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Sponsor: Ciba-Geigy Corp., Summit NJ

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REVIEW AND EVALUATION OF PHARMACOKINETIC AND TOXICOLOGY DATA

Supplement Review

Drug: pamidronate disodium for injection: CGP 23339A; APD; Aredia

Category: Bisphosphonate; Anti-resorptive agent

Proposed Clinical Indication: Hypercalcemia of malignancy. Aredia is already approved for this indication. The current supplement seeks to shorten the currently approved 24-hr infusion time for 60-90 mg to 4-hr infusion period.

Related IND: IND 30,145

Drug Lots used in Toxicity Studies: 800188
14/874/1 (000500)
14/406/1
14/612/1
13/632/1

PHARMACOKINETIC DATA

Whole-Body Autoradiographic Investigation of the Passage of Radioactivity Across the Placenta After Intravenous Administration of ^{14}C-Labeled Substance to Pregnant Rats
Report B 25/1989
Pregnant rats (one animal/time point) were given 1 mg/kg ^{14}C-APD (specific activity of 836 kBq/mg) by i.v. injection either on Day 14, 16, 18 or 19 of gestation. All animals were sacrificed on Day 20 of gestation, unless stated otherwise.

The results were as follows:

Day 14- Levels of radioactivity in fetal tissues and skeleton were below the detection limit. Some radioactivity was noted in the amnion.

Day 16- Trace levels of radioactivity were found in fetal bones. In other fetal tissues, level of radioactivity was below the detection limit.

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Day 18- This animal died 4-hr post dosing and thus autoradiographic data reflect this time point only. Radioactivity was easily evident in maternal spinal cord, kidney and intestine; and in fetal ribs, cranium and spinal cord.

Day 19- This dam reached parturition 4-hr post dosing. The mother and offspring were sacrificed shortly thereafter. Radioactivity was easily detected in the skeleton of the pups. Levels of radioactivity in soft tissues of the pups, were below the detection limit.

Single Dose Studies

Acute Intravenous Infusion Renal Toxicity Study in the Albino Rat
Test No. 91-6005
SD rats (2/sex/group) were given either 5 or 10 mg/kg APD over a 1-hr infusion period. Saline was used as vehicle and drug was administered through an indwelling catheter (femoral vein). The dose rates for 5 and 10 mg/kg were 16.7 and 33.3 ml/kg/hr, respectively. No control groups were included in the study. Animals were sacrificed 24 hr the infusion period.

There were no treatment effect on mortality, clinical chemistry and urinalysis. Aside from thrombosis at the injection site in one male, gross and histopathological findings were unremarkable in the 5 mg/kg group. At the 10 mg/kg group, one male had multiple pale areas in the kidney (bilateral), as well as tubular dilation in the kidney cortex (bilateral). Thrombosis at the injection site was also found in this male rat. In one 10 mg/kg female, the kidney was characterized by pelvic dilation, but there were no histological changes. In the other 10 mg/kg female, the liver was noted to have pale area and single fissure in the median lobe; and there was thrombosis at the injection site. A relationship of these effects to treatment cannot be established due to the absence of controls.

Acute Intravenous Infusion Renal Toxicity Study in the Albino Rat
Test No. 90-6253
SD rats (2/sex/group) received either 1, 2 or 3 mg/kg of APD over an 1-hr infusion period. Control group was not included.

There were no mortalities, clinical chemistry, gross or histopathological changes found in this study. On the other hand, without a control group and limited number of animals/group, it would be difficult to determine treatment related changes.

Pilot Intravenous Bolus Tolerability Study in Dogs
Test No. 89-6071
A female beagle dog was given a single i.v. bolus injection of 6 mg/kg and sacrificed 24 hrs later. A second male dog received two i.v. injections of 10 mg/kg, 48 hrs apart, and then sacrificed 48 hr after the last dose. No control dogs were included.

Although various histological findings were noted in the kidney, liver, lungs and site of injection; the use of single animal/dose group and absence of controls yield these data uninterpretable.

Pilot Study of the Acute Effects of Intravenous Infusion in Dogs
Test No. 89-6085
Female dogs (2) were given 10 mg/kg by 24-hr i.v. infusion. Each dog received two infusions at 24-hr intervals. No control dogs were included.

Compared to pretreatment, there were decreases in food consumption and body wt. However the sponsor attributed the decreased body wt to "stress of the infusion period". Hemorrhage in the kidney was observed in one dog. Significance of these findings are equivocal due to the absence of controls.

Acute Intravenous Infusion Renal Toxicity Study in the Beagle Dog
Test No. 90-6254
Dogs (1/sex/group) were given either 3, 5, 10, 20 or 40 mg/kg of APD by 1-hr infusion. No controls were included.

Observed Effects
Soft feces was noted in dogs given 5 mg/kg; female at 10 mg/kg; and in the female at 20 mg/kg. Large amounts of partially digested food was found with both dogs given 40 mg/kg.

Mortality
None

Body Weight
Wt loss was noted in dogs given 20 and 40 mg/kg, but was not dose related.

Clinical Chemistry
Compared to pretreatment values, increased BUN was observed at all doses (sponsor considered to be within normal limits). Although creatinine levels "exceeded the physiologically normal range" in 10 mg/kg dogs, a similar change was not seen at higher doses.

Urinalysis
No effects

Gross Pathology
According to the sponsor, treatment related changes included dark bilateral foci in kidneys of dogs given 3 mg/kg; and in males of the 5 and 10 mg/kg groups. Mottled surface on both kidneys was found in the 20 mg/kg female. Additionally, dark foci in the stomach mucosa was noted in both 40 mg/kg dogs.

Histopathology
Only the kidney and infusion site underwent such analysis. Tubular dilation in the cortex, necrosis in the outer medulla and hemorrhages in the corticomedullary junction were noted in dogs

given 5 and 10 mg/kg. Renal changes were not found in the 40 mg/kg group. Minimal focal hemorrhaging in the stomach mucosa was noted in 40 mg/kg dogs. Although perivascular hemorrhage was noted at the infusion site, the incidence was sporadic.

Acute Intravenous Infusion Renal Toxicity Study in the Beagle Dog with 14-Day Observation Period Test No. 91-6074
Male dogs (4/group) were given 4, 8 and 12 mg/kg of APD by 1-hr infusion. Respective dose rates (ml/kg/hr) were 1.33, 2.67 and 4.00. Control group received saline infusion at the same rate for the high dose.

Observed Effects
Redness of the eyes was noted in 2/4 dogs at 4 mg/kg and in all males given 8 and 12 mg/kg. Increased incidence of soft feces was noted in treated dogs (unrelated to dose). Incidence of emesis was found to be slightly greater in 8 and 12 mg/kg males.

Mortality
One 12 mg/kg male was sacrificed on Day 4 of the study. Tonic convulsions and vomiting were noted in this dog on Day 4. Necropsy findings included several dark areas on the right apical lobe and both diaphragmatic lobes of the lungs, mild multifocal tubular cell necrosis in the outer medulla of the kidneys, mild multifocal mononuclear cell infiltration of the interstitium and slight multifocal tubular dilation. Death was attributed to acute renal failure.

Body Weight and Food Consumption
Body wts were unaffected by treatment. Food consumption in the 8 and 12 mg/kg groups were slightly decreased during the observation period.

Clinical Chemistry
Sporadic changes in AST, cholesterol and ALKP were observed at 12 mg/kg. Although serum phosphorus levels were decreased in treated dogs, there was no dose relationship. Any treatment effect of APD on serum BUN was difficult to discern due to the fluctuations in control BUN values.

Hematology
No treatment effects.

Urinalysis
No treatment effects.

Gross Pathology
Raised areas in the lung were found in treated dogs only, but were unrelated to dose. An unusual finding was the presence of clots in the skeletal muscle of control and treated dogs.

Histopathology
Only data presented was from kidney tissue. Mononuclear inflammatory cell infiltration (3/4 LD, 3/4 MD and 2/4 HD) and

tubular basophilia (1/4 LD, 1/4 MD and 2/4 HD) were noted only in treated dogs. Tubular dilation was found at 8 and 12 mg/kg. Occurrence of tubular necrosis was restricted to the 12 mg/kg dose. These renal effects were of slight severity.

Sponsor noted that histological findings from other tissues were considered incidental.

Multiple Dose Studies

Seven Day Intravenous Infusion Toxicity Study in Beagle Dogs
Test No. 90-6183
Beagle dogs (2/sex/group) received the following treatments:

	Dose/Group (mg/kg/day)	Infusion Time (hr)	Dose Rate (ml/Kg/hr)
1.	Saline control	24	2.78
2.	3	1	10.00
3.	10	1	3.33
4.	20	1	6.67
5.	3	4	0.25
6.	10	4	8.33
7.	20	4	1.67
8.	3	24	0.04
9.	10	24	0.14
10.	20	24	2.78

Animals received topical antibiotics at the infusion site daily. Saline was used as the vehicle.

Observed Effects
Emesis was noted in all dogs in Groups 3, 4, and 7; 1/4 dogs each, in Groups 5 and 6; 2/4 dogs in Group 9; and 3/4 in Group 10. Presence of blood in the vomitus was noted in Groups 3, 4, 6, 7, 9, and 10. Thus doses of 10 and 20 mg/kg produced toxicity, regardless of the infusion time. Decreased activity were also noted in Groups 2-7 and Group 10.

Mortality
Animals that presented blood in the vomitus were sacrificed as moribund. Mortality data were presented by groups only. The animals were sacrificed as follows:

Day 3 - Group 4 (20 mg/kg/day; 1-hr infusion)
Day 4 - Group 3 (10 mg/kg/day; 1-hr infusion)
Day 4 - Group 7 (20 mg/kg/day; 4-hr infusion)
Day 5 - Group 6 (10 mg/kg/day; 4-hr infusion)
Day 6 - Group 10 (20 mg/kg/day; 24-hr infusion)
Day 7 - Group 10 (20 mg/kg/day; 24-hr infusion)

Body Weight and Food Consumption
Although body wt and food consumption in treated dogs appeared to be lower than saline controls, there was no relationship to the dose and infusion period.

Ophthalmoscopy
No treatment related changes.

Clinical Chemistry
These data are summarized in the following table (Vol 3, pg 22):

INFUSION TIME	1 HOUR	4 HOURS	24 HOURS
Dose Level			Group 1 (saline) No changes
3 mg/kg/day	Group 2 Inc. BUN 4/4 Inc. Creat. 1/4 Dec. K 2/4 Inc. Bili. 1/4	Group 5 Dec. K 1/4	Group 8 No changes
10 mg/kg/day	Group 3 Inc. BUN 4/4 Inc. Creat. 4/4 Dec. K 3/4 Inc. AST 4/4 Inc. ALT 1/4 Inc. ALP 1/4 Inc. Bili. 4/4	Group 6 Inc. BUN 3/4 Inc. Creat. 2/4 Dec. K 1/4 Inc. ALT 2/4	Group 9 Inc. BUN 2/4
20 mg/kg/day	Group 4 Inc. BUN 4/4 Inc. Creat. 4/4 Dec. K 4/4 Inc. AST 4/4 Inc. ALT 2/4 Inc. ALP 1/4 Inc. Bili. 3/4	Group 7 Inc. BUN 4/4 Inc. Creat. 3/4 Dec. K 3/3 Inc. AST 3/4 Inc. ALT 4/4 Inc. ALP 2/4 Inc. Bili. 2/4	Group 10 Inc. BUN 4/4 Inc. Creat. 3/4 Inc. ALT 2/4 Inc. Bili 1/4

Hematology
Compared to data from 24-hr infusion with saline controls and with the 1-hr infusion period, increases in RBC, HGB and HCT were noted in males and females of all doses (unrelated to dose). Increased APTT was noted in dogs given 20 mg/kg.

With the 4-hr infusion period and compared with data in the 24-hr infusion saline controls, increased RBC, HGB and HCT were noted in the males at all doses. However, these changes were not dose related. In females, increased RBC, HGB and HCT were found only with 20 mg/kg dose. One 10 mg/kg male and all dogs given 20 mg/kg had increased WBC. Increased MPV and APTT were noted in one 20 mg/kg male and APTT was increased in both females at 20 mg/kg.

With 24-hr infusion period, increases in RBC, HGB and HCT were observed in one 3 mg/kg male; both males at 10 mg/kg; and all dogs at 20 mg/kg. In addition, platelet count was increased in both males at 20 mg/kg and increased WBC was noted in males of 10 and 20 mg/kg.

Organ Weights

1-hr infusion: slight increase in relative liver wt in one male given 3 mg/kg.

4-hr infusion: increase in absolute and relative spleen wt in 3/4 dogs given 3 mg/kg.

24-hr infusion: increase in relative spleen wt in one female given 3 mg/kg.

Gross Pathology

1-hr infusion: Raised area in the liver was noted in males at 3 mg/kg. Dark area in the ileum; dark foci in the kidney; and dark area/foci in the stomach were noted in 10 mg/kg males. Kidney enlargement and discoloration were found only in 20 mg/kg males. Dark foci and discoloration of the Discoloration and enlargement of the lymph node; pale material and discoloration in the stomach were noted in males at 10 and 20 mg/kg. Depressed and raised areas in the lung; and presence of dark material and thickening of the stomach were found in the 20 mg/kg group.

4-hr infusion: Discoloration of the lymph nodes was seen only in 3 and 10 mg/kg males. Raised area in the lungs was found with all three doses. Discoloration and thickening of the urinary bladder were found in 20 mg/kg females only. Discoloration of the digesta; presence of dark foci, discoloration and depressed areas in the kidney; dark areas in the lungs; dark areas, discoloration, thickening and presence of dark material in the stomach were found in 20 mg/kg males and females.

24-hr infusion: Discoloration of the lymph node was found only in 20 mg/kg males. Raised area in the lung was found at all doses. Dark foci in the kidney was found in males at all doses and in 20 mg/kg females. Presence of pale/dark material and thickening of the stomach were observed in 10 mg/kg males. Discoloration of the stomach occurred in 10 and 20 mg/kg males. Dark foci in the stomach was found in 20 mg/kg females. Discoloration of the thymus was noted in 20 mg/kg males.

Histopatholcgy

The incidences of thrombosis, granuloma, pneumonia and bronchopneumonia that were noted at various doses and infusion times were attributed to lungworm infections. Target organs for APD toxicity were considered (by sponsor) to be stomach and kidney. The sponsor also noted that "Only the low dose level (3 mg/kg) as a 24-hour infusion for 7 consecutive days can be considered as the no-effect level for both renal and gastric lesions" (Vol 3, pg 25).

1-hr infusion: Adrenal hemorrhage; mixed cell infiltration in the heart; and hemorrhage in the ileum of 10 mg/kg males. Increased myelopoiesis in bone; mixed cell infiltration in the centrilobular/periportal region of the liver; and congestion of lymph nodes were observed in 10 and 20 mg/kg males. Congestion of the colon; and bronchopneumonia, pleuritis, interstitial pneumonia, emphysema, perivascular and/or peribronchiolar mononuclear cell in the lung were noted in 20 mg/kg males. Although interstitial pneumonia and pleuritis were noted in 20 mg/kg females, the saline controls also displayed these changes. Tubular necrosis, interstitial nephritis, tubular cast, tubular dilatation and hemorrhage in the kidney at all doses. Phlebitis at the infusion site was noted in all treated males.

4-hr infusion: Mixed cell infiltration of the liver (centrilobular/periportal) and bronchopneumonia, pleuritis, interstitial pneumonia, emphysema, perivascular and/or peribronchiolar mononuclear cell in the lung were noted in 3 and 20 mg/kg males. Increased myelopoiesis in the bone of 3 mg/kg male; adrenal hemorrhage in 20 mg/kg males Hemorrhage in the duodenum in 20 mg/kg male. Interstitial nephritis in the kidney was noted at all doses. Tubular necrosis, tubular cast and tubular dilation at 10 and 20 mg/kg. Hemorrhage in the kidney only at 20 mg/kg. Congestion of the lymph nodes was noted in males at all doses. Phlebitis was found at the infusion site of 3 and 20 mg/kg males. Fiber degeneration in the heart of 20 mg/kg female.

24 hr infusion: Dilation of ventricle in the brain in 20 mg/kg male and hemacyst in the heart of 20 mg/kg males and females. Interstitial nephritis and tubular cast at all doses in males and only in 10 and 20 mg/kg females. Tubular dilation, necrosis and hemorrhage in the kidney of 10 and 20 mg/kg males. In females, tubular necrosis was noted at 10 and 20 mg/kg; and hemorrhage and tubular dilation at 20 mg/kg only. Bronchopneumonia was noted in males at all doses. Congestion of the lymph nodes was also noted in 20 mg/kg males. Phlebitis at the infusion site in males at all doses. Although changes in the lungs were noted with 24-hr infusion there were of sporadic incidence.

A 7-Day Intravenous Toxicity Study (daily infusion) of CPG 233339A in the Beagle Dogs Test No. 91-6036

Dogs (2/sex/group) were given the following treatments:

	Dose/Group (mg/kg/day)	Infusion Time (hr)	Dose Rate (ml/Kg/hr)
1.	Saline control	24	0.42
2.	1	1	3.33
3.	3	1	10.00
4.	1	4	0.83
5.	3	4	2.5
6.	1	24	0.14
7.	3	24	0.42

Observed Effects and Mortality
No treatment effects

Body Weight and Food Consumption
There were slight variations in these parameters in treated dogs, but there was no relationship to dose or infusion times.

Clinical Chemistry
There were some changes in individual animals, but overall group values were unaffected by the various treatment regimens.

Hematology
No treatment related changes were observed.

Urinalysis
No dose-related effects.

Organ Weights
No treatment related changes.

Gross Pathology
Regardless of the infusion time, dark foci and depressed areas in the kidneys were found in females given 3 mg/kg. Dark foci in the stomach mucosa were noted in both control and treated males (1 mg/kg with 1, 4 and 24-hr infusion periods).

Histopathology
Although changes such as dark or raised areas in the lung, thickening of the infusion site; and enlargement or discoloration of lymph nodes were noted, the incidence appeared to be unrelated to dose and/or the infusion times. Additionally, aspermia in the epididymis; and aspermatogenesis or hypospermatogenesis in the testis were commonly noted in males of all groups. This was attributed to "sexually immaturity" of the male dogs used in the study. Main drug related effect was renal toxicity. There were no renal changes in the control group.

1-hr infusion: At 1 mg/kg, both males had slight to mild mixed cell infiltration of the renal sinus and one male also had slight dilation of the renal tubules. At 3 mg/kg, mixed cell infiltration of the renal sinus was also found in one female and the other female had slight to mild multifocal mononuclear inflammatory cell infiltration.

4-hr infusion: One male and female each at 1 mg/kg and 3 mg/kg had slight dilation of the renal tubules and slight to mild multifocal mononuclear inflammatory cell infiltration in the kidney. The 1 mg//kg male also had slight unilateral multifocal tubular necrosis and slight to mild mixed cell infiltration of the renal sinus.

24-hr infusion: One 1 mg/kg female had slight to mild mixed cell infiltration of the renal sinus. At 3 mg/kg, both males and one female displayed the same effect. Both 3 mg/kg females had

slight to mild multifocal mononuclear inflammatory cell infiltration. Slight dilation of the renal tubules was also found in one 3 mg/kg female.

A 3-Month Repeated Intravenous Infusion Toxicity Study of CPG 23339A in the Albino Rat, Followed by a 4-week Recovery Period
Test No: 91-6007
SD rats were given the following treatments:

	Dose/Group (mg/kg/day)	Dose Rate (ml/Kg/hr)
1.	Control	6.67
2.	2	0.67
3.	6	2.00
4.	20	6.67

Treatment was administered by 1-hr infusions, given once a week. Control and 20 mg/kg groups had 16/sex/group and the remaining groups had 8/sex/group. Following the treatment period, 8/sex from the control and 20 mg/kg groups continued into the recovery period.

Observed Effects
Discoloration, loose, broken or missing upper and/or lower incisors were noted in 6 and 20 mg/kg rats, from the beginning of mo 3 until the end of the recovery period. Incidences were 6/16 and 27/32 rats of the 6 and 20 mg/kg groups, respectively.

Mortality
Data are summarized below:

Controls- 1 male (day 46) and 2 females (days 63 and 92)
2 mg/kg- 1 female (day 21)
6 mg/kg- 2 females (days 63 and 87)
20 mg/kg- 5 males (days 22, 65,72, 92 and 93) and
4 females (days 22, 64 and 87)

Renal changes were found only in the 20 mg/kg rats. These changes included hydronephrosis and slight to moderate tubular degeneration.

Body Weight and Food Consumption
At 6 mg/kg, males had significantly decreased body wts and food consumption during the treatment and recovery periods. Significant decreases in body wt and food consumption occurred infrequently in 6 mg/kg females.

Clinical Chemistry
Significant increases in creatinine and BUN were noted in 20 mg/kg males on days 1, 22, and 64. BUN remained elevated in 20 mg/kg males up to the end of the treatment phase. In 20 mg/kg females, significantly increased creatinine and BUN were noted on day 1 and BUN remained elevated on days 22 and 64. Phosphorus levels were significantly decreased in 20 mg/kg dogs on days 22

and 64 of the treatment period. No significant changes in clinical chemistry were found following the recovery period.

Hematology
Significantly increased segmented neutrophils and decreased lymphocytes were noted in 20 mg/kg rats on days 1, 22 and 64. Significant changes in HCT, HGB, MCH, MCHC in 20 mg/kg males were noted during treatment but they were of sporadic incidence. Yet on day 92, HGB, HCT, MCV and MCH were all significantly decreased in 20 mg/kg males. There were no significant changes in hematological parameters following recovery.

Organ Weights
Absolute wt of liver was significantly decreased; and absolute and relative wt of thyroid/parathyroid glands were significantly increased in 20 mg/kg following treatment and recovery periods. Significantly increased absolute thyroid/parathyroid wts was noted in 20 mg/kg females only after the recovery period, but the relative wt was significantly increased during treatment. Significantly decreased absolute adrenal wt in 20 mg/kg males was found only after recovery.

The relative wts of kidneys, gonads and brain in 20 mg/kg males was significantly increased after treatment. Following the recovery period, relative kidney and brain wts remained significantly higher. Relative wts of kidneys and brain in 20 mg/kg females were significantly increased after treatment.

Gross Pathology
Post Treatment:
Pale area in teeth was noted in one 6 mg/kg males; and broken and missing teeth were noted in males and females at 20 mg/kg. Depressed or raised areas, irregular surface and adhesion in the kidney; and dark areas in the lung were noted in control and 20 mg/kg dogs. Enlargement of the mandibular lymph node and thickening at the infusion site were noted in all groups.

Post Recovery:
Irregular surface of the kidney was evident in one 20 mg/kg male. Additionally, changes in teeth noted after treatment were also evident following the recovery period.

Histopathology
Post Treatment:
Phlebitis, thrombosis and perivascular inflammation observed at the infusion site of 20 mg/kg animals were of greater severity vs controls (only groups examined). An increased incidence of periocular hemorrhage was noted in 20 mg/kg females. --

Renal changes included tubular degeneration in one 6 mg/kg female and 20 mg/kg rats; and increased incidence of interstitial inflammation in 20 mg/kg males. Histiocytosis in the lungs was found only in 20 mg/kg rats. In the femur, increased thickness of metaphysis was noted only in 20 mg/kg males.

Post Recovery:
Tubular degeneration and interstitial inflammation in the kidney and thymic atrophy were present in 20 mg/kg rats. Phlebitis, perivascular inflammation and thrombosis at the infusion site were of greater severity in 20 mg/kg rats vs controls.

A 3-month Repeated Intravenous Infusion Toxicity Study of CGP 23339A in the Beagle Dog Followed by a 4-week Recovery Period Test No. 91-6006
Dogs (4/sex/group) were given 2, 6 or 20 mg/kg of APD by 1-hr infusion period, once a week over three months (14 infusions total). The saline controls and the 20 mg/kg group contained additional animals (4/sex) for the recovery study.

However, the dogs in the 20 mg/kg were found dead or sacrificed as moribund either after the first or second infusion. Severely decreased activity, marked decreases in body wt and food consumption, diarrhea, emesis (with blood) and swollen eyelids were noted in the 20 mg/kg dogs. Clinical chemistry changes included increased BUN, creatinine, AST, ALT, ALKP, cholesterol and globulin (measured one day after 1rst dose). Significant changes in hematological parameters were also noted. Histological changes included slight to moderate renal tubular necrosis, tubular dilation, hyaline casts, tubular basophilia and focal mononuclear cell infiltration in the kidneys; hypo-or aspermia in the epididymis; gastritis and thymus atrophy. Due to the toxicity of the 20 mg/kg dose, the new high dose was 6 mg/kg and an intermediate dose of 4 mg/kg was added.

The revised treatment groups were as follows (recovery groups now had 2/sex):

	Dose/Group (mg/kg/day)	Dose Rate (ml/Kg/hr)
1.	Control	6.67
2.	2	0.67
3.	4	1.33
4.	6	2.00

Observed Effects
Injection of the conjunctiva, emesis and diarrhea were noted in all groups. Slightly increased incidence of conjunctival vessel changes and emesis was associated with 6 mg/kg dose. These effects were also found during the recovery period.

Mortality
None.

Body Weight and Food Consumption
Body wt was unaffected by the various treatment regimens. Significantly decreased food consumption was noted in 4 mg/kg females on wks 8, 9, 12-14; 6 mg/kg females on wks 9, 13 and 14 and 6 mg/kg males on wk 13. During the recovery period (wks 14-18) there was no significant effect on food consumption at 6 mg/kg.

Clinical Chemistry
Significantly increased creatinine was noted in 4 and 6 mg/kg males on wk 1, 4, 10 and only in 6 mg/kg males on wk 14. In 6 mg/kg females, significant increases in creatinine were noted on wks 4-14. Significantly increased AST was noted in 4 and 6 mg/kg males on wks 10 and 14. On wk 14, AST and ALT were significantly increased in 6 mg/kg females. Significant, decrease in phosphorus levels were noted at all doses on wk 4; and in 4 and 6 mg/kg males on wk 10. Sporadic, significant changes in serum electrolytes and globulin levels were also noted in the treatment groups. There were no significant changes in the 6 mg/kg group during the recovery period.

Hematology
Significant increase in segmented neutrophils and decrease in lymphocytes were noted in 6 mg/kg males on wk 10. In females, lymphocyte count was significantly decreased in 4 and 6 mg/kg females and segmented neutrophils were increased in 6 mg/kg females on wk 14. Total WBC was significantly elevated in 6 mg/kg males on wk 14. HD males also had significantly increased HCT on wk 4. Significantly decreased APTT was noted in 4 and 6 mg/kg males on wk 14. There were no significant changes in hematological parameters during the recovery period.

Organ Weight
There were no significant changes in absolute and relative organ wts in treated dogs during the treatment and recovery periods.

Gross Pathology
Post Treatment:
Raised area in the lung was noted at all doses. Increased incidence of raised area in the spleen was noted in 6 mg/kg females.

Post Recovery:
Small kidney or depressed area in females; dark or pale areas in the liver in females; and raised, dark or pale areas in the lungs of both sexes at 6 mg/kg dose.

Histopathology
Post Treatment:
Hypospermia in the epididymis was noted in 4 and 6 mg/kg males. Treatment related renal changes included mononuclear inflammatory cell infiltration in one 2 mg/kg male and in both sexes at the other doses. Tubular cell necrosis and tubular basophilia in the kidney occurred in males and females of the 4 and 6 mg/kg dose groups. Interstitial pneumonia in the lungs was evident in control and treated dogs. Fibrosis and siderotic plates in the spleen were noted only in 6 mg/kg females. Osseous changes included increased thickness of the primary spongiosa and loss/decrease of cartilage zone at all doses.

Post Recovery:
Mononuclear inflammatory cell infiltration, tubular dilation and fibrosis in the kidney; and hemorrhage and interstitial pneumonia were noted only in 6 mg/kg group. Both 6 mg/kg males were noted with hypospermatogenesis in the testis. Osseous changes found after the treatment period persisted during the recovery period.

REPRODUCTION STUDIES

Preliminary Intravenous Toxicity Study in Pregnant Rats (Dose Range Finding Study) Test No. 88-6179
Pregnant rats (8/group) received APD as i.v doses of either 5 or 10 mg/kg/day from Days 6-15 of gestation. Control group received vehicle (distilled water).

Observed Effects
F0: "Ventral recumbency", dyspnea, salivation, chromodacryorrhea, muscular hypertonia and tremors were noted in 10 mg/kg dam on Day 21 of the study. Irritation at the injection site was noted in two 10 mg/kg dams, from Days 6 or 8 and thereafter.

Mortality
F0 and F1: None.

Body Weight and Food Consumption
F0: Significant reductions in body wt of (Day 8-21) and body wt gain (Day 6-21) were noted in 10 mg/kg dams. This change was attributed to increased resorption rate and decreased uterine wt at 10 mg/kg. Significantly reduced food consumption was also noted at 10 mg/kg.

F1: Fetal body wts (males and females) from the 10 mg/kg group were significantly reduced.

Reproductive Performance
F0: These parameters were unaffected at 5 mg/kg. At 10 mg/kg there were increased number of resorptions and postimplantation loss.

Organ Weights
F0: A complete analysis of organ wts was not performed. However, significantly decrease wt of the gravid uterus was noted in 10 mg/kg group.

Gross Pathology
F0: No treatment effects.

F1: One malformed fetus (omphalocele) at 10 mg/kg.

Exploratory Segment II Littering Study in Rats Test No. 90-6270
Pregnant SD rats (14/group) were given 1, 3 or 6 mg/kg APD by i.v. injection, from Days 6-15 of gestation. Control group received vehicle (4% mannitol).

Observed Effects
F0: At parturition, hunched posture, piloerection, body/head/neck tremors, coldness of the extremities and ptosis were noted in all dose groups. Redness at the injection site was noted at 6 mg/kg.

Mortality
F0 and F1: All dams showing "distress" at parturition were sacrificed as moribund. Sponsor noted that pup viability could not be calculated due to majority of the dams being sacrificed at parturition.

Body Weight and Food Consumption
F0: Significantly decreased body wt gain was noted at 6 mg/kg, during Day 10-15 of gestation. Food consumption was significantly decreased at 6 mg/kg, throughout the study.

F1: No treatment effect.

Plasma Calcium
Blood samples were collected from only 4 dams that displayed "distress" during parturition. Decreased calcium levels (25% of controls) were noted at 1 mg/kg on Day 22 and at 3 and 6 mg/kg on Days 20-21 of gestation. Sponsor felt that the hypocalcemia was related to the "distress" observed in dams, at parturition.

Preliminary Intravenous Embryotoxicity Study in the Rabbit
Test No. 88-6180
Pregnant New Zealand White rabbits were given 0.75 or 1.5 mg/kg of APD by i.v. injection, from Day 6-18 of gestation. Control group received vehicle (5% mannitol solution). Rabbits were sacrificed on Day 28.

Observed Effects
F0: Swollen and violet colored eyes at 1.5 mg/kg, which was attributed to APD injection into the ear vein.

Mortality
F0: One 1.5 mg/kg rabbit on Day 13 of gestation. Death was considered unrelated to treatment. Another 1.5 mg/kg rabbit was sacrificed on Day 6, due to vertebral column injury.

Body Weight
F0: Decreased body wt gain at both doses; Days 12-15 at 0.75 mg/kg and Day 6-19 at 1.5 mg/kg.

F1: Decreased fetal body wts at both doses.

Reproductive Performance
F0: Sponsor stated that pre-and postimplantation loss was increased in control and treated groups, compared to normal range in this strain. This increase was thus attributed to the mannitol vehicle.

Gross Pathology
F0: Sponsor noted unspecified changes in the liver and kidney of all groups.

Preliminary Intravenous Embryotoxicity Study in the Rabbit (Comparison of Effects of Mannitol-Containing and Mannitol-Free Formulations) Test No. 89-6011
Pregnant New Zealand White rabbits (8-9/group) were given either 0.75 or 1.5 mg/kg APD by i.v. injection, using either a mannitol vehicle or saline. APD was administered on Day 6-18 of gestation. Controls groups received the appropriate vehicle.

Observed Effect
F0: Swollen and/or reddened ears were observed with both doses of APD, regardless of the vehicle used.

Body Weight and Food Consumption
F0: Decreased body wt gained and food consumption occurred occasionally at both doses (Day 6-19), regardless of type of vehicle.

Reproductive Performance
F0: % Preimplantation loss was increased in mannitol control group and thus a treatment effect could not be determined. In the saline-vehicle groups, % preimplantation loss was increased at 1.5 mg/kg.

Gross Pathology
F0: Unspecified changes in the kidneys and/or liver were of similar occurrence in control (both vehicles) and treated groups.

F1: No treatment effects.

Sponsor concluded that, "In view of the overall results of this preliminary study as well as the results of a preceding dose range-finding experiment, some caution should be exercised upon further use of mannitol-containing formulations of CGP 23339A for reproductive toxicity studies in rabbits." (Vol 10, pg 100).

Intravenous Developmental Toxicity (Teratogenicity) Study With CGP 23339A in Rats Test No. 89-6007
Pregnant rats were given 0, 6, 9, 12 and 15 mg/kg/day of APD by i.v. injection from Days 6-15 of gestation. Controls received vehicle (distilled water). Animals were sacrificed on Day 21.

Observed Effects
F0: Dose related irritation at the injection site was noted in all treatment groups.

Mortality
F0: One 6 mg/kg and one 12 mg/kg rabbit were found dead (unrelated to treatment). One female each in 12 and 15 mg/kg group were sacrificed on Days 16 and 20 respectively. Both animals had aborted.

F1: Significantly decreased number of viable fetuses at 12 and 15 mg/kg.

Body Weight and Food Consumption
F0: Dose related, significantly decreased body wt and body wt gain were noted at 9-15 mg/kg. At 9 mg/kg the body wts were consistently significantly decreased from Day 14-21 and in the other groups from Day 12-21. Food consumption was significantly reduced in all treatment groups from Days 6-21 (dose related to Day 16).

F1: Fetal body wts were significantly decreased in all treated groups, in dose a related manner.

Reproductive Performance
F0: Significantly increased number of resorptions and postimplantation loss at 12 and 15 mg/kg.

Organ Weights
F0: Complete analysis was not performed. Significantly decreased gravid uterine wt was noted at 9-15 mg/kg.

Gross Pathol
These data w[illegible] divided in to skeletal malformations, anomalies and fetal visceral observations.

F0: No treatment related effects.

F1: Total skeletal malformations were significantly increased at 12 and 15 mg/kg. Total skeletal anomalies were significantly increased at 9-15 mg/kg.

Malformations: Reduced scapula, shortened ulna, radius and humerus; and shortened or irregular ossification of the femur were noted at 12 and 15 mg/kg.

Anomalies: At 9-15 mg/kg, significantly increased incidence of absent or poor ossification of metacarpal 5. At 12 and 15 mg/kg, there were significant and dose related increases in the occurrence of asymmetrically shaped sternebrae 3 and 4; and bipartite ossification of sternebrae 1 and 3.

Visceral Changes: At 12 mg/kg, one pup with a cleft palate and two pups with subcutaneous edema in the thoracic region. At 15 mg/kg six pups had subcutaneous edema in the thoracic region and one pup displayed "generalized edema".

Additional Intravenous Segment II (Teratology) Study in Rats
Test No. 90-6269
Pregnant rats (25/group) received APD at i.v. doses of 1, 3 or 6 mg/kg/day, from Days 6-15 of gestation. Control group received vehicle (4% mannitol).

Observed Effects
F0: Majority of animals in the 6 mg/kg group had reddening at the injection site.

Mortality
F0 and F1: None.

Body Weight and Food Consumption
F0: Significantly decreased body wt gain was noted in 6 mg/kg group from Days 6-10 of gestation. Although food consumption was decreased at 3 and 6 mg/kg, it was not statistically significant.

F1: No treatment effect.

Reproductive Performance
F0: Significant increase in pre-implantation loss was observed at 3 mg/kg, only.

Gross- and Histopathology
F0: Only the kidney was examined. In the 6 mg/kg group, the kidney was characterized by "very slight exacerbation of typical progressive renal disease", tubular dilation, proteinaceous casts and/or basophilia.

F1: Incidences of fetal hematoma and placental hemorrhage were increased at 3 and 6 mg/kg, but not in a dose related manner. Extreme dilation and kinking/distortion or the ureters and renal pelvic cavitation were increased at 3 and 6 mg/kg. Incidence of incomplete occipital ossification in the skull and incomplete ossification of the sternebrae were noted at 6 mg/kg.

Intravenous Teratogenicity Study in the Rabbit Test No. 90-6065
Pregnant New Zealand White rabbits (18/group) were given i.v. APD injections at doses of 0.25, 0.75 and 1.5 mg/kg/day from Day 6-18 of gestation. Control groups were given vehicle (5% mannitol solution). Animals were sacrificed on Day 28.

Observed Effects
F0: Swollen and/or reddened ears were noted in 7/18 0.75 mg/kg and 14/18 1.5 mg/kg groups.

Mortality
F0: One 1.5 mg/kg rabbit was found dead on day 8. Death was considered unrelated to treatment.

F1: Number of live fetuses was decreased at 1.5 mg/kg, but was not significant.

Body Weight and Food Consumption
F0: Sporadic decreases in body wt gain were noted in 0.25 mg/kg group (Days 9-12 and 15-19). At 0.75 mg/kg decreased body wt gain was noted on Days 6-9. Overall body wt gain was significantly less at 1.5 mg/kg. Food intake was significantly decreased in 1.5 mg/kg rabbits from Days 6-19.

F1: Fetal body wts were unaffected by treatment.

Reproductive Performance
F0: No treatment effects.

Gross Pathology
F0: Increased incidence of pale kidneys was noted at 1.5 mg/kg.

F1: Data were presented as skeletal malformations and visceral findings.

Malformation: Extra rib between thoracic ribs, absent lumbar/sacral/caudal vertebrae, malformed or extra vertebrae and scoliosis were noted in 7 control fetuses. Two 0.25 mg/kg fetuses had scoliosis and another one had external arthrogryposis and a kinked/reduced tail. At 0.75 mg/kg, three fetuses had scoliosis or extra rib between thoracic ribs. With 1.5 mg/kg there were shortened body; absence of ribs; distally and proximally fused ribs; absent thoracic/lumbar/sacral and caudal vertebrae; and malformed and rudimentary vertebrae, in 2 fetuses. Two other fetuses in this group had scoliosis and fused ribs or vertebrae and another fetus had "skull misshapen".

Visceral Findings: Two control fetuses had abnormal brain shape and internal hydrocephaly. Three 1.5 mg/kg fetuses had internal hydrocephaly.

Summary

The current submission seeks to shorten the 24-hr infusion of 60-90 mg (approx. 1 and 2 mg/kg, respectively) of APD to a 4-hr infusion, for treatment of hypercalcemia of malignancy. However, the toxicology data provided in the submission did not adequately address this change in treatment regimen. Majority of the toxicology studies were conducted with 1-hr infusions; and those using 4-hr infusion period either lacked a control group or had a control group with 24-hr infusion.

In a 7-day study in dogs, i.v. doses of APD at 3, 10 or 20 mg/kg were given by 1-, 4- or 24-hr infusions. The NOEL in this study was 3 mg/kg given over a 24-hr infusion period. Yet in another 7-day study in dogs using lower doses (either 1 or 3 mg/kg APD given over either 1, 4-, or 24-hr infusion), failed to identify a NOEL.

3-Month i.v. toxicity studies with recovery periods in rats and dogs, were also conducted. Doses used in rat and dog studies were 2, 6 or 20 mg/kg and 2, 4, 6 and 20 mg/kg, respectively, given by 1-hr i.v. infusions, once a week. In both species, the NOEL was found to be 2 mg/kg. Main toxicity observed in both species, at 4 mg/kg and higher doses was renal tubular degeneration or dilation. Renal changes were irreversible with 20 mg/kg.

4 mg/kg in dogs

Reproduction studies (teratology) conducted with i.v. administration of APD were also contained in this submission. These studies were conducted in rats at 1-15 mg/kg and in rabbits at 0.25-1.5 mg/kg. Maternal and embyrotoxicity were observed in both species. However, validity of the teratology study in rabbits is unclear. Preliminary studies in rabbits had found that mannitol vehicle may affect reproductive performance. Yet the actual teratology studies in rats and rabbits were conducted with a mannitol vehicle. These reproduction studies conducted with i.v. APD do not change the "Pregnancy Category C" designation.

Recommendation: The toxicology data provided did not support the use of a 4-hr infusion with 60 and 90 mg APD. The toxicology studies failed to identify a NOEL for 4-hr i.v. infusions and thus recommend non-approval for the requested clinical change. The following comment should be conveyed to the sponsor:

1. Preliminary teratology studies in rabbits indicated that the use of a mannitol buffer vehicle in reproduction studies may not be appropriate. Yet reproduction studies conducted in rats and rabbits utilized a mannitol buffer vehicle. What evidence is there, that these reproduction studies were not comprimised by the use of a mannitol buffer vehicle?.

Chhanda Dutta, Ph.D.

HFD-510/L Lutwak/A Jordan/
Hedin

Supplement is approvable
for the 60 mg dose
AJ
4/2/93

APR 28 1993 APR 28 1993

ORIGINAL

NDA 20-036

SUBMISSION DATE: September 23, 1992

Aredia™
Pamindronate Disodium for Injection
CIBA-GEIGY Corporation.
Pharmaceutical Division
Summit, New Jersey 07901

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Labelling Changes (reduction in the iv infusion time from 24 to 4 hours).

SYNOPSIS:

The sponsor is submitting a Supplement to NDA 20-036 that was filed on September 23, 1992 for Aredia™ (pamindronate disodium for injection). In this submission the sponsor provides data to support the use of a 4 hr intravenous infusion of Aredia™ for the approved indication.

The original NDA for Aredia™ was approved on October 31, 1991. Aredia™ in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases. The recommended dose of Aredia™ in moderate hypercalcemia is (corrected serum calcium 12-13.55 mg/dL) 60-90 mg, and in severe hypercalcemia (corrected serum calcium of approximately >13.5 mg/dL), is 90 mg given as an initial single-dose intravenous infusion over 24 hours. Data presented in the Human Pharmacokinetics and Bioavailability Section of the original NDA 20-036 indicated that the disposition of the drug, particularly the percentage of dose recovered in urine, was unchanged whether Aredia™ was administered by infusion over either 4 or 24 hr. In the present NDA the sponsor is submitting for review clinical, pharmacokinetic, and toxicological data to support a 4 hour intravenous infusion of Aredia™ for the approved indication, as compared to the 24 hour infusion. To support the pharmacokinetic data included in the labelling for the 4 hr infusion, the sponsor is submitting for review four pilot and background studies (Report B39/1990, Trial Plan DPPK1b, Proceedings of 5th European Conference on Clinical Oncology, 1989, and Abstract from Journal of Cancer Research and Clinical Oncology, 1990), and four pharmacokinetic studies (Clinical Protocol 09, Report B54/1989, Trial Plan DP/BC6 Addendum, and Calcified Tissue International, 1991).

From the submitted studies, only Clinical Protocol 09 was sponsored in the US by the applicant (see Table 1). Clinical Protocol 09 is the most relevant and complete study, and the proposed pharmacokinetic changes included in the Clinical Pharmacology section of the labelling, are mainly based in the results obtained from this study.

RECOMMENDATION:

The Division of Biopharmaceutics has reviewed the Supplement to NDA 20-036 which was filed on September 23, 1992 and finds that the submitted pharmacokinetic information is acceptable

for characterizing what happens to the drug's systemic levels and urinary excretion when the infusion time is changed from 24 to 4 hours (i.e., the mean Cmax levels for the 30, 60, and 90 mg doses after the 4 hr intravenous infusion were approximately 3, 4, and 5 times higher than the mean Cmax values reached after the 24 hr infusion for the same doses, and for the 4 hr infusion the plasma pamindronate concentrations were below the assay quantitation limit in approximately 8-12 hr as compared to 24-28 hr for the 24 hr infusion).

Since the medical reviewer in HFD-510 is recommending approval of the change in infusion rates for the 60 mg dose but not for the higher 90 mg dose due to a lack of safety and efficacy data, the Division of Biopharmaceutics therefore recommends that some pamindronate blood levels be obtained (i.e., ideally peak and trough levels, so that a possible pharmacokinetic/pharmacodynamic relationship can be assessed from both an efficacy and safety prospective), when the safety/efficacy clinical trials are conducted for the higher 90 mg dose.

With respect to the package insert, the pharmacokinetic information included in the Clinical Pharmacology section of the package insert is acceptable, provided the changes that are recommended by the Agency are included in the labelling. After the labelling is modified, the firm should resubmit the package insert for its review.

Please convey the Recommendation as appropriate, and Labelling Comments 1 to 5 (page 20) to the sponsor.

NOTE: Attachments I to IV are being retained in the Division of Biopharmaceutics and may be obtained upon request.

TABLE OF CONTENTS:

III. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY OF AREDIA™ RAPID INFUSION

BACKGROUND:

Aredia™, a member of the bisphosphonate class of therapeutic agents, is currently approved in the US for administration via 24-hr intravenous infusion to patients with hypercalcemia of malignancy. Additional trials have been conducted since the original submission in which the pharmacokinetics of Aredia™ have been characterized following rapid infusions (i.e., 1 and 4 hr). A tabulated summary of the pharmacokinetic studies (4 Pilot and Background Studies and 4 Pharmacokinetic Studies) carried out with Aredia™ is provided in Table 1.

TABLE 1

Study Number	Study Type	Sponsor	Country
Basel Report B39/1990	Pilot Study	CIBA-GEIGY	Basel, Switzerland
Basel Trial Plan DPPK1b	Pilot Study	CIBA-GEIGY	Basel, Switzerland
Proc. 5th. Eur. Conf. on Clin. Oncol., 1989	Background Study	Published Ref.	UK
J. Cancer Res. and Clin. Oncol., 1990	Background Study	Published Ref.	US
Clinical Protocol 09	PK Study	CIBA-GEIGY	US
Basel Report B54/1989	PK Study	CIBA-GEIGY	Basel, Switzerland
Report UK R1, 1991	PK Study	CIBA-GEIGY	UK
Calcif Tissue Int'l, 1991	PK Study	Published Ref.	UK

Pilot and Background Studies

1. **Report B39/1990** - "*Pharmacokinetics of Pamindronate Disodium in Patients with Bone Metastases*". Single intravenous infusions of 60 mg administered over 1 hr.
2. **Trial Plan DPPK1b** - "*Pharmacokinetics of Pamindronate Disodium in Patients with Bone Metastases*". Repeated intravenous infusions of 60 mg administered over 1 hr.
3. **Proceedings of 5th European Conference on Clinical Oncology, 1989** - "*The Management of Bone Metastases and Hypercalcemia by Osteoclast Inhibition*".
4. **Abstract from Journal of Cancer Research and Clinical Oncology, 1990** - "*Intravenous Pamindronate: Pharmacokinetic and Duration of Effect Studies in Women with Skeletal Breast Cancer*".

Pharmacokinetic Studies in Patients

1. **Clinical Protocol 09** - "*Pharmacokinetics of CGP 23339A in Cancer Patients After a Single Intravenous Infusion of 30, 60, or 90 mg Drug Over 4 or 24 Hours*"
2. **Report B54/1989** - "*Pharmacokinetics of Pamindronate Disodium in Patients with Bone Metastases*". Single intravenous infusions of 60 mg at 2.5 or 15 mg/hr.
3. **Trial Plan DP/BC6 Addendum** (Report UK R1/1991)- "*To investigate the pharmacokinetics of a Nominal Dose of 60 mg APD Given Intravenously Over 1 or 4 Hours*".
4. **Calcified Tissue International, 1991** - "*The Clearance and Bioavailability of Pamindronate in Patients with Breast Cancer and Bone Metastases*".

A. DRUG FORMULATION

A summary of the formulations used in the non-US and US pharmacokinetic studies conducted by CIBA-GEIGY is described in Table 2.

TABLE 2

Study Number	Lot No.	Formula	Dosage Form & Strength	Batch Size	Formulation
PHARMACOKINETIC STUDIES - NON US STUDIES					
Trial Plan DPPK1b (B17/1991)	13/874/1	not reported	15 mg /5 ml intravenous solution ampul		Basic Solution Ampul Formulation
Basel Report B54/1989	13/874/1 13/885/1	not reported	15 mg /5 ml intravenous solution ampul		Basic Solution Ampul Formulation
Basel Report B39/1990	13/874/1 13/885/1	not reported	15 mg /5 ml intravenous solution ampul		Basic Solution Ampul Formulation
Trial Plan DP/BC6 (UKR1/1991)	13/350/1 14/119/1 14/415/1	not reported	15 mg /5 ml intravenous solution ampul		Basic Solution Ampul Formulation
PHARMACOKINETIC STUDIES - US STUDIES					
Clinical Protocol 09	E-13907 14/025/1	H-3109	15 mg lyophilized vial		Basic Lyophilized Ampul Formulation

NOTE: Formulation H-3109 is the marketed formulation and it was used in PK/Clinical Protocol 09 and safety/efficacy Clinical Protocols 06, 07, 12, 18, and 19.

B. ANALYTICAL METHODS

Plasma and urinary concentrations of pamindronate were assayed in the studies described in this submission by either i) HPLC with fluorescence detection of the fluorescamine derivative, or ii) high-performance anion chromatography with spectrophotometric detection of the phosphomolybdate complex. A summary of the analytical methods is presented in Attachment I.

C. PILOT AND BACKGROUND STUDIES

1. Report B39/1990

TITLE: "Pharmacokinetics of Pamindronate Disodium in Patients with Bone Metastases. Single Intravenous Infusions of 60 mg Administered Over One Hour".

OBJECTIVE: To measure the plasma concentrations and urinary excretion of pamindronate after a single 60 mg infusion (in one hour), in patients with cancer and extensive bone metastases.

ANALYTICAL METHOD: HPLC, J. Chromatogr., 489, 446-451, (1989).

SUMMARY: Fifteen patients (8 patients [F] from Lausanne and 7 patients[2 M, 5 F] from St. Gallen) with bone metastases, who ranged in age from 42 to 73 yr and ranged in weight from 52 to 81 kg, received a single 60 mg dose of pamidronate disodium by intravenous infusion over 1 hr in a two-center, open-label study. Urine samples were collected over 0-4 and 4-24 hr after the start of the infusion. Plasma samples were obtained pre-dose and at selected time points to 24 hr after the start of the infusion. The individual and pooled mean ± SD pharmacokinetic data from to study centers for plasma and urine are listed in Table 2.

The pharmacokinetics of pamidronate, administered intravenously over 1 hr, followed a multi-exponential course. The distribution of pamindronate was rapid with a mean ± SD plasma half-life(α) of 0.77 ± 0.26 hr. The terminal elimination half -life representing the elimination of pamindronate from the bone into circulation and into urine was not assessed. Steady-state levels plasma levels were not reached during this short infusion. The majority (69% of the dose) of pamidronate was eliminated via non-renal clearance, presumably representing the fraction bound to bone.

TABLE 2

Mean (SD)	Lausanne	St. Gallen	Laus. & St. G.
AUC(0-24h) [h·(µmol/l)]	24.79 (10.09) N = 8	18.20 (5.36) N =6	21.97 (8.79) N. = 14
Cmax [µmol/l]	11.77 (2.49) N = 8	7.02 (1.61) N = 6	9.74 (3.21) N = 14
Tmax [h]*	1	0.75	0.75
T1/2α [h]	0.75 (0.25) N = 8	0.81 (0.30) N = 6	0.77 (0.26) N = 14
TUE(0-24h) [% of dose]	33.19 (16.0) N = 7	28.37 (15.3) N = 6	30.96 (15.23) N = 13
#BR(0-24h) [% of dose]	66.81 (16.0) N = 7	71.63 (15.3) N = 6	69.04 (15.23) N = 13
CL_t [L/h]	8.99 (2.72) N = 7	12.72 (3.79) N = 6	10.71 (3.67) N = 13
CL_r [L/h]	2.97 (1.75) N = 7	3.58 (2.02) N = 6	3.25 (1.82) N = 13
CL_{nr} [L/h]	6.02 (2.54) N = 7	9.14 (3.19) N = 6	7.46 (3.17) N = 13

*: median; #Body retention

2. Trial Plan DPPK1b

TITLE: "Pharmacokinetics of Pamindronate Disodium in Patients with Bone Metastases. Repeated Intravenous Infusions of 60 mg Administered Over 1 Hour".

OBJECTIVE: To determine the pharmacokinetic parameters of pamindronate in plasma and urine after repeated infusions of 60 mg of pamindronate in 1 hr in patients with bone metastases.

ANALYTICAL METHOD: HPLC, J. Chromatogr., 489, 446-451, (1989) and J. Chromatogr., 568, 261-266, (1991).

SUMMARY: Four patients with bone metastases, who ranged in age from 43 to 66 yr, and ranged in weight from 52 to 72 kg, who received 60 mg doses of pamidronate disodium by intravenous infusion over 1 hr in a previous study, were treated with 1-3

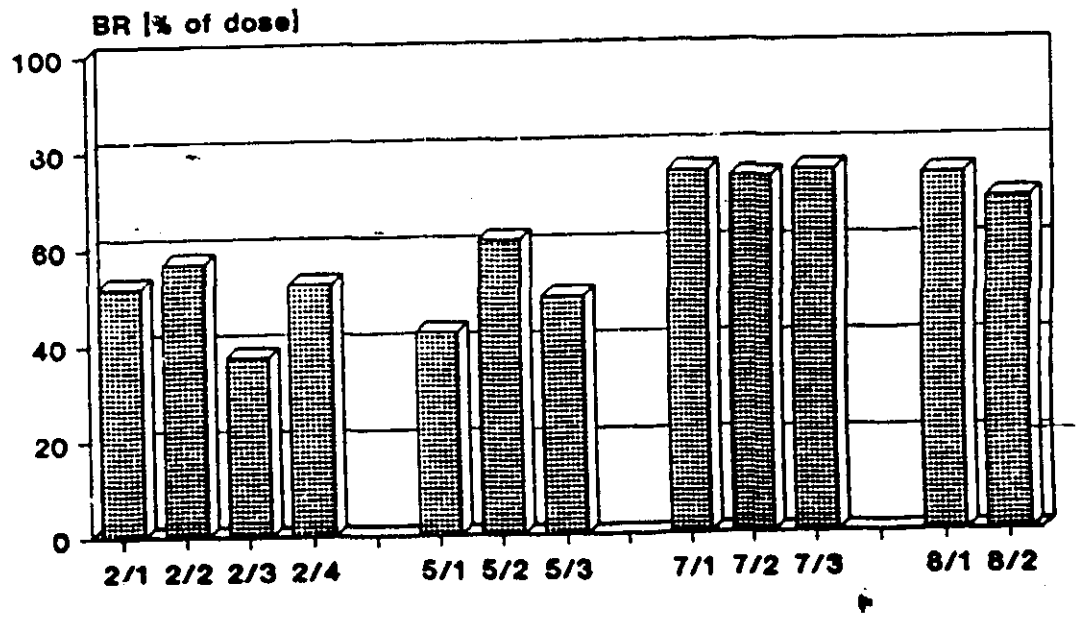
additional doses by the same regimen. The time interval between two consecutive doses ranged from 10-45 days. Urine samples were collected over 0-4 and 4-24 hr after the start of the infusion. Plasma samples were obtained pre-dose and at selected time points to 24 hr after the start of the infusion. Overall mean ± SD plasma and urine pharmacokinetic data are presented in Table 3.

TABLE 3

Cmax (μg/ml)	Tmax (hr)	AUC (μg•hr/ml)	CUE (% Dose)	CL_T (ml/min)	CL_R (ml/min)
3.049 (1.094)	0.75 (0.25-1.5)	7.58 (1.89)	40.1 (13.4)	138 (27.3)	56.6 (25.4)

The decline of pamindronate in plasma followed a multi-exponential time course. The distribution of pamindronate was rapid with a mean ± SD T1/2a of 0.89 ± 0.34 hr. Recovery of pamindronate in urine in 24 hr was between 25 and 62% of the dose, the major part was excreted during the first 4 hr. The plasma concentration profiles, renal clearance, and non-renal clearance remained practically unchanged in all patients after repeated dosing. This might indicate that no saturation of the bone compartment occurred after repeated administration of pamindronate. Body retention of pamindronate after repeated infusions of 60 mg pamindronate disodium given over 1 hr at a constant infusion rate is presented in Figure 1.

FIGURE 1



3. Proceedings of the 5th European Conference on Clinical Oncology, 1989

TITLE: "The Management of Bone Metastases and Hypercalcemia by Osteoclast Inhibition", D.J.Dowell, A. Howell, A. Morton, P.T. Daley-Yates, and C.R. Hoggarth, An international symposium held during the 5th European Conference on Clinical Oncology (ECCO 5), London, September 1989.

OBJECTIVE: To obtain pharmacokinetic information on intravenous pamindronate in a small group of patients.

ANALYTICAL METHOD: HPLC, J. Chromatogr., 490, 329-338, (1989).

SUMMARY: The pharmacokinetics of pamindronate, after 60 mg doses by intravenous infusion over 8 or 24 hr, were studied in five patients with hypercalcemia of malignancy. Blood samples were obtained at selected times up to the end of the infusion. Urine was collected for 24 hr after the start of the infusion. By analysis of plasma concentration-time data during the infusion, an initial half-life of 0.5 hr was estimated. The terminal half-life was estimated from the urinary excretion data to be 2 yr. During the infusion, approximately 25% of the dose was excreted in urine. The mean total clearance and renal clearance were 223 ml/min (range: 144-298 ml/min) and 49.9 ml/min (range: 31.4-68.6 ml/min), respectively, leaving a non-renal clearance for pamindronate of 173 ml/min. Since this drug is not known to be metabolized, the clearance may be predominantly by uptake into the skeleton. It is unclear from the paper whether these results are for the 8 hr infusion, 24 hr infusion or a combination of both.

4. Abstract From Journal of Cancer Research and Clinical Oncology, 1990

TITLE: "Intravenous Pamindronate: Pharmacokinetic and Duration of Effect Studies in Women with Skeletal Breast Cancer", D.J. Dowell, R. Coleman, P. Daley-Yates, R.C.F. Leonard, A. Rodger, and A. Howell, J. Cancer Res. Clin. Oncol. (D) 116, Suppl. I, 401, 1990.

OBJECTIVE: To assess the duration of suppression of calcium excretion and the plasma and urinary pharmacokinetics after a single infusion of 60 mg of pamindronate given to women with breast cancer to bone.

ANALYTICAL METHOD: HPLC, J. Chromatogr., 490, , 329-338, (1989).

SUMMARY: Plasma and urinary pharmacokinetics of pamindronate were studied in 7 normocalcemic patients with breast cancer metastatic to bone. Patients received 60 mg intravenous doses at an infusion rate of 15 mg/hr. The initial half-life was estimated to be 0.5 hr. The terminal half-life was estimated from the urinary excretion data to be 2 yr. During the infusion, approximately 25% of the dose was excreted in urine. This preliminary data show the drug to have a very high clearance, probably due to calcified tissue retention and partly to renal clearance.

D. PHARMACOKINETIC STUDIES -

1. Clinical Report 09

TITLE: "Pharmacokinetics of CGP 23339A in Cancer Patients After a Single Intravenous Infusion of 30, 60, or 90 mg Drug Over 4 or 24 Hours".

OBJECTIVE: The objective of this study was to determine the pharmacokinetics of pamindronate disodium in plasma and urine after single 4 or 24 hr intravenous infusions of either 30, 60, or 90 mg of the drug to cancer patients at risk for developing bone metastases.

CLINICAL CENTER: The clinical part of this study was conducted at two centers - the

The medical monitor was Steven Schoenfeld, M.D. (CIBA-GEIGY, Summit, NJ.). The Clinical Pharmacokinetics and Disposition Study Director was Wing Cheung, Ph.D. (CIBA-GEIGY, Ardsley, NY.).

STUDY DESIGN AND DOSING: This was a single-dose, open-label, parallel, randomized study with a total of 36 patients (32 F and 4 M), who ranged in age from 38 to 79 yr and ranged in weight from 48 to 91 kg (see demographic data in Table 1 of Attachment III). The patients were assigned to receive one of the following 6 treatments of pamindronate:

Treatment A: 30 mg pamindronate disodium infused intravenously over a 4 hr period

Treatment B: 30 mg pamindronate disodium infused intravenously over a 24 hr period

Treatment C: 60 mg pamindronate disodium infused intravenously over a 4 hr period

Treatment D: 60 mg pamindronate disodium infused intravenously over a 24 hr period

Treatment E: 90 mg pamindronate disodium infused intravenously over a 4 hr period

Treatment F: 90 mg pamindronate disodium infused intravenously over a 24 hr period

SAMPLE COLLECTION:

Blood samples (10 ml) for drug level estimation were drawn from the contra-lateral arm to the infusion site according to the following time schedules:

A: pre-dose (0 hr), 1, 2, 4, 5, 6, 8, 12, 16, 24, 48, 84, and 120 hr after initiating the 4 hr infusion; or

B: pre-dose (0 hr), 1, 2, 4, 10, 24, 25, 26, 28, 32, 36, 48, 84, 120, and 144 hr after initiating the 24 hr infusion.

Urine samples for drug levels estimation were collected over the following time intervals:

A: pre-dose (0 hr), 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, and 96-120 hr after initiating the 4 hr infusion; or

B: pre-dose (0 hr), 0-4, 4-8, 8-12, 12-24, 24-28, 28-32, 32-36, 36-48, 48-72, 72-96, 96-120, and 120-144 hr after initiating the 4 hr infusion.

ANALYTICAL: Drug assays were performed by CIBA-GEIGY in Ardslet, NY. Plasma and urine concentrations of pamindronate were measured using established and validated reverse-phase-phase high performance liquid chromatography methods (see Attachment II).

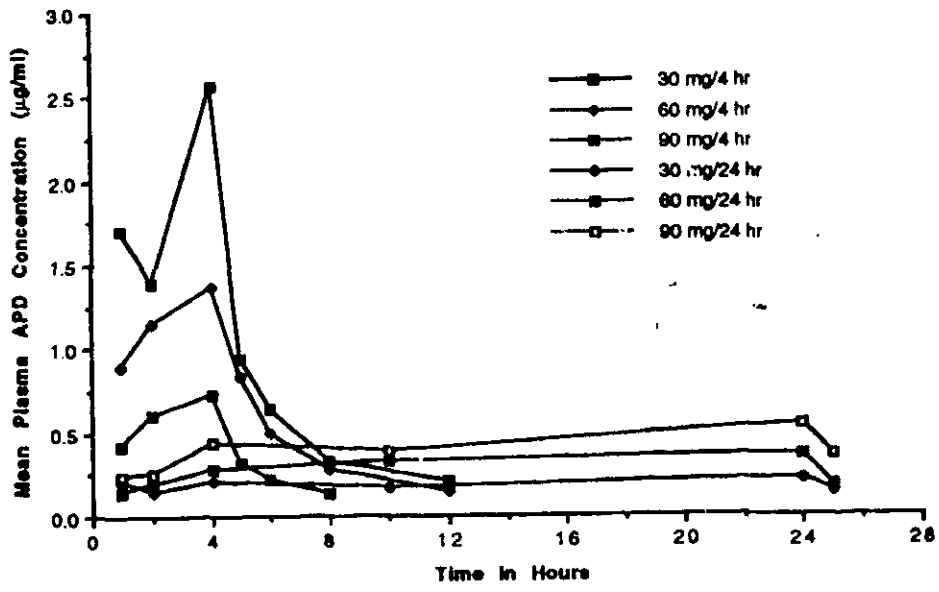
RESULTS:

Plasma Data: Plasma concentrations could be measured for 5-8 hr after the start of the 4 hr infusion and for 24-28 hr after the start of the 24 hr infusion. Mean plasma pamindronate concentrations after 4 or 24 hr are illustrated in Figure 2 (made by reviewer). The mean plasma pharmacokinetic parameters are listed in Table 4. Individual pamindronate disodium plasma concentrations and actual times of blood sampling are listed in Tables 3 and 4 of Attachment III, for the 4 and 24 hr infusions, respectively. The corresponding pharmacokinetic parameters for Cmax, Tmax, and AUC values are listed in Tables 5 and 6 of the same Attachment.

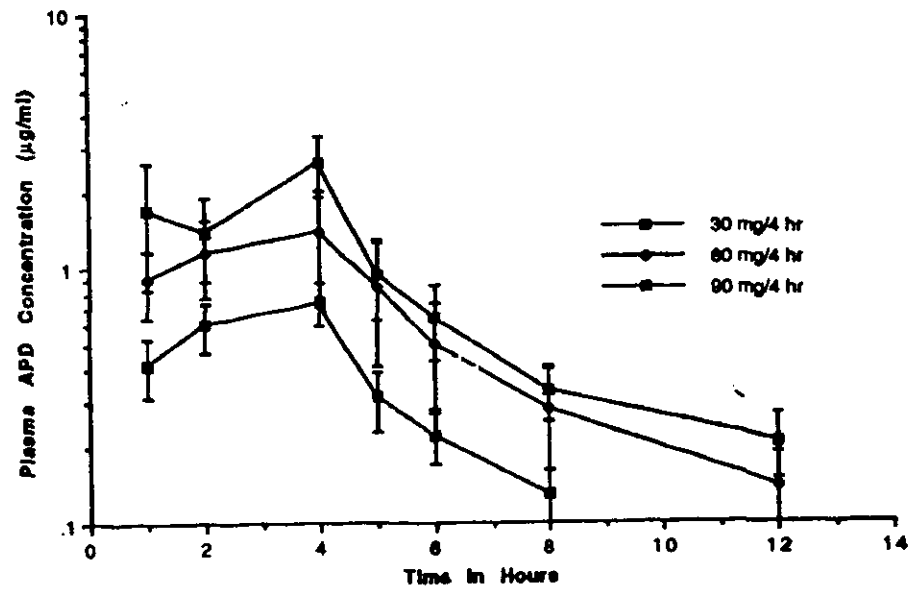
Urine Data: Figure 3 (made by reviewer) presents mean cumulative amounts of pamindronate in urine after 4 and 24 hr infusion. Mean ± SD urine pharmacokinetic parameters are listed in Table 4. Individual urine concentrations of pamindronate disodium are listed in Tables 8 to 13 of Attachment III. Also listed in these tables are the amounts of drug excreted during each collection period, the cumulative amounts of drug excreted [Ae_{0-T}], and the amounts of drug remaining to be excreted in urine (ARE). Both Ae_{0-T} and ARE are summarized in Tables 5 and 6 (Attachment III) for the 4 and 24 hr infusions, respectively. The relationships between dose and Ae_{0-T}, expressed in mg or as a percentage of the administered dose, are illustrated in Figures 3 and 4 of Attachment III, respectively.

FIGURE 2

PLASMA PAMINDRONATE DISODIUM CONCENTRATION
AFTER 4 OR 24 HOURS INTRAVENOUS INFUSION



PLASMA PAMINDRONATE DISODIUM CONCENTRATION AFTER 4 HOURS INTRAVENOUS INFUSION



PLASMA PAMINDRONATE DISODIUM CONCENTRATION AFTER 24 HOURS INTRAVENOUS INFUSION

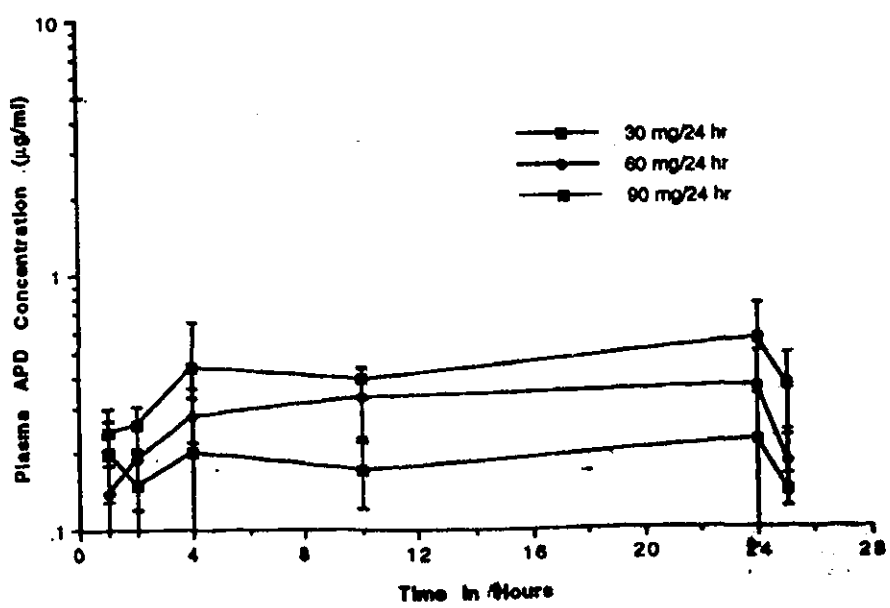
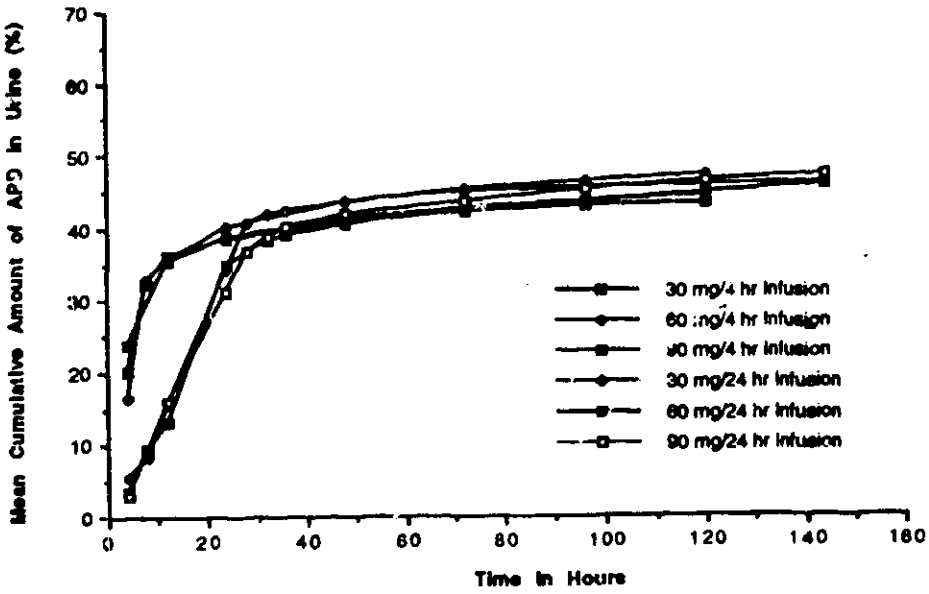
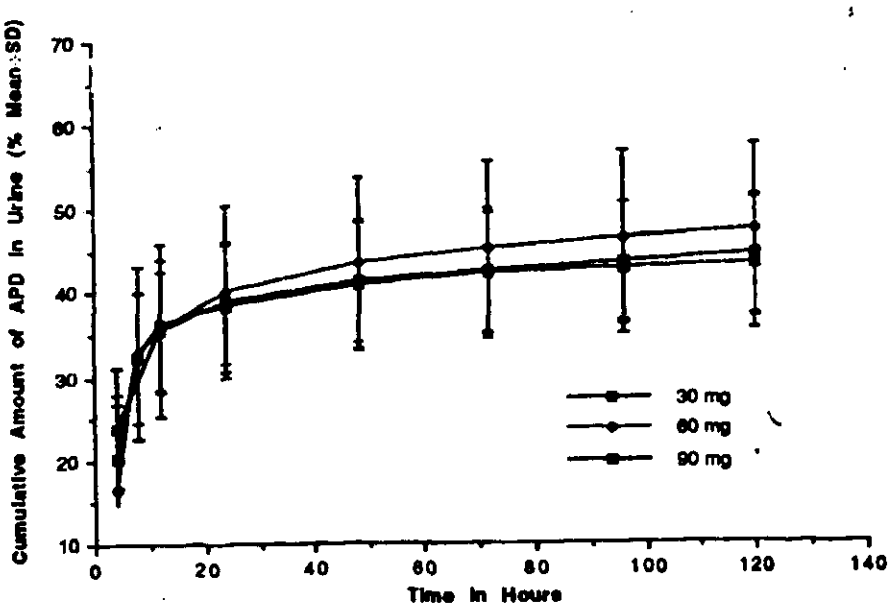


FIGURE 3

URINE DATA FOR PATIENTS WHO RECEIVED A SINGLE DOSE OF PAMINDRONATE DISODIUM AS 4 OR 24 HOURS INTRAVENOUS INFUSION



URINE DATA FOR PATIENTS WHO RECEIVED A SINGLE DOSE OF PAMINDRONATE DISODIUM AS A 4 HOURS INTRAVENOUS INFUSION



URINE DATA FOR PATIENTS WHO RECEIVED A SINGLE DOSE OF PAMINDRONATE AS A 24 HOURS INTRAVENOUS INFUSION

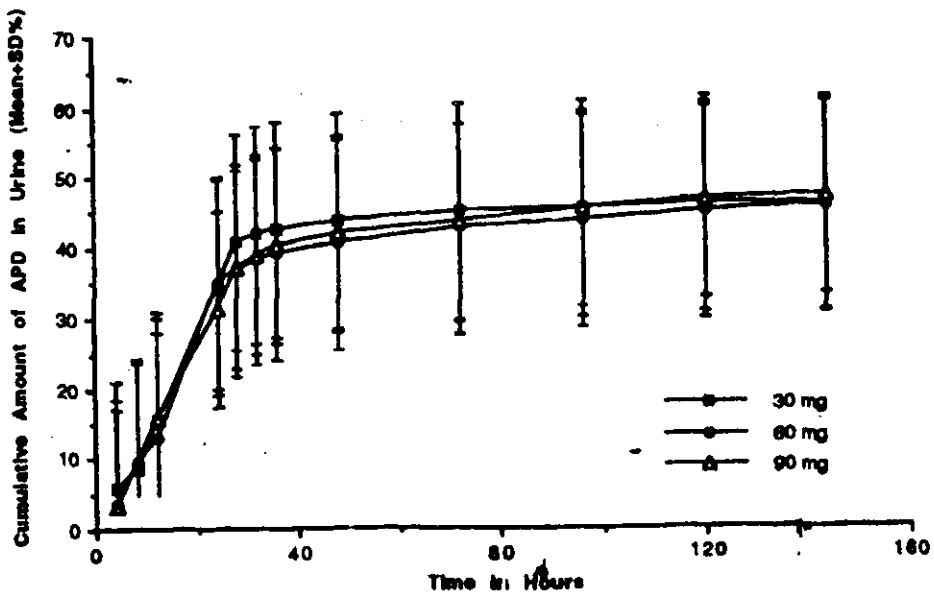


TABLE 4

A: 4-hr Infusion

Dose	Cmax (μg/ml)	Tmax (hr)	AUC (μg.hr/ml)	Ae(0-T) (mg)	Ae(0-T) (% Dose)	CL_r (ml/min)	CL_T (ml/min)
30-mg	0.73 ±0.14	4.0 (4.0-4.1)	4.35 ±2.53	13.2 ±4.2	43.9 ±14.0	58.1 ±27.0	136 ±44
60-mg	1.44 ±0.57	4.0 (2.0-4.3)	21.14 ±21.21	28.5 ±15.5	47.4 ±25.8	42.1 ±27.6	88 ±56
90-mg	2.61 ±0.74	4.0 (1.0-4.5)	17.12 ±8.29	40.8 ±12.5	45.3 ±13.9	43.7 ±15.8	103 ±37

B: 24-hr infusion

30-mg	0.31 ±0.13	24.0 (1.1-36.1)	6.88 ±4.62	14.2 ±3.9	47.2 ±13.0	45.3 ±20.6	104 ±66
60-mg	0.37 ±0.11	10 (4.0-24.1)	8.48 ±2.87	27.4 ±6.5	45.6 ±10.9	60.0 ±27.1	130 ±48
90-mg	1.38 ±1.97	17.2 (2.1-28)	19.85 ±11.44	42.8 ±9.1	47.5 ±10.2	51.9 ±42.1	101 ±58

Nonlinear Curve Fitting of Urine Data: Curve fitting of data (except patient 036) indicate that the disposition of the drug is biexponential. The estimated values of the macro-constants are listed in Table 17 of Attachment III. The overall mean ± SD half-life values for the α and β phases were 2.1 ± 1.8 and 27.7 ± 7.4 hr, respectively. There were no apparent differences in mean values of these macro-constants between the four treatment groups.

Assessment of Dose-Proportionality: Large inter-subject variations in both Cmax and AUC values were observed at all dose levels. An assessment of dose-proportionality based on plasma level data was difficult to establish, however, this assessment could be made based on urine data. There was a linear relationship between cumulative amount of drug excreted in urine and the administered dose (see Figures 3 and 4 in Attachment III). Total and renal clearances were independent of dose after 4 or 24 hr (see Figures 5 and 6 in Attachment III). Urine data indicate that pamindronate disodium exhibits dose-proportionality over the 30 to 90 mg range when administered as either 4 or 24 hr intravenous administration.

Comparison of 4 and 24 hr Infusions: At each dose level, Cmax values were higher for the 4 hr compared with the 24 hr infusion. There were no apparent differences in AUC and total clearance values between the 4 and 24 hr infusion for 30 or 90 mg doses. However, differences were observed for both parameters for the 60 mg dose. There are no apparent differences in renal clearance values between the 4 and 24 hr infusions at any dose level. Overall, the data indicates that infusion rate does not affect the disposition of pamindronate disodium in patients.

COMMENTS:

1. The plasma data for the 30, 60, or 90 mg dose of pamindronate (Figure 1 of review and Table 3 of Attachment III) are showing that steady state is not reached when the 4 hr intravenous infusion is given.

2. The percent of pamindronate excreted in urine (within 120-144 hr period) after 4 and 24 hr intravenous infusions of 30, 60, or 90 mg doses is about the same ( ). This means that after either 4 or 24 hr infusion approximately of the administered pamindronate dose is excreted unchanged in urine and approximately of the dose is distributed into deep compartments (animal studies show that "almost all" of this is in the bone).

3. Establishment of dose proportionality for the 30, 60, and 90 mg doses of pamindronate using plasma PK parameters (AUC and Cmax) for both infusion rates, is not conclusive*. However, when urine data are used (PK parameters; Beta, K21, and Ke, and cumulative amount of drug excreted in urine) there is a clear indication of dose proportionality (linear relationship) for the 3 doses of pamindronate at either 4 or 24 hr infusion.

*NOTE: It might be possible that plasma data is not showing conclusive dose proportionality results due to i) a parallel design was used, ii) there is high subject and drug variability , and iii) analytical method is not very sensitive to detect low concentrations.

4. It may be possible that the medical reviewer might have some concerns regarding safety and/or efficacy of pamindronate for the rapid 4 hr intravenous infusion due to i) the mean Cmax levels for the 30, 60, and 90 mg doses after the 4 hr intravenous infusion are approximately 3, 4, and 5 times higher than the mean Cmax values reached after the 24 hr infusion for the same doses*, and ii) for the 4 hr infusion the plasma pamindronate concentrations are below the assay quantitation limit in approximately 8-12 hr as compared to 24-28 hr for the 24 hr infusion.

*NOTE: Cmax ± SD levels for 30, 60, and 90 mg doses are 0.73 ± 0.14, 1.37 ± 0.61, and 2.57 ± 0.69 and 0.22 ± 0.13, 0.36 ± 0.14, and 0.55 ± 0.21 after 4 and 24 hr intravenous infusion, respectively. For the estimation of the 90 mg mean data, subject 007 was excluded.

CONCLUSION:

The information presented in Clinical Protocol 09 is adequate and supports i) the reduction in the infusion time from 24 hr to 4 hours, and ii) the new pharmacokinetic information that is to be included in the Clinical Pharmacological section of the labelling. Therefore, Clinical Protocol 09 is acceptable, provided the medical reviewer of HFD-510 has no safety/efficacy concerns regarding the shorter infusion time.

2. Report B54/1989

TITLE: "Pharmacokinetics of Pamindronate Disodium in Patients with Bone Metastases. Single Intravenous Infusions of 60 mg at 2.5 or 15 mg/hour".

OBJECTIVE: To measure the urinary excretion of pamindronate disodium given at two different rates, 2.5 mg/hr for 24 hr and 15 mg/hr for 4 hr, and to explore the influence of the infusion rate on the whole body retention of pamindronate, in patients with cancer and extensive bone metastases.

ANALYTICAL METHOD: HPLC, J. Chromatogr., 489, 446-451, 1989.

SUMMARY: Twenty-three patients (21 F and 2 M) with bone metastases, who ranged in age from 28 to 80 yr and ranged in weight from 52 to 85 kg, received a single 60 mg dose of pamindronate disodium by intravenous infusion in a two-center, open label study. Twelve patients were treated with 60 mg of pamindronate disodium infused over 4 hr, corresponding to an infusion rate of 15 mg/hr. Eleven additional patients received 60 mg of pamindronate disodium infused over 24 hr, corresponding to an infusion rate of 2.5 mg/hr. Urine samples were collected over discrete intervals up to 48 hr after the start of the infusion. All data for both treatments were reported separately by study center (St. Gallen and Lausanne). The total urinary excretion (TUE) of pamindronate (APD) after the different infusions in all patients is given in Table 5.

There were no apparent differences in data from the two centers. The clinically relevant body retention of pamindronate, assessed through the total renal excretion and the administered dose, ranged from 35.3% to 90.6% in the 23 patients. Correlation between creatinine clearance and total urinary excretion of pamindronate was low.

TABLE 5

Patient Number	TUE of APD % of dose	Patient Number	TUE of APD % of dose
St. Gallen (60 mg/4 hours)		Lausanne (60 mg/4 hours)	
103	9.4	1	35.8
105	34.8	3	52.3
108	38.8	8	47.0
109	43.6	9	12.1
111	28.6	10	29.9
114	33.0	12	53.9
Mean (SD)	31.4 (11.9)		38.5 (16.0)
St.Gallen (60 mg/24 hours)		Lausanne (60 mg/24 hours)	
102	30.4	2	49.1
104	28.8	4	56.9
107	30.6	5	34.3
110	55.9	6	64.8
112	41.0	7	46.6
		11	12.6
Mean (SD)	37.3 (11.5)		44.0 (18.5)

3. Trial Plan DP/BC6 (Report UK R1/1991)

TITLE: "To Investigate the Pharmacokinetics of a Nominal Dose of 60 mg APD Given Intravenously Over One or Four Hours".

OBJECTIVE: To obtain data on the pharmacokinetics of APD in plasma and urine after two different rates of infusion.

ANALYTICAL METHOD: HPLC with post-column reaction to produce a phosphomolybdate complex. J. Chromatogr. 490, 329-338, 1989.

SUMMARY: Twelve female cancer patients with bone metastases, who ranged in age from 45 to 73 yr and ranged in weight from 53 to 85 kg, were randomized into two treatment groups receiving a single 60 mg dose either 1 or 4 hr. Urine samples were collected up to 48 hr after the start of the infusion. Plasma samples were obtained before dosing and at selected times during the infusion.

Plasma concentrations of pamindronate rose rapidly during both infusions, although an apparent steady state was not achieved for all patients. Urinary excretion data also indicate that plasma concentrations fall rapidly when the infusion is stopped. Furthermore, it was evident from the urinary data that there are kinetic compartment(s) which cannot be characterized in plasma due to the relatively short duration of the infusions. Despite careful control of the infusion procedure, estimates of dose from analysis of the infusion solution and remaining infusate did not agree with the expected dose. For two patients the estimated dose was 40% less than the expected dose. These patients were excluded from subsequent analysis and, therefore, there were insufficient data to show a clear relationship between the urinary recovery of pamindronate and either the number of bone metastases or the infusion rate.

4. Calcified Tissue International, 1991

TITLE: "The Clearance and Bioavailability of Pamindronate in Patients with Breast Cancer and Bone Metastases", P.T. Daley-Yates, D.J. Dowell, M. Porgchaidecha, R.E. Coleman, and A. Howell, Calcif Tissue Int 49:443-435, 1991.

OBJECTIVE: To assess the pharmacokinetics of pamindronate following a single intravenous dose and to investigate the bioavailability of pamindronate after oral administration using an open parallel design..

ANALYTICAL METHOD: HPLC, J. Chromatogr. 490, 329-338, 1989.

SUMMARY: The pharmacokinetics and bioavailability of pamindronate were assessed in patients with breast cancer who ranged in age from 41 to 64 yr and ranged in weight from 53 to 72 kg. Six patients received a nominal 60 mg dose of pamindronate disodium as a 4 hr infusion. Seven patients received 300 mg per day orally, one tablet in the morning and one in the evening, at least 0.5 hr before food. Prior to the study, each patient had been on this regimen for the previous 3-9 months and thereby were considered to have attained steady state. Urine was collected at intervals up to 48 hr after the start of the infusion and blood samples were obtained pre-dose and throughout the course of the infusion. For patients receiving the oral dose, 24 hr urine samples and a blood sample for measurement of creatinine clearance were collected.

TABLE 6

Intravenous pamidronate dose group

Patient No	Age y	Weight kg	Creatinine clearance ml/min	Pamidronate clearance ml/min		Amount excreted 24 h (48 h) A_e mg
				Renal	Total	
1						
2						
3						
4						
5						
6						
X ± SD						

Clearance renal = $A_{e(0-4\ h)}$/plasma $AUC_{(0-4\ h)}$.
Clearance total = rate of infusion/plasma concentration at plateau.

TABLE 7

Oral pamidronate dose group

Patient No	Age y	Weight kg	Creatinine clearance ml/min	Amount excreted in 24 h mg (n = 3) (A_e) mean ± SD
1				
2				
3				
4				
5				
6				
7				
X ± SD				

Table 6 shows the pharmacokinetic parameters for the intravenous dose group and Table 7 the urine excretion data for the oral dose group. The initial plasma half-life of pamindronate was short (mean SD: 0.7 ± 0.45 hr). Steady-state plasma levels were projected using the Siphar pharmacokinetic package, which were in turn used to estimate clearance. The estimated mean ± SD total plasma clearance was 471 ± 298 ml/min. Mean ± SD renal clearance (74 ± 34 ml/min) was similar to creatinine clearance (66 ± 19 ml/min). Most of the renal elimination occurred during and immediately following the 4 hr infusion (23.2 ± 7.9% in 24 hr). The non-renal clearance was ascribed to uptake by bone and deep tissue compartments. The mean bioavailability was estimated using a parallel study design to be 0.3% for a 300 mg oral dose.

IV. OVERALL CONCLUSIONS FOR THE 8 STUDIES CONDUCTED WITH AREDIA™:

The following conclusions are drawn from the results of the human pharmacokinetic studies of the intravenous administration of Aredia:

1. The proportion of 30 to 90 mg doses of Aredia initially eliminated in urine was approximately 50%, regardless of whether a 4 or 24 hr infusion period was used.

2. Urinary excretion of pamindronate follows a biexponential process with more rapid elimination occurring during, and immediately following the infusion.

3. No apparent differences were evident in either total or renal clearance values determined from 4 or 24 hr infusions of 30 to 90 mg.

4. The half-lives (α and β) of pamindronate estimated from urinary excretion data were not influenced by changing the infusion rate between 2.5 and 15 mg/hr within the 30 to 90 mg dose range.

5. Peak plasma concentrations of pamindronate were higher and occurred earlier from 4 hr compared to 24 hr infusions, as expected from the higher input rate.

6. Dose proportionality for the 30, 60, and 90 mg doses was established based in urine data.

V. LABELLING

The labelling changes for the Clinical Pharmacology section of the package insert for Aredia™ are as follows:

> "Cancer patients who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of Aredia over 4 or 24 hours. Peak plasma concentrations, AUC values, and cumulative urinary excretion were linearly related to dose. Plasma pamindronate after 30, 60, and 90 mg doses reached mean peak concentrations of 0.7, 1.4, and 2.6 µg/ml, respectively, after the 4 hour infusions, and 0.3, 0.4, and 1.4 µg/ml, respectively, after the 24 hour infusions. Corresponding mean AUC values were 4.4, 21.2, and 17.1 µg hr/ml for the 4 hour infusions and [illegible], 8.5, and 19.9 µg hr/ml for the 24 hour infusions. After all doses, an overall mean of 46% (range 21%-96%) of the drug was excreted unchanged in the urine within 120 hours. Body retention during this

period was calculated to be 54% (range 54-79%) of the dose; this corresponded to 16 mg (range 11-24 mg), 32 mg (range 3-44 mg), and 48 mg (range 32-61 mg) for the 30, 60, and 90 mg doses, respectively. The urinary excretion rate profile exhibited biphasic disposition characteristics with an alpha half-life of 2.1 hours and a beta half-life of 28 hours. Total and renal clearances of pamindronate were 110 ml/min (range 16-216 ml/min) and 50 ml/min (range 5-131 ml/min), respectively".

LABELLING COMMENTS:

NOTE: The pharmacokinetic changes included in the Clinical Pharmacology section of the labelling are based exclusively on the pharmacokinetic results from "Clinical Protocol 09".

1. It should be included in the labelling the number of subjects and design (parallel) used in Clinical Protocol 09 (i. e., Cancer patients (36) who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of Aredia using a parallel design over 4 or 24 hours).

2. The plasma data presented in Clinical Protocol 09 do not support a conclusive establishment of linearity for the 30, 60, and 90 mg doses of pamindronate disodium after either 4 or 24 hr infusion. However, urine data support the linear relationship for the 3 doses. Therefore, the labelling statement "Peak plasma concentrations, AUC values, and cumulative urinary excretion were linearly related to dose", should be modified to indicate that based in urine data, linearity was established for the 30, 60, and 90 mg doses of pamindronate disodium after either 4 or 24 hr infusion. (i.e., cumulative urinary excretion was linearly related to dose).

3. The estimated AUC values for the three doses and 2 infusion rates do not follow a linear relationship. This discrepancy in the AUC results, specially for 60 mg dose, could be due to i) a parallel study design was used, ii) there is high subject and drug variability , and iii) the analytical method is not very sensitive to detect low concentrations. Therefore, to avoid misleading information, it is recommended to delete the AUC data from the labelling.

4. It is recommended to include mean ± standard deviation values instead of ranges (minimum-maximum) for all the pharmacokinetic data included in the labelling.

5. It is recommended that the sponsor include in the labelling the effect of renal impairment and hepatic dysfunction on the pharmacokinetics of pamindronate if information is available.

LABELLING CONCLUSION:

The pharmacokinetic information included in the labelling is adequate and supports the reduction in the infusion time from 24 to 4 hours. Therefore, the Clinical Pharmacology part of the package insert is acceptable, provided the changes that are proposed in the above comments are incorporated into the labelling.

Angelica Dorantes 4/9/93

Angelica Dorantes, Ph.D.
Pharmacokinetic Evaluation Branch

RD Initialed by John Hunt JPH 4/16/93
FT Initialed by N. Fleicher, Ph.D. for [illegible] 4/28/93

cc: NDA 20-036, HFD-510, HFD-426 (Dorantes), HFD-426 (Fleischer), Drug, Chron, and HFD-19 (FOI)