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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) as a single agent therapy for previously treated multiple myeloma.

Specific Changes: Recommend update of Kyprolis® (carfilzomib) as a single agent to category 1 for previously treated multiple myeloma and inclusion of the following studies as additional supportive evidence: the phase 1b/2 30-minute infusion dose-escalation study and the phase 2 monotherapy study in bortezomib-naïve patients.

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: The following two studies have been incorporated by the US FDA into the US Prescribing Information for Kyprolis® (carfilzomib) for Injection:

In a phase 1b/2 open-label, dose-escalation study (N = 33), carfilzomib was administered as a 30 minute intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle in patients with relapsed and/or refractory multiple myeloma. Doses on days 1 and 2 were 20 mg/m^2, subsequent doses were escalated to 36, 45, 56, or 70 mg/m^2. The maximum tolerated dose (MTD) was achieved at 56 mg/m^2. A total of 24 patients were enrolled at the MTD dose of 56 mg/m^2. The overall response rate (ORR) (partial response [PR] or better) was 50% (95% CI: 29, 71) and median duration of response (DOR) in patients who achieved ≥ PR was 8.0 months (1.4, 32.5).[1,2] As reported in the US Prescribing Information, the most frequent grade ≥ 3 adverse reactions (ARs) were thrombocytopenia (54%), lymphopenia (33%), anemia (29%), and hypertension (13%).[1] Two patients (6.1%) developed grade 1 peripheral neuropathy. Cardiac events were reported in five patients (20.8%).[1,2]

In a phase 2 open-label clinical trial of carfilzomib monotherapy, patients with relapsed or refractory multiple myeloma who were bortezomib-naïve and had received 1 to 3 prior lines of therapy received carfilzomib 20 mg/m^2 on days 1 and 2 of cycle 1 and then escalated to 27 mg/m^2 for all subsequent cycles for up to 12 cycles. Carfilzomib was administered as an IV infusion up to 10 minutes on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. A total of 70 patients were treated.[1,3] As reported in the US Prescribing Information, the ORR for these 70 patients was 50% (95% CI: 38, 62); the median DOR was not reached.[1] The most frequent grade ≥ 3 ARs were lymphopenia (18.6%), anemia (17.1%), neutropenia (14.3%), thrombocytopenia (11.4%) and pneumonia (11.4%).[3] Treatment-emergent peripheral neuropathy (any grade) occurred in 18.6% of patients and did not limit treatment. Serious ARs were reported in 27 patients (38.6%).[1,3]

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. Papadopoulos KP, Siegel DS, Vesole DH, et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. *J Clin Oncol*. 2014;33(7):732-739.

3. Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. *Blood*. 2012;119(24):5661-5670.

Sincerely,

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