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Name: Lisa Meadows Ambrose, RPh, PharmD-c, BCOP

Company/Organization: Janssen Biotech, Inc.

Address: 850 Ridgeview Drive Horsham, PA 19044

Phone: 804.539.7417

E-mail: Lmeadows@its.jnj.com

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NCCN Guidelines® Panel: Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma

Dear NCCN,

Pharmacyclics, Inc. and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA™ (ibrutinib) capsules. On behalf of Pharmacyclics Inc. and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Panel review the enclosed data for inclusion of IMBRUVICA™ (ibrutinib) for the treatment of patients with relapsed/refractory (RR) Waldenström's Macroglobulinemia (WM).

Specific Change:

Recommend IMBRUVICA™ (ibrutinib) for treatment of patients with RR WM.

FDA Clearance:

The FDA has approved IMBRUVICA™ (ibrutinib) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.

Rationale:

On February 12, 2013, Pharmacyclics and Janssen announced that the U.S. Food and Drug Administration (FDA) granted a Breakthrough Therapy Designation for ibrutinib as a monotherapy in the treatment of patients with WM.

An ongoing, open-label, multicenter, phase 2 study (NCT01614821) evaluated the efficacy and safety of ibrutinib 420 mg orally once daily in patients with RR WM (N=35). The best overall response rate of 81.3% (3 very good partial responses [VGPR]; 15 partial responses [PR]; 8 minor responses [MR]) was seen using criteria adapted from the Third International WM Workshop. The median time to response (MR or better) was 4 weeks. Median serum IgM levels decreased from 3190 mg/dL at baseline to 1232 mg/dL at best response ($P=5.1 \times 10^{-9}$) and median hematocrit increased from 30.8% at baseline to 39.7% at best response ($P=1.1 \times 10^{-11}$). Bone marrow assessment results in 16 patients demonstrated tumor reduction from a median of 80% to 50% at 6 months ($P=0.006$). Treatment related toxicities >grade 2 included thrombocytopenia (15.6%) and neutropenia (9.3%). A total of 32 patients remained on study at a median follow-up of ≥ 6 cycles (4 week cycles). Reasons for discontinuation included progressive disease in one patient, development of myelodysplastic syndrome/refractory anemia with excess blasts (MDS/RAEB) in a heavily pre-treated patient who attained VGPR but had 5q deletions pre-

dating protocol therapy (n=1) and a recurring thrombocytopenia caused by splenic entrapment which resolved after splenectomy (n=1).^{1,2}

The following study publications are submitted with the Full Prescribing Information.³ 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) Treon S, Tripsas CK, Yang G, et al. A prospective, multicenter, phase II study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed and refractory Waldenström's macroglobulinemia [abstract]. *Hematol Oncol*. 2013;31(suppl 1):119:067.
- 2) Treon S, Tripsas CK, Yang G, et al. A prospective multicenter phase II study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed and refractory Waldenström's macroglobulinemia. Data presented at the 12th *International Conference on Malignant Lymphoma*, June 19-20, 2013. Lugano, Switzerland.
- 3) IMBRUVICA™ (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc.
- 4) Treon SP, Tripsas CK, Yang G, et al. A prospective multicenter study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenström's macroglobulinemia. Data to be presented at the *American Society of Hematology 55th Annual Meeting*, December 7-10, 2013. New Orleans, LA.

Sincerely,

Lisa Meadows Ambrose, RPh, PharmD-c, BCOP
Therapeutic Manager, Oncology Medical Information
Janssen Scientific Affairs, LLC