

May 9, 2016

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Date of request: May 9, 2016  
NCCN Guidelines® Panel: Non-Hodgkin's Lymphomas

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® - Non-Hodgkin's Lymphomas Panel review the enclosed information for inclusion of IMBRUVICA (ibrutinib) for first-line treatment of patients with chronic lymphocytic leukemia (CLL) without del(17p)/TP53 mutation who are age <70 years without significant comorbidities.

Specific Change: Consider IMBRUVICA (ibrutinib) for first-line treatment of patients with chronic lymphocytic leukemia (CLL) without del(17p)/TP53 mutation who are age <70 years without significant comorbidities.

FDA Clearance:<sup>1</sup>

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 of clinical benefit in confirmatory trials.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
- Chronic lymphocytic leukemia/Small lymphocytic lymphoma (SLL) with 17p deletion.
- Waldenström's macroglobulinemia (WM).

On March 4, 2016 the U.S. Food and Drug Administration expanded the CLL indication of IMBRUVICA® to include treatment of CLL patients across all lines of therapy, including first-line and previously treated CLL. On May 6, 2016, the U.S. Food and Drug Administration expanded the approved uses of IMBRUVICA® to include treatment of patients with SLL.

Rationale:

Burger, et al. previously published results of the phase 3, open-label, multicenter, randomized, head-to-head RESONATE-2™ trial comparing ibrutinib vs chlorambucil in previously untreated patients with CLL/SLL who were 65 years of age or older (N=269; PCYC-1115, [NCT01722487](https://clinicaltrials.gov/ct2/show/study/NCT01722487)).<sup>2</sup> In a subgroup analysis of progression-free survival (PFS) in the 30% of patients age <70 years in the RESONATE-2™ trial, ibrutinib demonstrated a risk of disease progression or death that was 87% lower than that with chlorambucil (n=80; hazard ratio, 0.13; 95% confidence interval, 0.04-0.46).<sup>2,3</sup>

The following references are submitted with the full Prescribing Information<sup>1</sup> in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. IMBRUVICA® (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2016.

2. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Eng J Med*. 2015; 373:2425-2437. <http://www.nejm.org/doi/full/10.1056/NEJMoa1509388>.
3. Tedeschi A, Barr P, Robak T, et al. Results from the international, randomized phase 3 study of ibrutinib versus chlorambucil in patients 65 years and older with treatment-naïve CLL/SLL (RESONATE-2™) [oral presentation]. 57th Annual Meeting and Exposition of the American Society of Hematology; Dec 5-8, 2015; Orlando, FL. Abstract 495.

Sincerely,

A handwritten signature in black ink, appearing to read 'Judy Wu', with a stylized, cursive script.

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