Submitted by:
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Date of Request: August 25, 2016

Dear NCCN Multiple Myeloma Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request the NCCN Guidelines Panel for Multiple Myeloma review recently presented data on the continuous use of REVLIMID® (lenalidomide) and low-dose dexamethasone (Rd) in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM).

Specific Changes:
We respectfully request an update to the indication for lenalidomide in the primary therapy discussion section, MS-11, to reflect the full indication of REVLIMID *in patients with multiple myeloma in combination with dexamethasone,* which includes patients with NDMM. Additionally, we request an update to the Discussion surrounding the use of Rd as primary therapy for non-transplant candidates to reflect the most recently presented data from sub-analyses of the Phase III MM-020 study. These data further support the use of Rd Continuous[a] therapy as frontline treatment in patients with renal impairment, advanced age >75 years and in frail patients with all levels of severity.

FDA Clearance: REVLIMID is a thalidomide analogue indicated for the treatment of patients with MM in combination with dexamethasone. Please see the enclosed REVLIMID Prescribing information for additional approved indications (Celgene Corporation, 2015).

Rationale for Proposed Changes:
The survival benefit of Rd Continuous therapy compared to MPT[b] has consistently been demonstrated in various sub-populations. In an analysis of patients by renal function, Rd Continuous significantly reduced the risk of progression or death vs. MPT by 33%, 30% and 35%, in patients with normal, mild and moderate renal impairment (RI), respectively (Dimopoulos et al., 2016). Further, median progression-free survival (PFS) was longer with Rd Continuous vs. MPT for patients in all sub-groups except those with severe RI (CrCl <30 mL/min excluding dialysis). Adverse events were generally similar across renal groups and included anemia, neutropenia, thrombocytopenia, infections and sensory peripheral neuropathy. DVT and PE rates were not affected by renal function. Regardless of patient age (>75 years vs. ≤75 years), clinical outcomes (duration of response [DOR], PFS and overall survival [OS]) were favorable for Rd Continuous vs. MPT (Hulin et al., 2015). With regard to PFS, Rd Continuous was more effective vs. MPT for patients >75 years (median PFS: 20.3 months vs. 19.8 months, HR=.80) and ≤75 years (median PFS: 28.1 months vs. 22.4 months, HR=.64). Rd Continuous prolonged PFS and OS vs. MPT for all frailty groups (fit vs. intermediate vs. frail) (Facon et al., 2016). When assessed by frailty

(fit vs. intermediate vs. frail), overall, better fitness was associated with significantly improved survival (fit vs. frail: PFS, HR=.67; OS, HR=.42).

For further information regarding additional recently presented sub-analyses demonstrating similar outcomes and consistent survival advantage for Rd continuous vs. MPT, please refer to the following enclosures submitted in support of the proposed changes: (Hulin et al., 2015) (Dimopoulos et al., 2016) (Facon et al., 2016) (Dumontet et al., 2016) (Bahlis et al., 2015) (Lu et al., 2016) (Vogl et al., 2016).

Your consideration of this submission is greatly appreciated.

Sincerely,

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[a]Rd Continuous: Lenalidomide 25 mg on Days 1-21/28; Low-dose dexamethasone 40 mg on Days 1, 8, 15 and 22/28 until disease progression or unacceptable toxicity
[b]MPT: Melphalan 0.25 mg/kg on Days 1-4/42; Prednisone 2 mg/kg on Days 1-4/42; Thalidomide 200 mg on Days 1-42/42 for 72 weeks
Source: (Benboubker et al., 2014)

CITED REFERENCES:

1. Bahlis N, Corso A, Mugge L-O., et al. Assessing the Benefit of Continuous Treatment in The First Trial (MM-020): Impact of Response in Patients With Transplant-Ineligible Newly Diagnosed Multiple Myeloma [Poster]. Poster presented at: 20th Congress of the European Hematology Association (EHA); June 11-13, 2015; Vienna, Austria.
2. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med*. 2014;371(10):906-17. http://www.ncbi.nlm.nih.gov/pubmed/25184863.
3. Celgene Corporation. Revlimid (lenalidomide) [Package Insert]. Summit, NJ: Celgene Corporation. http://www.revlimid.com/.
4. Dimopoulos MA, Cheung MC, Roussel M, et al. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. *Haematologica*. 2016;101(3):363-70. http://www.ncbi.nlm.nih.gov/pubmed/26659916.
5. Dumontet C, Hulin C, Dimopoulos T, et al. Development of a Predictive Model to Identify Patients With Multiple Myeloma Not Eligible For Autologous Transplant at Risk for Severe Infections Using Data From the FIRST Trial [Poster]. Poster presented at: 21st Congress of the European Hematology Association (EHA); June 9-12, 2016; Copenhagen, Denmark.

6. Facon T, Hulin C, Dimopoulos MA, et al. A Frailty Scale Predicts Outcomes for Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the First (MM-020) Trial [Poster]. Poster presented at: 21st Congress of the European Hematology Association (EHA); June 9-12, 2016; Copenhagen, Denmark.
7. Hulin C, Shustik C, Belch A, et al. Effect of Age on Efficacy and Safety Outcomes in Patients With Newly Diagnosed Multiple Myeloma Receiving Lenalidomide and Low-Dose Dexamethasone (Rd): The FIRST Trial [Oral]. Oral presented at: 20th Congress of the European Hematology Association (EHA); June 11-13, 2015; Vienna, Austria.
8. Lu J, Lee JH, Huang SY, et al. The FIRST Trial: Analysis of the Asian Subgroup of Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma Treated with Continuous Lenalidomide and Low-Dose Dexamethasone [Poster]. Poster presented at: 21st Congress of the European Hematology Association (EHA); June 9-12, 2016; Copenhagen, Denmark.
9. Vogl D, Delforge M, Song K, et al. Effect of Lenalidomide Plus Low-Dose Dexamethasone Treatment Until Progression on Health-Related Quality of Life Over Time in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma [Poster]. Poster presented at: 21st Congress of the European Hematology Association (EHA); June 9-12, 2016; Copenhagen, Denmark.