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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
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NCCN Guidelines® Panel: CLL/SLL/Hairy Cell Leukemia

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/Hairy Cell Leukemia Panel to review the enclosed information of IMBRUVICA (ibrutinib) for the treatment of chronic lymphocytic leukemia (CLL) and/or small lymphocytic lymphoma (SLL).

Specific Change: Consider the available data on IMBRUVICA® in patients with CLL and/or SLL regardless of high-risk prognostic factors, including unmutated immunoglobulin heavy chain variable region (*IGHV*), deletion (del) 11q, and complex karyotype (CKT), for your updating purposes.

FDA Clearance:
IMBRUVICA® is a kinase inhibitor indicated for the treatment of 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.

Rationale: Several conference proceedings have reported on the role of high-risk prognostic factors, including unmutated *IGHV*, del11q, CKT, on clinical outcomes in analyses of ibrutinib versus comparators and ibrutinib alone in patients with treatment-naïve (TN) and relapsed/refractory (R/R) CLL/SLL.[2-5] Specific to *IGHV* mutational status, recent publication, conference proceedings, and International Workshop on CLL (iwCLL) guideline updates have highlighted the role of unmutated *IGHV* as a potential parameter for deciding therapy in CLL/SLL.[6-8]

- **Kipps et al (2017)[2]** reported results of an integrated analysis of patients with TN and R/R CLL/SLL with or without genomic risk factors, including *IGHV* mutation status, del11q, trisomy 12, and complex karyotype pooled from three ibrutinib phase 3, randomized, controlled trials (RESONATE™, RESONATE™-2, HELIOS) to examine the impact of certain genomic risk factors on clinical outcomes with ibrutinib and comparators (N=1210 all-treated; ibrutinib-treated only: unmutated *IGHV* [n=366], del11q [n=179], trisomy-12 [n=102], complex karyotype [n=63]).

- **Ghia et al (2017)[3]** reported results of an unadjusted naïve comparison of digitized Kaplan-Meier progression-free survival (PFS) curves of ibrutinib and chemoimmunotherapy regimens in studies which included fit patients with treatment-naïve CLL and unmutated *IGHV*.
- **O'Brien et al (2016)[4,5]** presented results of 5-year follow-up of a phase 1b/2 (PCYC-1102) and an extension study (PCYC-1103) of ibrutinib in patients with TN and R/R CLL/SLL, including outcomes by high-risk abnormalities not limited to *IGHV* mutational status, del11q, and CKT (N=132; unmutated *IGHV* [48% TN, 78% R/R], del11q [3% TN, 35% R/R], and CKT [13% TN, 37% R/R]).

The following references are submitted with the full prescribing information[1] in support of the update. 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. Kipps T, Fraser G, Coutre S, et al. Outcomes of ibrutinib-treated patients with chronic lymphocytic leukemia/small lymphocytic lymphoma with high-risk prognostic factors in an integrated analysis of 3 randomized phase 3 studies [oral presentation]. 17th International Workshop on Chronic Lymphocytic Leukaemia; May 12-15, 2017; New York City, New York.
3. Ghia P, Hillmen P, Moreno C, et al. Outcomes of standard of care regimens in treatment-naïve chronic lymphocytic leukemia (CLL) patients with unmutated immunoglobulin heavy chain variable (IGHV) genes [poster presentation]. 17th International Workshop on Chronic Lymphocytic Leukaemia; May 12-15, 2017; New York City, New York. Abstract 128.
4. O'Brien S, Furman RR, Coutre S, et al. Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. *Blood.* 2016;128(22):Abstract 233. https://ash.confex.com/ash/2016/webprogram/Paper89757.html.
5. O'Brien S, Furman RR, Coutre S, et al. Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [oral presentation]. 58th Annual Meeting and Exposition of the American Society of Hematology; December 3-6, 2016; San Diego, CA. Abstract 233.
6. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nature Reviews Disease Primers.* 2017;3:16096. http://dx.doi.org/10.1038/nrdp.2016.96. doi: 10.1038/nrdp.2016.96
7. Rossi D. Clinical approach to the diagnosis and initial evaluation of a CLL patient [oral presentation]. 17th International Workshop on Chronic Lymphocytic Leukaemia; May 12-15, 2017; New York City, New York.
8. Hallek M. Presentation and discussion of revised iwCLL guidelines for the approach to a CLL patient [oral presentation]. 17th International Workshop on Chronic Lymphocytic Leukaemia; May 12-15, 2017; New York City, New York.

Sincerely,

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