

PHARM

REVIEW

MAY 10 1990

NDA 20-036

May 10, 1990

Ciba-Geigy Corp.
Summit, N J.

Submission: Dec. 21, 1989

Pharmacology Review of NDA

Drug: Aredia (pamidronate disodium; APD; CGP 23339A; 3-amino-1-hydroxy-propane-1,1-bis-phosphonate).

Related: IND

Proposed use: APD is a bone resorption inhibitor to be given i.v. and is indicated for the treatment of hypercalcemia associated with malignancy. The recommended dose is 60-90 mg given as a single iv infusion over 24 hrs. Retreatment may be necessary if hypercalcemia recurs but it is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.

Pharmacology

Aredia (pamidronate disodium, APD) is a bisphosphonic acid which stabilizes bone turnover by inhibition of osteoclast-mediated bone resorption. Bisphosphonates bind to the hydroxyapatite crystal resulting in a decreased ability of osteoclasts to attach to bone. Also, perhaps at higher doses, bisphosphonates may decrease osteoclast production, differentiation (maturation), and recruitment to bone surfaces. The effects of APD on bone and calcium homeostasis has been discussed in the original pharm review including effects of APD on inhibiting hypercalcemia of malignancy in several animal models.

Bisphosphonates can decrease the performance of both osteoclasts and osteoblasts and can retard the mineralization (mole of Ca per mole of hydroxyproline) of osteoid. The first two properties act to reduce bone turnover in patients with Paget's disease but the reduced mineralization can result in excess of unmineralized osteoid in the diseased bones and an increased incidence of pathological fractures. For example, 0.4 mg/kg APD given i.m. daily for 60 days to pigs significantly increased trabecular bone volume and markedly decreased bone resorption but also decreased bone formation as assessed by mean wall thickness due to a decrease in number and activity of osteoblasts. In a comparative study with clodronate and etidronate (approved bisphosphonate, NDA 17-813), Lemkes, et.al, 1978, showed that APD was more potent with respect to bone formation and resorption with less disturbances of mineralization than either etidronate or clodronate. In general, APD is more effective in inhibiting bone resorption than in inhibiting bone formation.

ADME

Oral bioavailability is around 2 percent although it can be much lower, depending on delivery system (paste, pellet, or aqueous) and presence of food. Drug has short half-life in blood but seeks and is retained by bone (35% of dose remaining in bone after 114 days with an apparent $t_{1/2}$ of 300 days). Little or no drug metabolism. Little differences in ADME between species. Apparently the assay is not of sufficient sensitivity for estimation of the drug in plasma after oral administration and no C_{max} , plasma $t_{1/2}$, AUC, etc, were reported. In rats, i.v. injection of labeled APD showed that the drug is taken up not only by bone but by liver, spleen, teeth and tracheal cartilage as well. Some radioactivity was detectable in liver after one month and in the spleen after 3 months. In humans, approximately 50% of iv administered dose is excreted in urine within 72 hrs regardless of whether the dose of 60 mg was infused over 4 or 24 hrs. Half-lives calculated following the 4 hr infusion were 1.6 and 27.2 hrs for alpha and beta phases, respectively (this is a $t_{1/2}$ of the 50% APD excreted in urine measured over 72 hrs, the remaining 50% is incorporated into bone with no calculated $t_{1/2}$, to my knowledge.

TOXICOLOGY

Most studies have been reviewed in the original IND review or in subsequent amendment reviews. Below are studies submitted for the first time with the NDA.

3-month IV toxicity study in rats. No. 88-6176. Ciba-Geigy Limited, Pharma Tox, Basel, Switzerland. Aug. 29, 1989.

CGP 23 339 A (Aredia), batch 13/350/1, was given iv once every 2 weeks to Tif:RAIF (SPF) rats at doses of 0, 5, 10, or 20 mg/kg. There were 10 rats/gp in the main study and 5 rats/gp as follow-up. Drug was administered every other week for a total of 7 times over a period of 85 days, at a given concentration of 0.3% and injection volumes of 1.7, 3.3, or 6.7 ml/kg. The follow-up period entailed one month (at least 30 days) without dosing, starting 1 wk after the last injection.

Mortality: None

Clinical signs: Dose related broken incisors at end of study. Biphosphonates can prevent tooth eruption, retard growth or produce signs of runt disease but no previous study has produced tooth breakage. Seems to be rat only phenomenon.

Body wt/food consumption: Body wt gain and food consumption were slightly reduced in the HD perhaps related to tooth breakage.

Blood Chem: Alkaline phos activity was reduced in all treated gps. AST activity was slightly increased in females of all dose gps. with no dose effect. BUN and creatinine were increased in M and F in a dose dependent manner.

Hematology: At week 9, there were increased hemoglobin values and rbc counts and decreased reticulocyte counts in males and decreased thrombocyte counts in both sexes.

Urinalysis: No treatment-related effects.

Organ wts: Spleen wts were slightly to moderately increased in a dose dependent manner at all doses in males and at MD and HD in females. After 1 mo. follow-up, wts were still slightly elevated in MD and HD males and HD females. Thyroid wt elevated in MD and HD males and in females at all doses.

Histopathology: Kidneys: tubular lesions were present in males and females at all doses with 8/10 males and 1/10 females with minimal to moderate acute tubular lesions and 8/10 males and 7/10 females with slight to moderate chronic tubular lesions in the HD gp. Neither acute nor chronic tubular lesions are listed in the histopath tables; focal fibrosis, epithelial degeneration, basophilic proliferation, casts, dilation, and decreased activity (?) were all increased in a more or less dose-dependent manner. Degeneration of tubular epithelium was followed by regeneration (completely gone at recovery), accompanied by inflammatory infiltrates and in some cases fibrosis. The lesions noted above were localized in cortical and medullary regions and were somewhat but not totally reversed during the follow-up phase.

Bones/bone marrow: Marked increase of metaphyseal bone in all treated animals in sternum, femur, and tibia (only bones examined). Bone trabeculae adjoining epiphyseal cartilage were markedly thickened and increased in number, almost filling the marrow cavity. The remaining hematopoietic tissue showed hypercellularity with decreased adipose cells. There was no reversal of these changes.

Spleen: Extramedullary hematopoiesis was increased slightly to moderately in all dose gps. Mostly reversible.

Thyroid: Dose-dependent reduction in activity with densely stained colloid lined by flattened epithelium at all doses (20/20 rats at HD, 19/20 at MD and 3/10 males at LD). At MD and HD essentially all animals affected with grading slight to moderate. Effects were not reversible.

Pituitary: Dose-dependent vacuolization of anterior pit cells in males (8/10 HD, 5/10 MD, and 3/10 LD). No effect in females. Little reversibility. Cells stained positive for TSH.

Lungs: Slight increase in alveolar foam cells at HD only (both sexes) with little reversibility. Slight focal epithelialization of alveolar walls in 4 HD rats.

Injection sites: There was a dose-related increase in focal perivascular inflammation, edema and granulation tissue of minimal to marked (one animal) severity.

3-month IV toxicity study in dogs: No. 88-6177. Ciba Geigy Pharma tox, Basel, Switzerland. Aug. 31, 1989.

Aredia, batch 13/350/1 was given iv once a week to gps of pedigree Beagle dogs at doses of 0, 1, 3, or 6 mg/kg. There were 3 dogs/sex/gp except for HD 3p which had an additional 3 dogs/sex for follow-up. Follow-up was drug free for 1 month starting 1 wk after the last injection.

Mortality: None

Clinical signs: None

Body wt/food consumption: HD females lost some wt not particularly correlated with decreased food consumption.

Eye exam, cardiography and neurological exam: No drug effects.

Blood chemistry: There was increased AP and AST activity and urea and cholesterol levels in the HD gp of both sexes. These effects were essentially reversible. Blood creatinine was increased, particularly in HD females.

Hematology: No drug related changes

Urinalysis: No drug related changes.

Organ wts: decreased: thymus, HD
lymph nodes, HD females
increased: spleen, MD and HD males and females
kidney, all males, MD and HD females
lung, all males, MD and HD females
pituitary, MD and HD males
adrenal, HD males

Histopathology: Kidneys: Areas with slight to marked subacute and chronic tubular lesions characterized by casts, tubular dilation, inflammation and a diffuse interstitial fibrosis within the damaged areas were seen in MD and HD dogs. Additional areas of moderate subacute tubular lesions with minimal necrosis of the tubular epithelium, were seen in the same 2 females affected by the chronic tubular lesions in the HD gp. Essentially all of the kidney lesions were as bad, if not worse, after the one month recovery period.
Lung: acute lesions including marked edema, slight to moderate hemorrhage.

fibrin deposition, and a subacute to chronic inflammation (marked to massive bronchopneumonia) and proliferation of pneumocytes and foam cells occurred in MD and HD dogs. Mostly reversible except for slight hemorrhage in one male, fibrin deposition in one male, and increased presence of foam cells (2 males and 1 female).

Liver: Accumulation of inflammatory cells throughout the parenchyma, particularly around the central veins, was seen in HD gp.

Bones: Persistence and extension of the primary spongiosa in ribs, sternum, and iliac crest (only bones examined). Irregular and prominent osteoid seams along the primary spongiosa in all treated dogs, slight at low dose, moderate to massive at MD and HD. Bone effects were not reversible.

Thymus: Moderate reduction of thymus tissue in 2 HD females, probably due to thymus involution.

Spleen: Massive congestion in 1 HD male, slight congestion in some dogs of all other (including control) dogs.

Injection sites: Severe tissue lesions in the thigh muscle above the injection site in 2 MD and 1 HD female dogs, two of which had thrombi in the affected veins. In the 3 affected dogs, the vein showed fibrin deposition, inflammatory cell infiltration with granulation tissue, moderate necrosis, and intimal thickening. The perivenous tissue showed massive necrosis and fibrin deposition, hemorrhage, inflammatory cell infiltration and granulation tissue, moderate to marked edema and slight pigment deposition.

6/12 month oral toxicity study in beagle dogs: No. 86-5084,
August 25, 1988.

This study was reviewed in pharm review of 6/6/89. There were 8 dogs/sex/gp in the original study with 2/sex/gp sacrificed at 6 months and 12 months with 4/s/gp left for 1 yr recovery. Doses were 0, 2.5, 12.5, and 25 mg/kg/day in 0.1% aqueous solution given by gavage. As far as I can tell, no data on recovery was submitted. This may reflect the fact that there were few untoward effects of the drug at 6 or 12 months. Thus all the data submitted in the NDA has been reviewed in pharm review of 6/6/89.

80-week carcinogenicity study in the mouse: No. 864004/CGP 23339
Oct 26, 1989.

104-week carcinogenicity study in the rat: Toxicol report ARP/26/82. No
Ciba-Geigy no. Aug, 1989, revised
Oct, 1989.

Both studies were reviewed in the original pharm review of 6/29/87 which included all information except the histology. I have appended the pathologist report for the mice and rats to this review. It was clear from the mortality that the MTD was exceeded for both rats and mice.

Mice

Group and sex percent mortality	1♂	2♂	3♂	4♂	1♀	2♀	3♀	4♀
	22	27	31	71	20	18	20	40

these numbers are slightly different from original data. I am not sure why.

Rats

	35	36	40	87	30	31	47	47
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In rats, from wk 57 on, signs of piloerection, hunched posture and pale eyes were seen in surviving animals of both sexes of the HD gp.

Significant malignancies are discussed below.

First a note about the tumor incidence tables: They include a listing called lung or liver carcinoma, initial. According to the sponsor, the pathologist labeled tumors comprised of mostly benign cells but with a small portion of malignant cells as initial. Regardless, the initial carcinomas should be combined with carcinomas for an accurate picture of tumor incidence.

Male mice: There was an increased incidence of benign hepatomas by trend test and by pairwise comparison if differences in mortality are considered. The combination of benign and malignant liver tumors is significantly increased in LD and MD only (vs control). No other tumors were significantly increased. Female mice: There were 0, 1, 1, and 2 benign hepatomas and 0, 0, 0, and 2 hepatocellular carcinomas. These data seem to indicate a drug effect, particularly if tumors are combined and when the higher mortality in the HD gp is considered. P value of combined tumors for trend = 0.0017.

Lung carcinomas were significantly (by trend test) elevated in females. I assume there was no significance in the pairwise comparison.

Male rats: There was increased incidence of nonmalignant adrenal pheochromocytomas in the HD gp. The incidence was 7, 3, 7, 9; C to HD. Remember, controls had 105 animals vs 55 for treated and there was significant increased mortality in the HD gp.

There were two HD rats with myeloproliferative disorder of the spleen which was statistically significant by trend (none in any other gp, but one in a control female).

Female rats: As in males, there was an increase in nonmalignant adrenal pheochromocytomas in the HD gp. Incidence of 3, 3, 0, 5; C to HD.

There were leiomyomas of the small intestine in 2 HD females with none in any other gp of either sex.

2 HD females had mammary carcinomas, none in any other gps of either sex.

In general, the biological significance of any of these tumors is doubtful. The trend test is, in my opinion, too lenient and results in false positives. The pairwise test, which I assume is the Fishers exact test, is more conservative and demonstrated some significant increases in tumor incidence. In male mice, benign liver tumors increased in all treated gps ($p < 0.05$) and the incidence of combined benign and malignant tumors was increased in the LD and MD ($p < 0.01$) but not in the HD. In female mice, liver tumors (benign and malignant) were significantly increased in the HD gp, p value unknown but probably < 0.01 .

In rats, significant increases by pairwise comparisons were pheochromocytomas in HD males ($p=0.0028$) and females ($p=0.05$).

Aredia seems to increase the incidence of liver tumors in mice and benign adrenal pheochromocytomas in rats. By pairwise comparisons, no tumors were significantly increased in both rats and mice. Historical controls for rat pheochromocytomas would be useful.

In the rat carcinogenicity study with Aredia, there were two high dose males with myeloproliferative disorder of the spleen. One case also occurred in a control female. All three cases were characterized by a spectrum of proliferating myeloid and erythroid cells which obliterated the normal splenic architecture. There were also proliferating cells in the liver and mesenteric lymph nodes but apparently not in the bone marrow.

Comments

Aredia is one of several bisphosphonates being developed for treatment of hypercalcemia of malignancy, pagets disease and osteoporosis. Efficacy has been shown in animal models and the mechanism of action seems to be inhibition of osteoclast activity although other mechanisms are possible.

Toxicity studies of i.v. administered Aredia include acute studies in the mouse, rat, and rabbit and subchronic (2 wks to 3 months) in rats and dogs.

The i.v. LD50 in male and female mice, rats, and rabbits was 20.3 mg/kg, 80 mg/kg, and 18.5 mg/kg, respectively (little or no sex difference).

In two studies, Aredia was given i.v. daily for 28 days to rats at doses of 0, 0.3, 1, and 3 mg/kg and to dogs at doses of 0, 0.2, 0.6, and 2 mg/kg. Common findings were inflammation (and worse) at the injection site, some effects on liver function (enzyme elevations in dogs, serum protein changes in rats), and changes in bone. Minimal to moderate nephropathy in dogs was not seen in rats.

Another 28 day study in dogs with i.v. doses of 0, 2.5 and 12.5 mg/kg/day resulted in death of 5/6 HD dogs and 1 LD dog. Before death there was convulsions, ataxia, labored breathing, hypoactivity and loss of weight. Organs systems affected included the lungs, liver, heart, kidneys, spleen, stomach, and injection sites.

From the 28 day studies mentioned above and the 3 month studies reviewed in the NDA, it seems clear that i.v. administered Aredia can produce severe insult to the lungs, kidneys, possibly thyroid and liver, and the site of injection. The effects on the bone and spleen are the result of the expected action of the drug. Even when the injections are 2 weeks apart, 3 mg/kg is a toxic dose and 1 mg/kg is the NOEL in dogs which is about the proposed human dose.

In dogs, s.c. administration of etidronate (NDA 17-831) at doses of 0.1, 0.2, 2, or 10 mg/kg/day for 1 or 2 yrs increased bone fracture rate, lesions and nerosis (due to decreased mineralization). Other findings included thyroid/parathyroid hyperplasia, fatty degeneration of the liver with bile pigment retention, glomerular sclerosis of the kidney with chronic interstitial nephritis and membranous glomerulonephritis, and megakaryocytic hematopoiesis and RE cell hyperplasia of the spleen. The s.c. administration of clodronate to dogs at doses of 2.5, 10, or 25 mg/kg/day for 1 yr produced decreased bone mineralization, slight anemia, increased liver enzymes, impaired renal function, and irritation at the injection sites.

Conclusion: The effects of APD on bone, adrenal, liver, and kidney have been seen with other bisphosphonates, particularly etidronate. The unique toxicities of APD seem to be on the lung in rats and dogs and the thyroid and pituitary in rats. The effects on thyroid and pituitary in rats occurred at 20 and 10 mg/kg with some effect on the pituitary at 5 mg/kg (no no-effect dose). In dogs, the effect on the lung occurred at 6 and 3 mg/kg with no effect at 1 mg/kg (human dose approximately 1 mg/kg). Although the mechanism(s) of the toxicities are unknown, they should not prevent drug approval.

Labeling revisions:

Pregnancy category C. AREDIA has been shown to increase the length of gestation and parturition in rats resulting in an increase in pup mortality when given orally at daily doses of 60 and 150 mg/kg/day from before pregnancy until after parturition. When corrected for oral bioavailability, each daily dose is approximately 0.7 to 1.7 times the highest recommended human dose for a single i.v. infusion. Oral doses of 25 to 150 mg/kg/day during the period of gestation failed to demonstrate any teratogenic, fetotoxic, or embryotoxic effects in rats or rabbits. Animal reproduction studies have not been conducted with intravenously administered AREDIA. It is not known if intravenous AREDIA can cause fetal harm when administered to pregnant women or can affect reproduction capacity. There are no adequate and well-controlled studies in pregnant women. AREDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *not per*

Carcinogenesis, etc. Labeling unsatisfactory but I want to wait for statistics review before making changes.

Pharmacology recommends approval of Aredia for the treatment of hypercalcemia of malignancy.



Alex Jordan, PhD

NDA 20-036
HFD-510
AJordan

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APR 17 1991

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NDA 20-036

April 12, 1991

Sponsor: Ciba-Geigy Corporation, Summit, NJ

Date Submitted: November 21, 1990

REVIEW OF SAFETY UPDATE

Drug: Aredia; APD; CGP 23339A; 3-amino-1-hydroxy-propane-1,1-bisphosphonate

Category: Bisphosphonates; Hypocalcemic Agent

Proposed Clinical Indication: Hypercalcemia of Malignancy

Proposed Labeling Change

The following information should be incorporated into the "Warning" section of the package insert:

Studies conducted in young rats have reported the disruption of dental enamel formation with single dose administration of bisphosphonates. The clinical significance of these findings is currently unknown.

Chhanda Dutta
Chhanda Dutta, Ph.D.

A Jordan
4/17

CC: NDA;HFD-510
HFD-510/A Jordan/C Dutta

DEC 20 1990

DIV

NDA 20-036

December 6, 1990

Sponsor: Ciba-Geigy Corporation, Summit, NJ

Submission Date: November 13, 1990

Date Received: November 14, 1990

LABELING REVISIONS

Drug: Aredia; APD; CGP 23339A; 3-amino-1-hydroxy-propane-1,1-bisphosphonate

Category: Bisphosphonates, Hypocalcemic agent

Proposed clinical indication: Hypercalcemia of malignancy

Proposed Labeling Changes

The "Warning" section should read as follows:

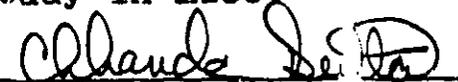
In both rats and dogs, nephropathy has been associated with intravenous, bolus administration of Aredia. A 3-month study in rats found cortical tubular changes including epithelial degeneration with i.v doses of 5 mg/kg, given once every two weeks. Following a recovery period (1 month), the degenerative changes were completely reversed. Other tubular lesions were partially reversed.

In two studies conducted in dogs, Aredia was given as a bolus intravenous injection either daily for 1 month or once a week for 3 months. In the 1-month study, tubulointerstitial nephritis, tubular degeneration and dilation occurred at 2 mg/kg. At recovery (1 month) the severity of these lesions was minimal or trace. Similar lesions (slight to marked severity) were noted in the 3-month study at 3 mg/kg and higher. However, no improvement of the lesions was observed following the 1 month recovery period.

Patients with hypercalcemia receiving Aredia IV infusion should have periodic evaluations of standard laboratory and clinical parameters of renal function.

Under "Carcinogenesis, Mutagenesis, Impairment of Fertility" the first paragraph should read:

In a 104-week carcinogenicity study (oral administration) in rats, there was a positive dose response relationship for benign adrenal pheochromocytoma in males ($p < 0.00001$). Although this condition was also observed in females, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited oral bioavailability of Aredia in rats, the lowest dose associated with adrenal pheochromocytoma was similar to the intended clinical dose. Aredia (oral administration) was not carcinogenic in an 80-week study in mice.


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CC: NDA, HFD-510
HFD-510/A Jordan/N Clagett/C Dutta


12/20/90