May 9, 2011

Submission Request
National Comprehensive Cancer Network

RE: Updated Clinical Evidence in Support of Zometa® use in the adjuvant breast cancer setting

Name: Neilda Baron, MD
Company/Organization: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936
Phone: 862-778-5494
Email: neilda.baron@novartis.com
Date of request: May 9, 2011
NCCN Panel: Breast Cancer

To Whom It May Concern:

As the NCCN Breast Cancer Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer, v 2.2011 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with Zometa® (zoledronic acid) Injection. This information is highlighted below:

- Data to support a Compendium listing for zoledronic acid use as an adjuvant anti-cancer agent in women with postmenopausal reproductive hormone levels with early breast cancer

Zometa® Anti-Cancer Properties in Postmenopausal Breast Cancer Patients
This request is for the Panel to consider the addition of Zometa® (zoledronic acid) injection for the adjuvant treatment of breast cancer in women with low endogenous levels of reproductive hormones with early breast cancer in the Breast Cancer Guidelines and the associated “NCCN Drugs and Biologics Compendium™”. Numerous pre-clinical and clinical studies have demonstrated anti-cancer properties of zoledronic acid in breast cancer and other tumor types via direct and indirect anti-cancer mechanisms. Grant et al. (2009) conducted a phase III trial examining the effect of adding zoledronic acid to a combination of goserelin and endocrine therapy (either tamoxifen or anastrozole) in premenopausal women with hormone receptor-positive early stage breast cancer. Most of these women were expected to have low endogenous levels of reproductive hormones due to treatment. The addition of zoledronic acid to goserelin and endocrine therapy resulted in a 36% relative reduction in the risk of disease progression (P=.01 log rank), a 35% reduction in the risk of recurrence (P=.01 log rank), and a trend toward reduction for the risk of death (P=.11). Adverse events were consistent with known drug-safety profiles and no cases of osteonecrosis of the jaw or serious renal events were reported. In another phase III trial, Coleman et al. (2010) conducted a phase III study examining the effect of standard adjuvant systemic therapy with or without zoledronic acid in pre- and post-menopausal women with early stage breast cancer. The addition of zoledronic acid in the adjuvant management of breast cancer did not significantly improve disease free survival (DFS) when the entire population of women enrolled (N=3,360) was analyzed. However, in a planned subset analysis of 550 patients in the zoledronic acid arm and 551 patients in the control arm, zoledronic acid was found to significantly improve DFS (HR=0.76, 95% CI 0.60-0.98) and OS (adjusted HR=0.71, 95% CI 0.54-0.94, P=.017) in women who were ≥5 years postmenopausal or age ≥60 (i.e. those with low endogenous levels of reproductive hormones). Serious adverse events were similar in both treatment arms. There were 17 confirmed cases of osteonecrosis of the jaw (P=.001) in the zoledronic acid arm vs. none in the control arm.
The scientific basis for the anti-cancer effects of zoledronic acid in the adjuvant setting has yet to be elucidated. The loss of the tumor growth promoting properties of reproductive hormones combined with the direct and indirect anti-cancer effects seen with zoledronic acid may be responsible for the anti-cancer effects in this clinical setting.6-7

**Specific changes recommended for the Guidelines & Compendium**
Please add the use of zoledronic acid for the adjuvant treatment of women with postmenopausal reproductive hormone levels with early breast cancer.

**FDA Status**
Zometa® (zoledronic acid) for use as adjuvant therapy in breast cancer patients is not FDA approved.

**Rationale for recommended change**
Two Phase III randomized trials with zoledronic acid have shown favorable disease progression and overall survival results in women with postmenopausal reproductive hormone levels with early breast cancer.4-5

* * * * *

**Literature support**


* * * * *

We appreciate the opportunity to provide this additional information for consideration by the NCCN Breast Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at 862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time and consideration.

Sincerely,

[Signature]

Neilda Baron, MD
Senior Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Copies of referenced primary literature