December 21, 2017

Name: Alex Young, PharmD
Company/Organization: Pharmacyclics LLC, an AbbVie Company
Address: 995 East Arques Avenue, Sunnyvale, CA 94085
Phone: 408.215.3412
E-mail: alyoung@pcyc.com
Date of request: December 21, 2017
NCCN Guidelines® Panel: CLL/SLL

Dear NCCN:

Pharmacyclics LLC and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib) capsules. On behalf of Pharmacyclics LLC and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - CLL/SLL Panel to review the enclosed information of IMBRUVICA (ibrutinib) for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Specific Change: Recommend single-agent ibrutinib in patients with del17p/TP53 CLL/SLL as an evidence category 1 rating.

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

- 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: **Brown et al (2017)**[2,3] published updated results of high-risk genomic subgroups at median follow-up of 19 months from the open-label, multicenter, randomized, phase 3 RESONATE™ study (PCYC-1112, NCT01578707) of ibrutinib vs ofatumumab in patients with relapsed/refractory (R/R) CLL/SLL (N=391), including outcomes by del17p/TP53 and by prior line of therapy. No significant difference in median progression-free survival (PFS) was found in ibrutinib-treated patients with del17p and/or TP53 aberration (n=86) (not estimable [NE]) vs those with neither abnormality (NE) (n=68) (HR, 0.590; 95% CI: 0.295-1.179; log rank *P*=0.1306). Median overall survival (OS) was also not significantly different in ibrutinib-treated patients with del17p or TP53 mutation (NE) vs those with neither aberration (NE) (HR, 0.554; 95% CI: 0.226-1.359; *P*=0.1903). In ibrutinib-treated patients with 1 prior vs >1 prior therapy, median PFS was significantly different (NE vs NE, respectively; HR, 3.294; 95% CI: 1.019-10.65; log-rank *P*=0.0348) while the median OS showed no significant difference (NE vs NE, respectively; HR, 2.874; 95% CI: 0.681-12.13; log-rank *P*=0.1324).

Among ibrutinib-treated patients, most common adverse events (AEs) of any-grade (≥20%) were diarrhea (53.8%), fatigue (34.4%), nausea (31.3%), pyrexia (29.7%), cough (26.2%), neutropenia (25.6%), anemia, and

upper respiratory tract infection (25.1% each). Grade 3/4 AEs (≥5%) were neutropenia (19.5%), pneumonia (10.3%), anemia (6.2%), and thrombocytopenia (5.6%). Grade 5 pneumonia was reported in 2.1%.

For further information, additional longer-term follow-up of RESONATE™ has been recently presented at the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO).

- **Byrd et al (2017)[4,5]** presented updated efficacy and safety results with up to 4 years of follow-up from the phase 3, open-label, multicenter, randomized study of ibrutinib vs ofatumumab in patients with R/R CLL/SLL (N=391) (RESONATE™, PCYC-1112, NCT01578707).

The following references are submitted with the full prescribing information[1] in support of the proposed change. 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; 2017.
2. Brown JR, Hillmen P, O'Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE™ study in patients with previously treated CLL/SLL. *Leukemia.* 2017. doi: http://dx.doi.org/10.1038/leu.2017.175.
3. Brown JR, Hillmen P, O'Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE™ study in patients with previously treated CLL/SLL [supplementary appendix]. *Leukemia.* 2017. doi: http://dx.doi.org/10.1038/leu.2017.175.
4. Byrd JC, Hillmen P, O'Brien SM, et al. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): up to four years follow-up of the RESONATE study [abstract]. *J Clin Oncol.* 2017;35:Abstract 7510. http://abstracts.asco.org/199/AbstView_199_181625.html
5. Byrd JC, Hillmen P, O'Brien SM, et al. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): up to four years follow-up of the RESONATE study [poster presentation]. 53rd Annual Meeting of the American Society of Clinical Oncology; June 2-6, 2017; Chicago, IL. Abstract 7510.

Sincerely,

Alex Young, PharmD
Manager, Scientific Communications
Pharmacyclics LLC, an AbbVie Company