Oncologic Drugs Advisory Committee

Questions to the Committee

January 31, 2002

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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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)	0.026
	Zol 8mg	35%	-9 (-18, -1)	0.023	0.74	(0.56, 0.98)	0.035
	Placebo	44%	---	---	---	---	---

Questions to the Committee:

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

In Study 010, 44% of Aredia patients had an SRE on study versus 46% of Zometa patients. Using the conservative *two-95% confidence interval method*, 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?

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

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?

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

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?

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.