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NCCN Guidelines Panel: B-Cell Lymphomas

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for "B-Cell Lymphomas" for the inclusion of CALQUENCE® (acalabrutinib) for the treatment of adult patients with mantle cell lymphoma (MCL). CALQUENCE® is an inhibitor of Bruton tyrosine kinase (BTK).

Specific Changes:

Request inclusion of CALQUENCE® as a treatment option for Mantle Cell Lymphoma in the B-cell Lymphoma guidelines (MANT-A).

FDA Status:

On August 1, 2017, the US Food and Drug Administration granted breakthrough therapy designation to acalabrutinib for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Acalabrutinib was approved by the FDA on 10/31/2017 under the brand name CALQUENCE for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.<sup>1</sup>

Please refer to the CALQUENCE [prescribing information](#) for the full FDA-approved indication and safety information.

Rationale: The FDA based its approval of acalabrutinib on results from Study LY-004. Background and results from publicly available information are as follows:

- Acalabrutinib is a selective, small-molecule, irreversible inhibitor of BTK with minimal off-target interactions. In a screen of 395 mammalian wild-type kinases, acalabrutinib IC<sub>50</sub> concentrations for ERBB4 and BMX were 3 and 9 fold higher (less potent) than for BTK in biochemical kinase assays<sup>1</sup>. IC<sub>50</sub> values for BTK, ERBB4 and BMX are as follows: 5.1 nM, 16 nM, and 46 nM, respectively. IC<sub>50</sub> values for other kinases were greater than 100 nM. Acalabrutinib had minimal activity on other immune cells (T cells and NK cells).<sup>2,3</sup>
- In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.<sup>1</sup>
- Acalabrutinib demonstrates rapid oral absorption and a short half-life, allowing for more frequent dosing. An increase in the de novo synthesis rate of BTK has been theorized for B-cell malignancies with more rapidly proliferating cells. Dosing acalabrutinib twice daily achieved a continuous BTK binding of ≥ 95% over a period of 24 hours.<sup>2,3</sup>

Study Details:<sup>1</sup>

- LY-004 was a single arm, open-label, Phase 2 trial evaluating safety and efficacy of acalabrutinib in Mantle Cell Lymphoma patients who had received one prior therapy (NCT02213926). Acalabrutinib was administered to 124 patients orally at 100 mg twice daily until disease progression or unacceptable toxicity. The median follow-up was 15.2 months.

- CALQUENCE demonstrated the following clinical activity: ORR of 80% (95% CI; 72, 87), a complete response of 40% (95% CI; 31, 49) and a partial response of 40% (95% CI; 32, 50) per Independent Review Committee. The median duration of response (DOR) was not reached. The median time to best response was 1.9 months.
- The most common non-hematologic adverse reactions ( $\geq 20\%$ ) of any grade were headache (39%), diarrhea (31%), fatigue (28%), myalgia (21%), and bruising (21%). The majority of these events were Grade 1 and as follows: headache (25%), diarrhea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common grade  $\geq 3$  non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea (3.2%).
- The most common hematologic adverse reactions were anemia, thrombocytopenia, and neutropenia. The most common hematological adverse reactions based on laboratory measurements and adverse reactions were hemoglobin decreased (46%), platelets decreased (44%), and neutrophils decreased (36%). Grade  $\geq 3$  hematological adverse reaction based on laboratory measurements and adverse reactions were hemoglobin decreased (10%), platelets decreased (12%), and neutrophils decreased (15%).
- Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.
- Dosage reductions or discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

An in-depth safety analysis of CALQUENCE monotherapy was undertaken on a combined safety database of 612 patients with hematological malignancies (CLL, DLBCL, FL, MCL, MM and WM). The results of this analysis formed the basis of the warnings and precautions for CALQUENCE monotherapy and included: hemorrhage, infection, cytopenias, second primary malignancies, and atrial fibrillation and flutter.

These materials may include information that is not found in the currently approved prescribing information for CALQUENCE. The enclosed information is intended to provide pertinent data and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for CALQUENCE. This information is provided to NCCN evaluators for guideline review purposes only.

Reference(s):

A copy of the approved [Package Insert](#) and publications for acalabrutinib are included for the support of this data.

1. CALQUENCE® (acalabrutinib) Prescribing Information.
2. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): A Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
3. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med.* 2016;374(4):323-332.

Sincerely,

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