Vial stoppers do not contain natural rubber latex.

**APPROVED**  
Los Angeles, CA 90024

401971

**APPROVED**

NDC 63323-736-10 730610  
Sterile, Lyophilized

**PAMIDRONATE  
DISODIUM**

FOR INJECTION  
**30 mg/vial**

For Intravenous Infusion  
Do not mix with calcium-  
containing infusion solutions.  
Rx only

Each vial contains pamidronate disodium 30 mg, mannitol USP, 47.0 mg in lyophilized form, and phosphoric acid to adjust pH. The pH of the reconstituted solution is 6.0 to 7.4.

**MAY - 6 2002**

Important: Reconstitution differs for each indication. See insert for Dosage, Administration and Preparation of Solution.

Pamidronate disodium reconstituted with water for injection, USP, may be stored under refrigeration (2°-8°C (35°-46°F)) for up to 24 hours. Do not store above 30°C (86°F). Vial stoppers do not contain natural rubber latex.

**APPROVED**  
Los Angeles, CA 90024

401970

**APPROVED**

**CENTER FOR DRUG  
EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

**75-773**

**CHEMISTRY REVIEW(S)**

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-773

3. NAME AND ADDRESS OF APPLICANT

American Pharmaceutical Partners, Inc.  
2045 North Cornell Ave.  
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that the U.S. Patent 4711880 held by Novartis Pharmaceuticals Corporation will not be infringe by the manufacture, use or sale of Pamidronate Disodium for injection. This patent will expire July 29, 2005. The firm certifies that the exclusivity period expired on July 16, 1999.

5. SUPPLEMENT(s)

Original 12/29/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

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

N/A

9. AMENDMENTS AND OTHER DATES:

10. PHARMACOLOGICAL CATEGORY

Hypercalcemia of malignancy

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

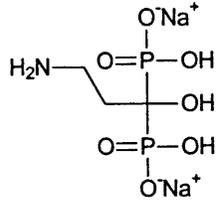
Injectable (lyophilized)

14. POTENCY

30 mg/vial in 10 mL vial  
90 mg/vial in 10 mL vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. C<sub>3</sub>H<sub>9</sub>NNa<sub>2</sub>O<sub>7</sub>P<sub>2</sub>. 109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS



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. 7/11/00

**Redacted** 7

**pages of trade**

**secret and /or**

**confidential**

**commercial**

**information**

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-773

3. NAME AND ADDRESS OF APPLICANT

American Pharmaceutical Partners, Inc.  
2045 North Cornell Ave.  
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that the U.S. Patent 4711880 held by Novartis Pharmaceuticals Corporation will not be infringe by the manufacture, use or sale of Pamidronate Disodium for injection. This patent will expire July 29, 2005. The firm certifies that the exclusivity period expired on July 16, 1999.

5. SUPPLEMENT(s)

Original 12/29/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 3/13/01  
Amendment 6/18/01  
Amendment 7/27/01 (typographical error corrections in the finished product and stability specs and in the test methods in the 3/13/01 major amendment)

10. PHARMACOLOGICAL CATEGORY

Hypercalcemia of malignancy

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Injectable (lyophilized)

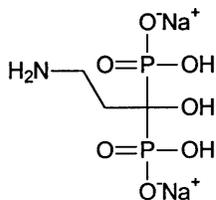
14. POTENCY

30 mg/vial in 10 mL vial

90 mg/vial in 10 mL 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 microbiology portion of the application is satisfactory 8/7/00.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable - pending acceptable method validation.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 7/27/01

Acting Team Leader: Gil Kang, Ph.D. 7/27/01 revised 8/20/01

cc: ANDA 75-773  
Dup  
Division File

Endorsements:

HFD-620/N. Nashed/  
HFD-620/Gil Kang, Ph.D. Acting TL/  
HFD-620/S.Ho, PM/

V:\FIRMSAM\APP\LTRS&REV\75-773.2.DOC  
F/T by: DJ 8/22/01

**Redacted**     

**pages of trade**

**secret and /or**

**confidential**

**commercial**

**information**

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-773

3. NAME AND ADDRESS OF APPLICANT

American Pharmaceutical Partners, Inc.  
2045 North Cornell Ave.  
Melrose Park, IL 60160

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that the U.S. Patent 4711880 held by Novartis Pharmaceuticals Corporation will not be infringe by the manufacture, use or sale of Pamidronate Disodium for injection. This patent will expire July 29, 2005. The firm certifies that the exclusivity period expired on July 16, 1999.

5. SUPPLEMENT(s)

Original 12/29/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Pamidronate Disodium

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 3/13/01

Amendment 6/18/01

Amendment 7/27/01 (typographical error corrections in the finished product and stability specs and in the test methods in the 3/13/01 major amendment)

New Correspondence - 11/8/01

New Correspondence - 11/21/01

Minor Amendment 1/25/02 (request final approval)

New Correspondence 4/1/02 (MV commitment)

10. PHARMACOLOGICAL CATEGORY

Hypercalcemia of malignancy

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

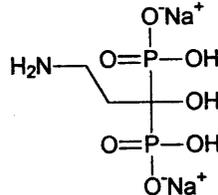
14. POTENCY

Injectable (lyophilized)

30 mg/vial in 10 mL vial  
90 mg/vial in 10 mL vial

15. CHEMICAL NAME AND STRUCTURE

Pamidronate Disodium. Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt. C<sub>3</sub>H<sub>9</sub>NNa<sub>2</sub>O<sub>7</sub>P<sub>2</sub>.  
109552-15-0. Suppressant.



16. RECORDS AND REPORTS

17. COMMENTS

The microbiology portion of the application is satisfactory  
8/7/00.

8/24/01 - TA

The firm indicated that no updated information to submit for  
the application (1/25/02 Minor amendment - requests final  
approval).

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable - Final approval pending  
method validation.

19. REVIEWER:

DATE COMPLETED:

*/s/*  
Nashed E. Nashed, Ph.D.

*4/22/02*  
2/20/02

cc: Supervisor: James M. Fan  
ANDA 75-773  
Dup  
Division File  
Field Copy

3/3/02

*/s/* *4/22/02*

Endorsements:

HFD-627/NNashed/4/19/02  
HFD-627/JFan/

*/s/* *4/22/02*

*/s/* *4/22/02*

V:\FIRMSAM\APP\LTRS&REV\75-773.3.DOC  
F/T by: DJ 4/4/02

**Redacted** 9

**pages of trade secret and/or**

**confidential**

**commercial**

**information**

**CENTER FOR DRUG EVALUATION  
AND RESEARCH**

**APPLICATION NUMBER:**

**75-773**

**MICROBIOLOGY REVIEW**

1.1

OFFICE OF GENERIC DRUGS, HFD-620  
Microbiology Review #1  
July 31, 2000

A. 1. ANDA 75-773

APPLICANT: American Pharmaceutical Partners, Inc.

2. PRODUCT NAME: Pamidronate Disodium for Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 30 mg in 10 mL vial and 90 mg in 10 mL vial as Lyophilized powder for Intravenous infusion.

4. METHOD(S) OF STERILIZATION: \_\_\_\_\_

5. PHARMACOLOGICAL CATEGORY: Hypercalcemia of malignancy

B. 1. DATE OF INITIAL SUBMISSION: December 29, 1999  
Subject of this Review (Received December 30, 1999)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: July 26, 2000

C. REMARKS: The subject drug product is manufactured by American Pharmaceutical Partners, Inc. at its manufacturing facility located in Melrose Park, IL. The subject drug is \_\_\_\_\_ in 10-mL glass vials followed by \_\_\_\_\_

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.

CC: Original ANDA  
Duplicate ANDA  
Division Copy  
Field Copy  
Drafted by N. Nath, HFD 600; V:\microrev\75773.doc  
Initialed by A. High

/S/ 8/7/00

**Redacted** 10

**pages of trade secret and/or**

**confidential**

**commercial**

**information**

- commercial lots of the subject drug product and one lot yearly there after (volume 1.3, page 1010).
- e. Reprocessing Statement: The applicant stated that it will not reprocess the commercial Pamidronate Disodium for Injection (volume 1.1, page 216).

Acceptable

APPEARS THIS WAY  
ON ORIGINAL

**CENTER FOR DRUG  
EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

*75-773*

**BIOEQUIVALENCE REVIEW**

BIOEQUIVALENCY COMMENTS

ANDA:75-773

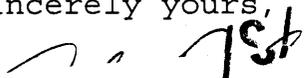
APPLICANT: American Pharmaceutical  
Partners, Inc.

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,



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

APPEARS THIS WAY  
ON ORIGINAL



OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA #75-773

SPONSOR : American Pharmaceutical Partners, Inc

DRUG AND DOSAGE FORM: Pamidronate disodium for injection  
STRENGTH(S): 30 mg/vial and 90 mg/vial

TYPES OF STUDIES: Waiver request

CLINICAL STUDY SITE: Not applicable

ANALYTICAL SITE: Not applicable

STUDY SUMMARY: Waiver request granted

DISSOLUTION: Not applicable

DSI INSPECTION STATUS

|                          |                                 |                     |
|--------------------------|---------------------------------|---------------------|
| Inspection needed:<br>NO | Inspection status:              | Inspection results: |
| First Generic _____      | Inspection requested:<br>(date) |                     |
| New facility _____       | Inspection completed:<br>(date) |                     |
| For cause _____          |                                 |                     |
| Other _____              |                                 |                     |

PRIMARY REVIEWER: James Chaney      BRANCH: I  
INITIAL:   /  /        DATE: 2/24/00

TEAM LEADER: Yih-Chain Huang      BRANCH: I  
INITIAL:   /  /        DATE: 2/24/2000

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

INITIAL:   /  /        DATE: 3/3/00

Pamidronate Disodium for Injection

30 mg/vial

90 mg/vial

ANDA #75-773

Reviewer: James E. Chaney

V:\FIRMSAM\AMERICAN\LTRS&REV\75773dw.d99

American Pharmaceutical  
Partners, Inc.

Melrose Park, Illinois

Submission Date:

December 29, 1999

## REVIEW OF WAIVER REQUESTS

### I. Background

1. The firm has requested waivers of *in vivo* bioequivalence study requirements for its proposed pamidronate disodium for injection, 30 mg/vial and 90 mg/vial. The reference listed product is Novartis Pharmaceuticals Corporation's Aredia® (pamidronate disodium for injection), 30 mg/vial and 90 mg/vial. Each strength of the reference listed drugs and the proposed products is a lyophilized powder to be reconstituted with 10 ml of sterile water for injection resulting in 30 or 90 mg of pamidronate disodium per 10 mL of solution. 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.

### 2. Formulations:

Table 1. Formulations of the test and reference products. Values are mg/vial.

| Ingredient              | Test              | Reference         | Test              | Reference         |
|-------------------------|-------------------|-------------------|-------------------|-------------------|
|                         | 30 mg<br>Strength | 30 mg<br>Strength | 90 mg<br>Strength | 90 mg<br>Strength |
| Pamidronate<br>Disodium | 30 mg             | 30 mg             | 90 mg             | 90 mg             |
| Mannitol                | 470 mg            | 470 mg            | 375 mg            | 375 mg            |
| Phosphoric<br>Acid      | pH<br>adjustment  | pH<br>adjustment  | pH<br>adjustment  | PH<br>adjustment  |

The generic firm converted \_\_\_\_\_

\_\_\_\_\_ In each case the pH was adjusted with phosphoric acid as required.

3. The test products, pamidronate disodium for injection, 30 mg/vial and 90 mg/vial, contain the same active and inactive ingredients in the same amounts as the reference products, Aredia® (pamidronate disodium for injection), 30 mg/vial and 90 mg/vial.
4. The test and the reference listed products are both administered intravenously.

## II. Comments

1. A waiver is granted under 21 CFR 320.22 (b) (1), in that the drug products are parenteral solutions (upon reconstitution) intended solely for administration by injection and they contain the same active and inactive ingredients in the same concentrations as a drug product that is the subject of an approved full NDA.
2. In the Components and Composition section (Section VII) the



## III. Recommendation

The Division of Bioequivalence agrees that the information submitted by American Pharmaceutical Partners, Inc. on its drug product, pamidronate disodium for injection, 30 mg/vial and 90 mg/vial, falls under 21 CFR section 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study requirements for the drug is granted. The Division of Bioequivalence deems the test product, pamidronate disodium for injection, 30 mg/vial and 90 mg/vial, bioequivalent to the reference product, Novartis Pharmaceuticals Corporation's Aredia® (pamidronate disodium for injection), 30 mg/vial and 90 mg/vial.

James E. Chaney, Ph.D.  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHuang  
FT INITIALED YCHuang

ISI

2/24/2000

Concur \_\_\_\_\_ Date 3/3/00  
Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

ISI

JEC/022400

V:\FIRMSAM\AMERICAN\LTRS&REV\75773dw.d99

Pamidronate Disodium for Injection, 30 mg/vial and 90 mg/vial,  
American Pharmaceutical Partners, Inc.

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**75-773**

**ADMINISTRATIVE  
DOCUMENTS**

FINAL APPROVAL PACKAGE SUMMARY FOR 75-773

ANDA: 75-773

FIRM: American pharmaceutical partners, Inc.

DRUG: Pamidronate Disodium

DOSAGE: Injectable (lyophilized)

STRENGTH: 30 mg/vial in 10 mL vial  
90 mg/vial in 10 mL vial

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 9/27/01

BIO STUDY/BIOEQUIVALENCE: Bio waiver was granted 3/3/00

METHOD VALIDATION: Pending (MV package was re-submitted on 4/18/02)

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40 C/75%RH and 18 months room temperature stability data at 25 C/60%RH for both batches. The stability samples were stored upright and inverted.

LABELING REVIEW STATUS: Labeling is satisfactory 5/31/01

SERILIZATIN VALIDATION: The microbiology portion of the application is satisfactory 8/7/00.

BATCH SIZES: The firm has provided blank master batch record for intended production of \_\_\_\_\_ Also submitted copies of the executed batch records lot R199-010 \_\_\_\_\_ for 30mg and lot R199-011 \_\_\_\_\_ for 90 mg. The firm will be using same drug substance manufacture, same process, and same equipment.

COMMENTS: The Application is approvable - Final approvable pending method validation

REVIEWER: Nashed E. *JSI* Nashed, Ph.D.

DATE: *4/22/02*  
2/20/02; 4/5/02

SUPERVISOR: James M. *JSI*

DATE: 3/3/02; 4/7/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

|  |   |
|--|---|
| NAME OF APPLICANT<br>American Pharmaceutical Partners, Inc.  | DATE OF SUBMISSION<br>01/25/02  |
| TELEPHONE NO. (Include Area Code)<br>(708) 343-6100  | FACSIMILE (FAX) Number (Include Area Code)<br>(708) 343-4269  |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,<br>and U.S. License number if previously issued):<br>2045 North Cornell Avenue<br>Melrose Park, IL 60160 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,<br>ZIP Code, telephone & FAX number) IF APPLICABLE |

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 75-773

|   |  |                                 |
|---|--|---------------------------------|
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Pamidronate<br>Disodium for Injection   | PROPRIETARY NAME (trade name) IF ANY                             |                                 |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Phosphonic acid (3-amino-1-<br>hydroxypropylidene) bis-, disodium salt   | CODE NAME (If any) 730610, 730710                                |                                 |
| DOSAGE FORM: Injectable<br>(lyophilized)  | STRENGTHS: 30 mg/vial in 10 mL vial, 90<br>mg/vial in 10 mL vial | ROUTE OF ADMINISTRATION: IV use |
| (PROPOSED) INDICATION(S) FOR USE: Hypercalcemia of malignancy, Paget's disease and osteolytic bone metasases of breast cancer and<br>osteolytic 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 Aredia (Pamidronate Disodium for Injection) Holder of Approved Application 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 Minor Amendment-Final Approval Requested

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

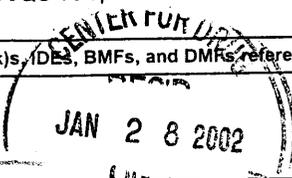
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

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.

Drug substance  
Contact person:  
Drug Product: APP, Melrose Park, contact person: Rajesh Kapoor, VP QA/QC Telephone: 706-486-2121

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

Type II DMF # \_\_\_\_\_  
Type III DMF # \_\_\_\_\_  
Type III DMF # \_\_\_\_\_  
Type III DMF # \_\_\_\_\_



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

ANDA Number: 75-773

Date of Submission: December 29, 1999

Applicant's Name: American Pharmaceutical Partners

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

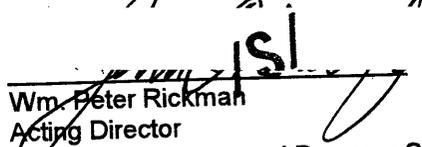
Labeling Deficiencies:

1. CONTAINER (30 mg and 90 mg)
  - a. Revise " \_\_\_\_\_ to read "Important"  
Reconstitution differs for each indication."
  - b. Relocate "Sterile, lyophilized" to appear on the principle display panel.
  - c. Revise " \_\_\_\_\_ " to read "Vial stoppers do not contain natural rubber latex."
2. CARTON (1 x 90 mg)
  - a. See comment (b) under CONTAINER.
  - b. Revise " \_\_\_\_\_ " to read "Important"  
Reconstitution differs for each indication."
  - c. Revise " \_\_\_\_\_ " to read "Vial stoppers do not contain natural rubber latex."
3. SHELF PACK (4 x 30 mg only)- See comments under CONTAINER.
4. INSERT
  - a. CLINICAL PHARMACOLOGY(Hypercalcemia of Malignancy-Clinical Trials) – Revise the first sentence in paragraph four to read as follows:  
  
...or 7.5 mg/kg of etidronate disodium as a 2-hour intravenous infusion daily for 3 days.  
  
In addition, replace \_\_\_\_\_ with "etidronate disodium" throughout the text as necessary.
  - b. CLINICAL PHARMACOLOGY(Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma-Clinical trials)
    - i. First Table- Revise \_\_\_\_\_ to read "PD" in the fourth row of this section.
    - ii. Second Table- Revise the table heading to read as follows:  
  
Mean Change ( $\Delta$ ) from Baseline at Last Measurement  
  
You inadvertently left out the " $\Delta$ " symbol.
  - c. HOW SUPPLIED – Revise " \_\_\_\_\_ " to read "Vial stoppers do not contain natural rubber latex."

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and 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](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.

  
Wm. Peter Rickman  
Acting 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:**

***75-773***

**CORRESPONDENCE**

**ARCHIVAL**

April 1, 2002

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

NC  
**NEW CORRESP**

Re: **ANDA #: 75-773**  
**Pamidronate Disodium for Injection**  
**30 mg/vial in 10 mL vial (Code 730610)**  
**90 mg/vial in 10 mL vial (Code 730710)**  
**Manufacturing Site: Melrose Park, IL**

**CORRESPONDENCE CONCERNING  
METHOD VALIDATIONS**

Dear Mr. Buehler:

American Pharmaceutical Partners, Inc. (APP) hereby commits to resolve any issues identified by the FDA Detroit District Laboratory which may result from the review of APP's method validation studies on Pamidronate Disodium Injection in conjunction with ANDA75-773.

If you have any questions or require additional information concerning this correspondence, please contact the undersigned at (708) 486-2071.

Sincerely,



Dale Carlson  
Associate Director, Regulatory Affairs

**RECEIVED**

**APR 03 2002**

**OGD/CDER**



January 25, 2002  
Gary Buehler, Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

*NET*  
*MMS*  
*1-30-02*

ORIG AMENDMENT

Re: **ANDA 75-773**  
**Pamidronate Disodium for Injection**  
**30 mg/vial in 10 mL vial (Code 730610)**  
**90 mg/vial in 10 mL vial (Code 730710)**  
**Manufacturing Site: Melrose Park, IL**

**MINOR AMENDMENT TO AN ORIGINAL ANDA  
FINAL APPROVAL REQUESTED**

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA 75-773) for Pamidronate Disodium for Injection submitted on December 29, 1999. Reference is also made to the August 24, 2001 tentative approval letter received for this ANDA.

Further reference is made to our November 8, 2001 correspondence notifying the Agency of a Consent Order entered by the U.S. District Court for the Northern District of Illinois. This Consent Order constituted a judgment of non-infringement and found that the Pamidronate Disodium for Injection lyophilized drug product described in our ANDA 75-773 does not infringe U.S. Patent # 4,711,880 held by Novartis Corporation. Additionally, reference is made to our November 21, 2001 letter, in which APP notified the Agency of a Minute Order entered by the U.S. District Court for the Northern District of Illinois dismissing all claims and terminating the case on November 6, 2001. This Minute Order of November 6, 2001 activated the 180-day generic drug market exclusivity period for Bedford Laboratories. The 180-day exclusivity period will expire on May 5, 2002, and thus, APP expects to get the final approval for ANDA 75-773 on that date.



*2016/11*  
*1/29/02*  
*MR*

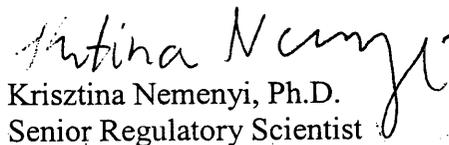
ANDA 75-773  
Minor Amendment-Final Approval Requested  
January 25, 2002  
Page 2

As described in the tentative approval letter, American Pharmaceutical Partners, Inc., hereby submits this minor amendment to inform the Agency that APP has no updated information to submit for ANDA 75-773.

Furthermore, in compliance with 21 CFR 314.96(b), a true and complete copy (the Field Copy) of this minor amendment is being provided to the Acting Director, FDA Chicago District Office.

If you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 486-2137 or Dale Carlson, Associate Director, Regulatory Affairs at (708) 486-2071.

Sincerely,

  
Kristina Nemenyi, Ph.D.  
Senior Regulatory Scientist

APPEARS THIS WAY  
ON ORIGINAL

November 21, 2001

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

*Acknowledged  
NAI  
Summers  
12/18/01*

~~CONFIDENTIAL~~

**NEW CORRESP**  
NC

Re: **ANDA 75-773**  
**Pamidronate Disodium for Injection**  
**30 mg/vial in 10 mL vial (Code 730610)**  
**90 mg/vial in 10 mL vial (Code 730710)**  
**Manufacturing Site: Melrose Park, IL**

**GENERAL CORRESPONDENCE**

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA 75-773) for Pamidronate Disodium for Injection submitted on December 29, 1999. Reference is also made to the August 24, 2001 tentative approval letter received for this ANDA. Further reference is made to our November 8, 2001 correspondence notifying the Agency of a Consent Order entered by the U.S. District Court for the Northern District of Illinois. This Consent Order constituted a judgment of non-infringement and found that the Pamidronate Disodium for Injection lyophilized drug product described in our ANDA 75-773 does not infringe U.S. Patent # 4,711,880 held by Novartis Corporation.

American Pharmaceutical Partners, Inc. (APP) is submitting this correspondence to notify the Agency of a Minute Order entered by the U.S. District Court for the Northern District of Illinois dismissing all claims and terminating the case on November 6, 2001. This Minute Order of November 6, 2001 activates the 180-day generic drug market exclusivity period for Bedford Laboratories. The 180-day exclusivity period will expire on May 5, 2002, and thus, APP expects to get the final approval for ANDA 75-773 on that date.

Should you have any questions or require additional information concerning this submission, please contact the undersigned at (708) 486-2117 or Dale Carlson, Associate Director, Regulatory Affairs, at (708) 486-2071.

Sincerely,

*Lincy Michael*

Lincy Michael  
Senior Regulatory Scientist



Cc: Donald Hare

*ML*



*Acknowledged  
NAI  
12/28/01*

*NAI  
MMS  
11-21-01*

*NC*

**NEW CORRESP  
ARCHIVAL**

November 8, 2001

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

**Re: ANDA 75-773  
Pamidronate Disodium for Injection  
30 mg/vial in 10 mL vial (Code 730610)  
90 mg/vial in 10 mL vial (Code 730710)  
Manufacturing Site: Melrose Park, IL**

**GENERAL CORRESPONDENCE**

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA 75-773) for Pamidronate Disodium for Injection submitted on December 29, 1999. Further reference is made to the August 24, 2001 tentative approval letter received for this ANDA.

American Pharmaceutical Partners, Inc. (APP) is submitting this correspondence to notify the Agency of a Consent Order entered by the U.S. District Court for the Northern District of Illinois on November 6, 2001. This Consent Order constitutes a judgment of non-infringement and finds that the Pamidronate Disodium for Injection lyophilized drug product described in APP's ANDA 75-773 does not infringe U.S. Patent # 4,711,880 held by Novartis Corporation. A copy of this Consent Order is provided as an attachment to this submission.

Further more, it was stated in the August 24, 2001 tentative approval letter that Bedford Laboratories is deemed eligible for 180-days of generic drug market exclusivity for Pamidronate Disodium for Injection lyophilized drug product. Given the entry of this Order, which is a judgement of non-infringement, APP would like to bring to the Agency's attention that the 180- days of generic drug market exclusivity given to Bedford Laboratories started on November 6, 2001.

Should you have any questions or require additional information concerning this submission, please contact the undersigned at (708) 486-2117 or Dale Carlson, Associate Director, Regulatory Affairs, at (708) 486-2071.

Sincerely,

Lincy Michael  
Senior Regulatory Scientist



*MMS*

Cc: Donald Hare



June 18, 2001

Gary Buehler, Acting Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

**ARCHIVAL**

ORIG AMENDMENT  
N/AC

Re: **ANDA #: 75-773**  
**Pamidronate Disodium for Injection**  
**30 mg/vial in 10 mL vial (Code 730610)**  
**90 mg/vial in 10 mL vial (Code 730710)**  
**Manufacturing Site: Melrose Park, IL**

**AMENDMENT TO THE ORIGINAL APPLICATION**

Dear Mr. Buehler:

Reference is made to our December 29, 1999 submission of an original Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection, ANDA # 75-773. Reference is also made to the major amendment submitted March 14, 2001. American Pharmaceutical Partners, Inc. is amending this application to revise existing information.

Included in this submission are revised analytical method summaries, specifications for pamidronic acid active pharmaceutical ingredient, and finished product stability summaries.

The revised analytical method summaries with the changes specified are included in the following attachments:



**Redacted** \_\_\_\_\_

**pages of trade secret and/or**

**confidential**

**commercial**

**information**

In compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 547-3617 or Dale Carlson, Associate Director, Regulatory Affairs at (708) 547-2373.

Sincerely,



Lincy Michael  
Sr. Regulatory Scientist

APPEARS THIS WAY  
ON ORIGINAL

March 13, 2001

Gary Buehler, Acting Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

MAJOR DRUG AMENDMENT

JPL

Ac

Re: **ANDA #: 75-773**  
**Pamidronate Disodium for Injection**  
30 mg/vial in 10 mL vial (Code 730610)  
90 mg/vial in 10 mL vial (Code 730710)  
Manufacturing Site: Melrose Park, IL

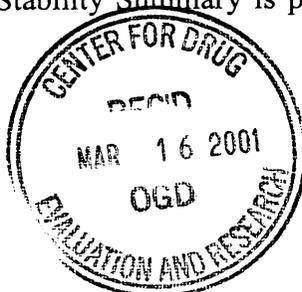
**MAJOR AMENDMENT  
FOR  
CHEMISTRY, LABELING AND BIOEQUIVALENCE DEFICIENCIES**

Dear Mr. Buehler:

Reference is made to our December 29, 1999 submission of an original Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection, ANDA # 75-773. Reference is made to the attached July 31, 2000 Major Deficiency to this application. Reference is also made to an August 8, 2000 telephone conference between M. Clark, D. Szymanski, D. Humprey, L. Michael, P. Torralba of APP and Dr. Nashed, Dr. Schwarz, E. Hue of FDA in which APP sought clarification of the comments #1, #2, and #4.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to each of the comments made in your communication dated July 31, 2000. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response. Final Printed Labeling (FPL) is also included in this response.

APP is also submitting the available (12-month) long-term stability data to support the subject ANDA. A copy of the Stability Summary is provided in **Attachment 2** of this amendment.



March 14, 2001

Page 2

APP has made some editorial changes to the blank batch record (step 3 of M-2, page 2 of 3) for both product codes provided in our original ANDA, pages 001 00230-001 00231, and 001 00310-000311, respectively. A copy of the revised pages is enclosed in **Attachment 8**.

In addition, a test for  has been added to the finished product specification to monitor the structure of the active ingredient in Pamidronate Disodium for Injection. The cGMP Certification Letter from the outside testing laboratory that conducts the test is provided in **Attachment 3**. Furthermore, the "Other Requirements" test has been added to the drug product release specification to comply with current USP requirements for injections under General Chapter <1>. A copy of the revised regulatory and stability specification for the finished product is included in **Attachment 4**.

Additionally, in compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 547-3617 or Dale Carlson, Associate Director, Regulatory Affairs at (708) 547-3373.

Sincerely,



Lincy Michael  
Sr. Regulatory Scientist

FOXKISER  
750 17TH STREET, N. W.  
SUITE 1100  
WASHINGTON, D. C. 20006  
(202) 778-2300

NEW CORRESP.

NC

May 5, 2000



Hand-Delivered

Mr. Gary Buehler  
Acting Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place, Suite 286-N  
Rockville, Maryland 20855

Re: Novartis Corporation v. American Pharmaceutical Partners, Inc., N.D. Ill., Civil  
Action No. 00C-2313  
American Pharmaceutical Partners, Inc. ANDA No. 75-773

Dear Mr. Buehler:

On behalf of Novartis Corporation, the purpose of this letter is to inform the Office of Generic Drugs that Novartis Corporation, on April 14, 2000, filed a patent infringement lawsuit against American Pharmaceutical Partners, Inc. ("APP"), in the U.S. District Court for the Northern District of Illinois, Novartis Corporation v. American Pharmaceutical Partners, Inc., N.D. Ill., Civil Action No. 00C-2313, in response to APP's Notice of Paragraph IV Patent Certification, dated February 28, 2000, covering APP's 505(j) application, ANDA No. 75-773, submitted December 29, 1999, which the notice states is for "pamidronate disodium for injection (30 mg in 10 mL vials and 90 mg in 10 mL vials)."

Enclosed for the Office's reference is a copy of the Complaint that was filed in the above-referenced action.

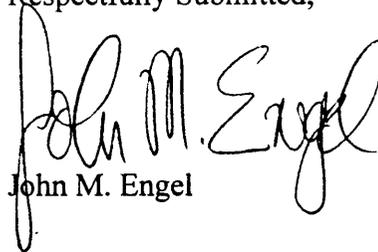


FOXKISER

Mr. Gary Buehler  
May 5, 2000  
Page 2

Please feel free to contact me, on (202) 778-2354, if you have any questions or require additional information in connection with this matter.

Respectfully Submitted,



John M. Engel

Enclosure

cc: Document and Records Section (*via* First Class Mail)  
12229 Wilkins Avenue  
Rockville, Maryland 20852

**APPEARS THIS WAY  
ON ORIGINAL**

March 23, 2000

**ARCHIVAL**

Gary Buehler, Acting Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

**NEW CORRESP**

*nc*

*Return receipt date  
for Novartis  
Corp  
is unclear.*

**Re: ANDA 75-773  
Pamidronate Disodium for Injection  
30 mg/vial in 10 mL vial (Code 730610)  
90 mg/vial in 10 mL vial (Code 730710)  
Manufacturing Site: Melrose Park, IL**

*Will call firm  
for better  
copy.*

**PATENT AMENDMENT**

*IST 4/20/00  
IST*

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection submitted December 29, 1999 in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). Reference is also made to the FDA Acceptance for Filing Letter dated February 18, 2000.

As described in the FDA letter, and in accordance with 21 CFR 314.95(b) American Pharmaceutical Partners, Inc. (APP) is submitting this Patent Amendment to ANDA 75-773. American Pharmaceutical Partners, Inc. hereby certifies that in accordance with 21 CFR 314.95(a) notice regarding the Paragraph IV certification has been given to Novartis Corporation, the holder of U.S. Patent # 4,711,880, and to Novartis Pharmaceuticals Corporation the holder of the approved New Drug Application (NDA) for Pamidronate Disodium for Injection.

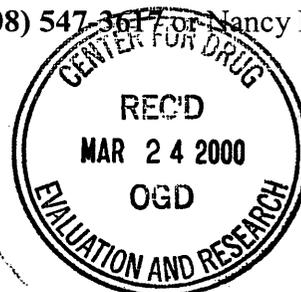
Enclosed please find copies of the return receipt postcards documenting delivery of the aforementioned Paragraph IV certification notice patentee and to the NDA holder (on March 2, 2000).

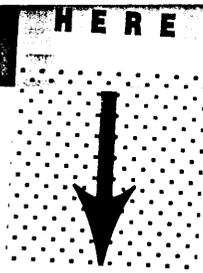
Should you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 547-3617 or Nancy Bauer, Associate Director, Regulatory Affairs, at (708) 547-2381.

Sincerely,

*Lincy Michael*

Lincy Michael  
Senior Regulatory Scientist





NEW CORRESP  
NC

August 14, 2000

Gary Buehler, Acting Director  
Office of Generic Drugs  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Metro Park North II HFD-600, Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

NAI  
151  
8/28/00

Re: **ANDA 75-773**  
**Pamidronate Disodium for Injection**  
**30 mg/vial in 10 mL vial (Code 730610)**  
**90 mg/vial in 10 mL vial (Code 730710)**  
**Manufacturing Site: Melrose Park, IL**

**INTENT TO FILE AN AMENDMENT**

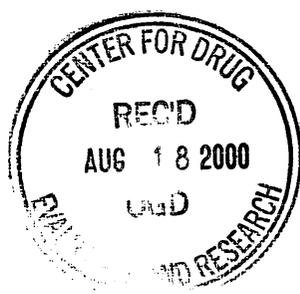
Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection. Reference is also made to the deficiency letter dated July 31, 2000. In accordance with 21 CFR 314.120(a)(1), American Pharmaceutical Partners, Inc. is informing you of our **intent to file an amendment** in response to this deficiency letter.

If you have any questions concerning this submission, please do not hesitate to contact the undersigned at (708) 547-3617 or Nancy Bauer, Associate Director, Regulatory Affairs at (708) 547-2381.

Sincerely,

Lincy Michael  
Senior Regulatory Scientist





May 8, 2000

Gary Buehler, Acting Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

**ARCHIVAL**

NEW CORRESP  
NC

*Copy of pending litigation!*

Re: **ANDA 75-773**  
**Pamidronate Disodium for Injection**  
30 mg/vial in 10 mL vial (Code 730610)  
90 mg/vial in 10 mL vial (Code 730710)  
Manufacturing Site: Melrose Park, IL

*OK!*  
*ISI*  
*5/26/00*  
*ISI*

**PATENT AMENDMENT**

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection submitted December 29, 1999 in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). Reference is made to the Patent Amendment submitted March 23, 2000. Reference is also made to the May 4, 2000 telephone conversation between L. Michael of APP and G. Davis of FDA.

American Pharmaceutical Partners, Inc. (APP) is submitting this Patent Amendment to notify the Agency of an action of patent infringement filed by Novartis Corporation, the holder of - U.S. Patent # 4,711,880, in the U.S. District Court for the Northern District of Illinois on April 14, 2000. As acknowledged in paragraph 7 (page 4) of the attached Complaint, Novartis Corporation received APP's notice regarding the Paragraph IV certification on March 2, 2000.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 547-3617 or Nancy Bauer, Associate Director, Regulatory Affairs, at (708) 547-2381.

Sincerely,

Lincy Michael  
Senior Regulatory Scientist



March 23, 2000

**ARCHIVAL**

Gary Buehler, Acting Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

**NEW CORRESP**

*nc*

Return receipt date  
for Novartis  
Corp

is unclear.

Will call firm  
for better  
copy.

13/4/20/a

15/

Re: **ANDA 75-773**  
**Pamidronate Disodium for Injection**  
30 mg/vial in 10 mL vial (Code 730610)  
90 mg/vial in 10 mL vial (Code 730710)  
Manufacturing Site: Melrose Park, IL

**PATENT AMENDMENT**

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application (ANDA) for Pamidronate Disodium for Injection submitted December 29, 1999 in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). Reference is also made to the FDA Acceptance for Filing Letter dated February 18, 2000.

As described in the FDA letter, and in accordance with 21 CFR 314.95(b) American Pharmaceutical Partners, Inc. (APP) is submitting this Patent Amendment to ANDA 75-773. American Pharmaceutical Partners, Inc. hereby certifies that in accordance with 21 CFR 314.95(a) notice regarding the Paragraph IV certification has been given to Novartis Corporation, the holder of U.S. Patent # 4,711,880, and to Novartis Pharmaceuticals Corporation the holder of the approved New Drug Application (NDA) for Pamidronate Disodium for Injection.

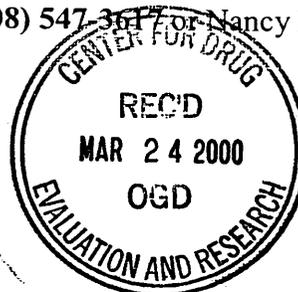
Enclosed please find copies of the return receipt postcards documenting delivery of the aforementioned Paragraph IV certification notice patentee and to the NDA holder (on March 2, 2000).

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at (708) 547-3617 or Nancy Bauer, Associate Director, Regulatory Affairs, at (708) 547-2381.

Sincerely,

*Lincy Michael*

Lincy Michael  
Senior Regulatory Scientist





- 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.

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:

Michelle Dillahunt  
Project Manager  
(301) 827-5848

Sincerely yours,

*[Handwritten signature]*

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 75-773  
cc: DUP/Jacket  
Division File  
HFD-82  
Field Copy  
HFD-330  
HFD-610/R.West  
HFD-610/P.Rickman  
HFD-615/M.Bennett

Endorsements: HFD-615/NMahmud, Chief, RS  
HFD-615/SMiddleton, CSO  
HFD-625/MSmela, Sup. *[Handwritten initials]*  
Word Document  
V:\FIRMSAM\AMERICAN\LTRS&REV\75773.ACK  
F/T by mjl/2/17/00  
ANDA Acknowledgment Letter!

*[Handwritten initials]*

date *2/18/00*  
date *2/17/00*  
date

ack fore  
filing 5/5/99  
505(j) B

December 29, 1999

**CONTAINS MICROBIOLOGICAL  
AND STERILITY ASSURANCE  
INFORMATION IN SECTION XXII  
VOLUMES 4 and 5**

Douglas Sporn, Director  
Office of Generic Drugs  
Metro Park North II, HFD-600, Room 150  
Center for Drug Evaluation and Research  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

**Re: Pamidronate Disodium for Injection  
30 mg/vial in 10 mL vial (Code 730610)  
90 mg/vial in 10 mL vial (Code 730710)  
Manufacturing Site: Melrose Park, IL  
Number of Volumes: 5 Volumes**

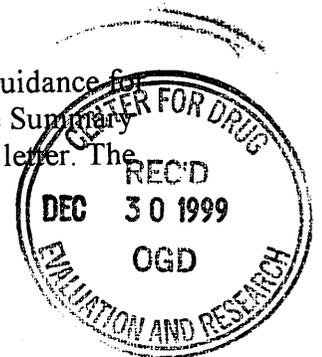
**ORIGINAL ANDA**

Dear Mr. Sporn:

This Abbreviated New Drug Application is submitted in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Pamidronate Disodium for Injection. The reference listed drug is Aredia® manufactured by Novartis Pharmaceuticals Corporation.

American Pharmaceutical-Partners, Inc. will manufacture this product in manufacturing facilities located at 2020 Ruby Street, Melrose Park, IL 60160. This application contains all the information required describing the chemistry, manufacturing and control of Pamidronate Disodium for Injection 30 mg/vial in a 10 mL vial and 90 mg/vial in a 10 mL vial. This application contains a request for the waiver of *in vivo* bioequivalence studies. **This application also contains microbiology and sterility assurance information, which is provided in Section XXII.**

The application has been formatted according to the information in the Guidance for Industry: Organization of an ANDA, dated February 1999. An Executive Summary explaining the organization of this application is included after the cover letter. The application consists of 5 volumes.



December 29, 1999  
Page 2

American Pharmaceutical Partners Inc. is filing an archival copy (in a blue folder) of the ANDA that contains all the information required in the ANDA, and a technical review copy (in a red folder) which contains all of the information in the archival copy with the exception of the bioequivalence section (Section VI). Three copies of the analytical methods validation section are included in red folders. Four copies of the draft labeling are included in both the archival and the review copies. A separate copy of the bioequivalence section is provided in an orange folder. The bioequivalence section consists of a request for a waiver from the need to conduct a bioequivalence study.

Furthermore, in compliance with 21 CFR 314.94(d)(5), a true and complete copy (the Field Copy) of this Abbreviated New Drug Application is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606. We certify that the Field Copy is a true and complete copy of this Abbreviated New Drug Application.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at (708) 547-3617 or Nancy Bauer, Associate Director, Regulatory Affairs, at (708) 547-2381.

Sincerely,



Lincy Michael  
Senior Regulatory Scientist

APPEARS THIS WAY  
ON ORIGINAL