On behalf of Amgen Inc, I respectfully request the NCCN Prostate Cancer Guideline Panel review the enclosed data for updating the NCCN Prostate Cancer Guidelines for the use of denosumab to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.

**Specific Changes:** In the *Principles of Androgen Deprivation Therapy* section under *Monitor/Surveillance* (PROS-E: page 3 of 3), recommend that the dosing regimen of denosumab be corrected to 60 mg SQ every 6 months from 120 mg SQ monthly.

**FDA Clearance:** Prolia® (denosumab) is FDA-approved to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer. In these patients Prolia® (denosumab) also reduced the incidence of vertebral fractures.

**Rationale:** Denosumab is FDA-approved under the brand name, Prolia®, at a dosing regimen of 60 mg every 6 months as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer. In these patients Prolia® (denosumab) also reduced the incidence of vertebral fractures.

In the registrational, phase 3 study conducted in patients with non-metastatic prostate cancer undergoing androgen deprivation therapy (N = 1468), denosumab, at a dose of 60 mg every 6 months, increased bone mineral density (BMD) at the lumbar spine by 6.7% compared to placebo at 24 months (P < 0.001). Patients who received denosumab had significantly higher BMD at all sites (lumbar spine, total hip, 1/3 distal radius, whole body) compared to placebo at all measured time points, from 1 to 36 months (P < 0.001 for all comparisons). The cumulative incidence of new vertebral fractures at 36 months was significantly lower in patients who received denosumab (1.5%; 10/679) compared to those who received placebo (3.9%; 26/673) for a relative risk of 0.38 (95% CI: 0.19 to 0.78; P = 0.006).

Please note, denosumab is also FDA-approved under the brand name, XGEVA®, at a dosing regimen of 120 mg every 4 weeks for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

As Amgen only recommends the use of its products in accordance with the applicable FDA-approved prescribing information, we request that the dosing regimen for denosumab use to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer be corrected to 60 mg SQ every 6 months, as reflected in the Prolia® prescribing information.

Since Prolia® contains the same active ingredient (denosumab) found in XGEVA®, patients receiving Prolia® should not receive Xgeva®.

The following documents are submitted in support of this proposed change. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors on some of these publications.

1. Prolia® (denosumab) prescribing information. Amgen Inc.

Thank you for your attention to these revisions. Please contact me should you have any questions.

Sincerely,

[Signature]

Helen Collins, MD
Medical Director, North America

Enclosures