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Date of request: February 11, 2016
NCCN Guidelines Panel: Multiple Myeloma Panel

On behalf of Amgen Inc., I respectfully request the NCCN Multiple Myeloma panel members to review the enclosed data on the use of Kyprolis® (carfilzomib) in combination with dexamethasone for previously treated multiple myeloma.

Specific Changes: Recommend update of Kyprolis® (carfilzomib) in combination with dexamethasone to category 1 for previously treated multiple myeloma and update of the narrative section of the Guidelines, specifically page MS-32 of version V3.2016 with data from the published phase III ENDEAVOR* clinical trial.

FDA Approval: On January 21, 2016, the US FDA expanded the indication of Kyprolis® (carfilzomib) for Injection to be used:

- in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.[1]

Rationale: ENDEAVOR was a randomized, phase 3, open-label superiority trial evaluating carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² thereafter; 30 minute intravenous infusion) + dexamethasone (20 mg oral or intravenous infusion) versus bortezomib (1.3 mg/m²; intravenous bolus or subcutaneous injection) + dexamethasone (20 mg oral or intravenous infusion) in 929 patients with relapsed or refractory multiple myeloma who had 1–3 previous treatments. Randomization stratification factors included previous proteasome inhibitor therapy and previous lines of treatment. The primary endpoint was progression-free survival (PFS); key secondary endpoints included overall response rate, overall survival, duration of response, and safety.[1,2]

Carfilzomib + dexamethasone (n = 464) achieved superior PFS compared with bortezomib + dexamethasone (n = 465), with a median PFS of 18.7 vs 9.4 months, respectively (hazard ratio [HR] = 0.53; 95% CI 0.44–0.65; *P* < 0.0001). The PFS benefit in the carfilzomib group was consistent regardless of prior proteasome inhibitor exposure. Overall response rate was 77% in the carfilzomib group vs 63% in the bortezomib group; rates of complete response or better were 13% and 6% and very good partial response were 42% and 22%, respectively. Median duration of response was 21.3 months in the carfilzomib group and 10.4 months in the bortezomib group.[1,2]

*A randomized, open-label, phase 3 study of carfilzomib plus dexamethasone vs. bortezomib plus dexamethasone in patients with relapsed multiple myeloma

As reported in the US Prescribing Information, rates of on-study death due to adverse reactions (ARs) and serious ARs were 5% (n = 464) and 48% (n = 463), respectively, in the carfilzomib group and 5% (n = 465) and 36% (n = 456) in the bortezomib group. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% vs 9%). The most frequent grade ≥ 3 ARs were anemia (12% [n = 463] in the carfilzomib group vs 9% [n = 456] in the bortezomib group), hypertension (6% vs 3%), thrombocytopenia (10% vs 14%), and dyspnea (5% vs 2%). Rates of grade ≥ 2 peripheral neuropathy were 6% vs 32% in the carfilzomib and bortezomib groups, respectively; and were observed irrespective of peripheral neuropathy status at baseline.[1]

Supporting Documentation: The following data have been submitted in support of this request:

1. Kyprolis® (carfilzomib) US Prescribing Information, Amgen Inc. (v10 01/2016)

2. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol.* 2016;17:27-38

Sincerely,

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