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Date of request: January 19, 2017
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 the second-line treatment of patients with marginal zone lymphoma (MZL).

Specific Change: Recommend IMBRUVICA (ibrutinib) for second-line or subsequent therapy for recurrent or progressive disease in gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, and splenic MZL as a category 2A rating.

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 confirmatory trials
- 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: On January 18, 2017 the U.S. Food and Drug Administration approved updates to the IMBRUVICA® PI. Please refer to the IMBRUVICA® PI for complete information about the use of IMBRUVICA® in its approved indications.

- Section 1, Indications and Usage
  - 1.5 Marginal Zone Lymphoma
- Section 2, Dosage and Administration
  - 2.2 Mantle Cell Lymphoma and Marginal Zone Lymphoma
  - 2.3 Dose Modifications for Adverse Reactions
- Section 5, Warnings and Precautions
  - 5.2 Infections
  - 5.3 Cytopenias

- 5.6 Second Primary Malignancies
- 5.8 Embryo-Fetal Toxicity

- Section 6, Adverse Reactions
  - 6.1 Clinical Trials Experience
    - Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Studies 2, 3, and 4)
    - Waldenström's Macroglobulinemia (Study 5) and Marginal Zone Lymphoma (Study 6)
  - Additional Important Adverse Reactions
    - Diarrhea
    - Visual Disturbance
  - 6.2 Postmarketing Experience
- Section 8.5, Geriatric Use
- Section 14, Clinical studies
  - 14.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
  - 14.4 Marginal Zone Lymphoma

The full prescribing information[1] is submitted for your reference.

1. IMBRUVICA® (ibrutinib) capsules [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC. Revised 01/2017.

Sincerely,

Alex Young, PharmD
Senior Specialist, Scientific Communications
Pharmacyclics LLC