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NCCN Guidelines® Panel: B-Cell 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® - B-Cell Lymphomas Panel to review the enclosed information of IMBRUVICA (ibrutinib) for the treatment of mantle cell lymphoma (MCL).

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

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: Several conference proceedings have reported on a pooled analysis and updated follow-up of studies with ibrutinib as a single-agent and as combination therapy in patients with MCL.

- **Rule et al (2017)^{2,3}** presented 3-year follow-up efficacy and safety data from a phase 3, open-label study of ibrutinib vs temsirolimus in patients with R/R MCL (N=280) (MCL3001 [RAY]).
- **Rule et al (2016)^{4,5}** performed a pooled analysis on the impact of baseline factors on response rates and survival outcomes in ibrutinib-treated patients with relapsed/refractory (R/R) MCL from 3 international, open-label, phase 2 and/or phase 3 studies (N=370) (PCYC-1104, MCL2001 [SPARK], and MCL3001 [RAY]).
- **Wang et al (2017)^{6,7}** presented further follow-up efficacy and safety results from a phase 2 study of induction therapy with ibrutinib in combination with rituximab followed by shortened hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with rituximab plus high-dose methotrexate-cytarabine in newly diagnosed patients ≤65 years of age with MCL (N=50) (NCT02427620).

The following references are submitted with the full prescribing information¹ 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. Rule S, Jurczak W, Jerkeman M, et al. Ibrutinib vs temsirolimus: three-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Hematol Oncol*. 2017;35:143-144. http://dx.doi.org/10.1002/hon.2437_133. doi: 10.1002/hon.2437_133
3. Rule S, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus: three-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study [oral presentation]. 14th International Conference on Malignant Lymphoma; June 14-17, 2017; Lugano, Switzerland.
4. Rule S, Dreyling M, Hess G, et al. Overall survival outcomes in patients with mantle-cell lymphoma (MCL) treated with ibrutinib in a pooled analysis of 370 patients from 3 international open-label studies [abstract]. *Haematologica*. 2016:Abstract S438. <http://learningcenter.ehaweb.org/eha/2016/21st/135194/simon.rule.overall.survival.outcomes.in.patients.with.mantle-cell.lymphoma.html?f=m3>.
5. Rule S, Dreyling M, Hess G, et al. Overall survival outcomes in patients with mantle-cell lymphoma treated with ibrutinib: a pooled analysis of 370 patients from 3 international open-label studies [oral presentation]. 21st Congress of the European Society of Hematology; June 9-12, 2016; Copenhagen, Denmark.
6. Wang ML, Lee H, Thirumurthi S, et al. Ibrutinib-rituximab followed by reduced chemo-immunotherapy consolidation in young, newly diagnosed mantle cell lymphoma patients: a window of opportunity to reduce chemo. *Hematol Oncol*. 2017;35:142-143. http://dx.doi.org/10.1002/hon.2437_132. doi: 10.1002/hon.2437_132
7. Wang ML, Lee H, Thirumurthi S, et al. Ibrutinib-rituximab followed by reduced chemo-immunotherapy consolidation in young, newly diagnosed mantle cell lymphoma patients: a window of opportunity to reduce chemo [oral presentation]. 14th International Conference on Malignant Lymphoma; June 14-17, 2017; Lugano, Switzerland.

Sincerely,



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