Submitted by: Shyam Parikh, PharmD, NCMP
Company/Organization: AstraZeneca/Medical Affairs
Address: One MedImmune Way, Gaithersburg, MD 20878
Phone: 1-877-212-6597
E-mail: MedinfoUS@astrazeneca.com
Date of Request: June 11, 2018
NCCN Guidelines Panel: Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for "Waldenström's Macroglobulinema/Lymphoplasmacytic Lymphoma" (WM/LPL) for the inclusion of CALQUENCE® (acalabrutinib) for the treatment of adult patients with Waldenström's Macroglobulinemia. CALQUENCE® is an inhibitor of Bruton tyrosine kinase (BTK).

Specific Changes:
Request inclusion of CALQUENCE® as a primary therapy for the treatment of WM/LPL (WM/LPL-B, 1 of 3) and as a therapy for previously treated WM/LPL patients (WM-LPL-B, 2 of 3).

FDA Status:
CALQUENCE is not FDA-approved for the treatment of Waldenström's Macroglobulinemia.

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.[1]

Please refer to the CALQUENCE prescribing information for the full FDA-approved indication and safety information.

Rationale: There remains a need for new treatment options for WM/LPL patients. Results from the Phase 2, ACE-WM-001 study support the use of acalabrutinib in this population. 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_{50} concentrations for ERBB4 and BMX were 3 and 9-fold higher (less potent) than for BTK in biochemical kinase assays. Acalabrutinib had minimal activity on other immune cells (T cells and NK cells).[2,3]

- 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.[2,3]

Study Details:[4]
- The ACE-WM-001 study is a Phase 2, multicenter, international, open-label study that evaluated acalabrutinib monotherapy in treatment-naïve (n=14) or R/R (n=92) patients with WM.
- The co-primary endpoints were the overall response rate by the investigator assessed 6th International Workshop on WM (IWWM) criteria and modified 3rd IWWM criteria.
- At a median study follow-up of 27.4 months, key efficacy results are summarized in the table below:

	6th IWWM Criteria		Modified 3rd IWWM Criteria	
Characteristic	**TN n=14**	**R/R n=92**	**TN n=14**	**R/R n=92**
ORR (≥ MR), n (%)	13 (93)	86 (93)	13 (93)	86 (93)
95% CI	66, 100	86, 98	66, 100	86, 98
MRR (≥ PR), n (%)	11 (79)	74 (80)	11 (79)	72 (78)
95% CI	49, 95	71, 88	49, 95	68, 86
Best response, n (%)				
CR	0	0	0	0
VGPR	0	8 (9)	1 (7)	30 (33)
PR	11 (79)	66 (72)	10 (71)	42 (46)
MR	2 (14)	12 (13)	2 (14)	14 (15)
SD	1 (7)	6 (7)	1 (7)	4 (4)
24-month rate, %				
DoR	NR*	NR*	90	82
95% CI			47.3, 98.5	71.9, 88.7
PFS	NR*	NR*	90	81.9
95% CI			47.3, 98.5	72.1, 88.5
OS	NR*	NR*	91.7	88.9
95% CI			53.9, 98.8	80.4, 93.9

*Results were consistent with those using the 6th IWWM Criteria.
CR = complete response; IWWM = International Workshop on Waldenström macroglobulinemia; MR = minor response; MRR = major response rate; NR = not reported; ORR = overall response rate; PR = partial response; R/R = relapsed/refractory; TN = treatment-naive; VGPR = very good partial response

- The most common adverse events (AEs) in ≥15% of all patients (N=106) were headache, diarrhea, contusion, dizziness, fatigue, nausea, upper respiratory tract infection (RTI), constipation, arthralgia, back pain, cough, lower RTI, neutropenia, pyrexia, vomiting, decreased appetite, and rash.

- Grade ≥3 AEs occurring in ≥5% of all patients were neutropenia 17(16%), lower RTI 18(17%), anemia 5(5%), pneumonia 7(7%), alanine aminotransferase increased 5(5%), and hynonatremia 5(5%).

- Nine patients (3 in TN, and 6 R/R) discontinued therapy due to AEs. There were 5 (grade 5) AEs, of which one was considered treatment-related i.e. grade 5 intracranial hematoma was observed in a patient with a history of pulmonary embolism and who was on concomitant anticoagulant therapy.

An in-depth safety analysis of CALQEUNCE 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.[1]

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.[1]

A copy of the approved Package Insert and articles are submitted in support of this proposed change.

Reference(s):

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.
4. Owen R, McCarthy H, Rule S, et al. Acalabrutinib in patients (pts) with Waldenström macroglobulinemia (WM). [abstract]. Presented at: American Society of Clinical Oncology; June 1-5, 2018; Chicago, USA. *J Clin Oncol*. 2018;36(suppl) Abs 7501.

Sincerely,

Michelle Dawson

Michelle Dawson, PhD
Franchise Head Hematology
US Medical Affairs
AstraZeneca Pharmaceuticals
1-301-398-0797
Michelle.dawson@astrazeneca.com