Oncologic Drugs Advisory Committee
DRAFT MINUTES
January 31, 2002

The 70th meeting of the Oncologic Drugs Advisory Committee was held at Advisors and Consultants Staff Conference Room at 5630 Fishers Lane, Rockville, Maryland. Approximately 150 people were in attendance. The meeting was chaired by Stacy Nerenstone, M.D.

Open Public Hearing Ann E. Fonfa – The Annie Appleseed Project (letter)

sNDA 21-386 Zometa ® (zoledronic acid for injection) Novartis Pharmaceuticals Corporation

Indication: for the treatment of bone metastases in patients with multiple myeloma, breast cancer, prostate cancer and other solid tumors

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Sponsor Presentation	**Novartis Pharmaceuticals Corporation**
Introduction	Burkhard Daldrup, Ph.D.
Pathophysiology of Metastatic Bone Disease and the Role of Bisphosphonates	Robert Coleman, M.D., FRCP
ZOMETA® in Breast Cancer and Multiple Myeloma	James Berenson, M.D.
FDA Presentation	
ZOMETA® in Breast Cancer and Multiple Myeloma (Study 010)	Grant Williams, M.D. Medical Team Leader Division of Oncology Drug Products
Sponsor Presentation	**Novartis Pharmaceuticals Corporation**
ZOMETA® in Prostate Cancer and Solid Tumors Other Than Prostate Cancer and Breast Cancer	Matthew Smith, M.D. Robert Coleman, M.D., FRCP
Conclusions	David Parkinson, M.D.
FDA Presentation	
ZOMETA® in Prostate Cancer and Solid Tumors Other Than Prostate Cancer and Breast Cancer (Studies 039 and 011)	Amna Ibrahim, M.D. Medical Officer Division of Oncology Drug Products
Safety Review (Studies 010, 011 and 039)	Nancy Scher, M.D. Medical Officer Division of Oncology Drug Products
Introduction to the Issues	Grant Williams, M.D.

Questions to the Committee:

Introduction

Studies 010, 039, and 011 evaluated Zometa treatment of patients with bone metastases from breast cancer and myeloma, prostate cancer, and other solid tumors, respectively. Study 010 compared Zometa and Aredia using non-inferiority analyses. Studies 039 and 011 compared Zometa to placebo using superiority analyses. A decrease in skeletal related events (SRE) was the treatment goal. The following tables display results of two closely related analyses:

- the proportion of entered patients having an SRE on study, and
- the time to first SRE

The protocol-specified primary analysis was the proportions analysis. The analysis recommended by FDA statisticians was the time to first SRE analysis. Results from both analyses are presented below.

Active Control Study 010 (Myeloma and Breast Cancer)

Study	Study Arm	Analysis of proportion of patients with an SRE			Analysis of time to first SRE		
		Proportion	Difference & 95% ci	P value	Time to First SRE (HR)	95% ci	P value
Myeloma & Breast CA (010)	Zol 4mg	44%	-2 (-7.9, 3.7)	0.461	0.92	(0.77,1.09)	0.31
	Zol 8mg	46%	0 (-6.1, 5.8)	0.963	0.99	(0.83,1.18)	0.91
	Aredia	46%	---	---	---	---	---

Placebo Controlled Studies 039 (Prostate Cancer) and 011 (Other Solid Tumors)

Study	Study Arm	Analysis of proportion of patients with an SRE			Analysis of time to first SRE		
		Proportion	Difference & 95% ci	P value	Time to First SRE (HR)	95% ci	P value
Prostate Cancer (039)	Zol 4mg	33%	-11 (-20, -2)	0.021	0.66	(0.48, 0.90)	0.009
	Zol 8mg	38%	-6 (-15, 4)	0.222	0.91	(0.68, 1.23)	0.541
	Placebo	44%	---	---	---	---	---
Solid Tumors (011)	Zol 4mg	38%	-6 (-15, 2)	0.127	0.73	(0.56, 0.97)	0.024
	Zol 8mg	35%	-9 (-18, -1)	0.023	0.74	(0.56, 0.98)	0.036
	Placebo	44%	---	---	---	---	---

For new drug approval, "substantial evidence" of efficacy from adequate and well-controlled investigations is required. Evidence from multiple clinical trials is usually submitted, but robust results from a single multi-center trial have been accepted. In your deliberations of the following questions, consider whether the results from trials fulfill the regulatory requirement.

1. Study 010 in breast cancer and myeloma

Corrected to: In Study 010, 46% of Aredia patients had an SRE on study versus 44% of Zometa patients. Using the conservative *two-95% confidence interval method* (worst-case scenario), FDA calculates that Zometa retains at least 49% of Aredia' s efficacy (demonstrated historically in comparison to placebo).

a. Do other studies (011 and 039) provide supportive evidence for Zometa's efficacy in breast cancer and myeloma?

YES - 10 N – 0 A - 1

b. Is there substantial evidence from adequate and well-controlled investigations of Zometa (4 mg) efficacy in breast cancer and myeloma?

YES - 11 N – 0 A - 0

2. Study 039 in prostate cancer

a. Zometa studies 010 and 011 have evaluated Zometa efficacy in predominantly lytic metastases. Can results from these studies provide supportive evidence for Zometa's efficacy in prostate cancer, which produces predominantly blastic bone metastases?

YES - 11 N – 0 A – 0

b. Is there substantial evidence of Zometa (4 mg) efficacy in prostate cancer from adequate and well-controlled investigations?

YES - 10 N – 1 A - 0

3. Study 011 in other solid tumors

a. Analyses from both the 4 mg and 8 mg Zometa arms of study 011 support the efficacy of Zometa. Do you agree with FDA that these results provide substantial evidence of Zometa (4 mg) efficacy in the population studied?

YES - 10 N – 0 A - 1

b. The sponsor's proposed indication includes:

"treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors."

This indication infers treatment is indicated for patients with bone metastases from all solid tumors irrespective of the primary tumor. Do you agree with this proposed indication? Please provide suggestions for wording of the indication section or the clinical trials section of the Zometa labeling with regard to this issue.

YES - 11 N – 0 A - 1

The Committee discussed the inconsistencies between the two Zometa arms (4 mg and 8 mg) and recommended that, since there was no biological explanation for the lesser activity of the 8 mg arm, that these inconsistencies were probably due to chance. As such, it would be legitimate to pool the two Zometa arms.

The Committee considered whether the benefit seen in these trials was clinically meaningful, as the pooled data translate into approximately one patient out of 12 receiving benefit from treatment with Zometa. It is worthwhile if one patient out of twelve can avoid pain or fracture. Additionally, the lesser infusion time of Zometa (15 minutes, as compared to 2 hours for Aredia) is a significant improvement.

It was recommended that the sponsor develop studies to determine if there might be prognostic criteria to help predict which patients will benefit from Zometa.

Labeling should include recommendations for monitoring of renal function by measurement of serum creatinine and for concomitant administration of vitamin D and calcium.