December 20, 2018

Name: Judy Wu, PharmD
Company/Organization: Pharmacyclics LLC, an AbbVie Company
Address: 995 East Arques Avenue, Sunnyvale, CA 94085
Phone: 408.990.7357
E-mail: juwu@pcyc.com
Date of request: December 20, 2018
NCCN Guidelines® Panel: Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL)

Dear NCCN:

Pharmacyclics LLC and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib). On behalf of Pharmacyclics LLC and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - WM/LPL Panel to review the enclosed information regarding IMBRUVICA (ibrutinib) for the treatment of Waldenström macroglobulinemia (WM).

Specific Change: Consider the available data on IMBRUVICA in patients for WM for your updating purposes.

FDA Clearance:
IMBRUVICA® is a kinase inhibitor indicated for the treatment of adult patients with:[1]

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Rationale:
Updated efficacy and safety results from the Phase 3 iNNOVATE study (PCYC-1127-CA, NCT02165397) and its accompanying open-label substudy were recently presented at the 2018 American Society of Hematology (ASH) Annual Meeting by **Buske et al (2018)**[2].

In the Phase 3 study, patients with symptomatic treatment-naïve or relapsed/refractory WM (N=150) were randomized to ibrutinib + rituximab (i+R) vs placebo + rituximab (R). In the updated analysis[2], at a median follow-up of 33.4 months, i+R continued to demonstrate superiority over R as shown by improved investigator-assessed progression-free survival (median PFS, not reached vs 20.3 months; HR 0.22; 95% CI, 0.12-0.39, p<0.0001), and this was consistently observed in relevant subgroups, including *MYD88*^{L625P}/*CXCR4*^{WT} (36-month PFS rates: 84% vs 29%), *MYD88*^{L625P}/*CXCR4*^{WHIM} (36-month PFS rates: 64% vs 26%), and *MYD88*^{WT}/*CXCR4*^{WT} (36-month PFS rates: 82% vs 44%). The estimated 36-month

overall survival rates were 93% and 90% in the i+R and R arms, respectively. In addition, higher response rates by investigator assessment and shorter time to response were seen with i+R compared to R (ORR: 95% vs 48%; Major response: 79% vs 33%; Time to partial response or greater: median, 2 vs 6 months). Grade ≥3 adverse events that occurred more frequently with i+R vs R included atrial fibrillation (13% vs 1%) and hypertension (15% vs 4%), whereas Grade ≥3 infusion-related reactions (1% vs 16%) and any grade IgM flare (8% vs 47%) occurred less frequently with i+R. 93% of patients in the i+R arm completed rituximab treatment, compared to 71% in the R arm. The primary analysis of this study was published earlier this year by **Dimopoulos et al (2018)**[3] at a median follow-up of 26.5 months.

In the open-label substudy (n=31), patients with rituximab-refractory WM (defined as relapse after <12 months of treatment or failure to achieve at least a minor response) were treated with single-agent ibrutinib. In the updated analysis[2], at a median follow-up of 42.2 mo, investigator-assessed median PFS with single-agent ibrutinib was 41 months; overall response rate by investigator assessment was 90% (Major response rate: 77%; VGPR: 26%). The median duration of treatment with single-agent ibrutinib was 38.4 mo, and during this time, the most common adverse events (≥25%) included diarrhea, pyrexia, back pain, and neutropenia. No fatal adverse events, no atrial fibrillation events, no major bleeding events, and no IgM flare have been reported in this cohort. Results from this substudy were previously described by **Dimopoulos et al (2016)**[4] at a median follow-up of 18.1 months.

The following references are submitted with the full prescribing information[1] for your reference. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors of these publications.

1. IMBRUVICA® (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2018.
2. Buske C. Ibrutinib Treatment in Waldenström's Macroglobulinemia: Follow-up Efficacy and Safety from the iNNOVATE Study [oral presentation]. 60th Annual Meeting and Exposition of the American Society of Hematology; December 1-4, 2018; San Diego. Abstract 149.
3. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *The New England Journal of Medicine.* 2018;378(25):2399-2410.
4. Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol.* 2016;18(2):241-250.

Sincerely,

Judy Wu, PharmD
Senior Manager, Scientific Communications
Pharmacyclics LLC, an AbbVie Company