A Guide for Management of Patients With R/R MCL on **CALQUENCE**

R/R=relapsed or refractory

CALQUENCE: Recommended Dose

100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity

Advise patients[1]:

- Swallow capsule **whole with water**
- **Do not** open, break, or chew the capsules
- Take with ***or*** without food
- **Missed dose:**
  - **If <3 hours, take** the CALQUENCE dose
  - **If >3 hours, skip** the CALQUENCE dose and take the next dose at the regularly scheduled time

CALQUENCE: Use With Gastric Acid Reducing Agents[1]

- **Proton Pump Inhibitors: Avoid concomitant use; consider switching patient to an H2 receptor blocker or antacid**

  Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE

  Examples[a]: NEXIUM® (esomeprazole), Prevacid® (lansoprazole), Prilosec® (omeprazole)[2]

- **H2 Receptor Blockers: Take CALQUENCE 2 hours before taking an H2 receptor blocker**

  Examples[a]: Axid® (nizatidine), Pepcid AC® (famotidine), Tagamet® (cimetidine), Zantac® (ranitidine)[3]

- **Antacids: Separate dosing by at least 2 hours**

  Examples[a]: Tums®, Rolaids®[4]

[a]*These examples do not represent all drugs in this class.*
H2, histamine-2.

CALQUENCE: Indication and Usage

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) 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 confirmatory trials.

Important Safety Information About CALQUENCE® (acalabrutinib) capsules

Serious and Opportunistic Infections

- Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.
- Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

(continued on reverse side)

CALQUENCE Safety Profile: LY-004 Trial

- The most common (≥20%) adverse drug reactions were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising[1]
- Warnings and precautions include serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, and atrial fibrillation/flutter[1]

Rates of Dose Reduction and Discontinuation due to AEs[1,5] (N=124)

2%
DOSE-MODIFICATION RATE[5]

8%
DISCONTINUATION RATE[5]

Median duration of treatment was 17.3 months (range: 0.3-35.1)[5]

- 1.6% dose-reduction rate and 6.5% discontinuation rate in the initial analysis with a median duration of treatment of 16.6 months (range: 0.1-26.6 months)[1]

CALQUENCE: Drug Interactions

Strong CYP3A Inhibitors

- **Avoid co-administration with CALQUENCE[1]**
- **Alternatively, if the strong CYP3A inhibitor will be used short-term, interrupt CALQUENCE[1]**

Examples[6,7,a]:

Antifungal	*Hep C Antiviral*	*HIV Antiretroviral*	Other
Itraconazole	*Boceprevir*	*Cobicistat*	*Grapefruit juice*
Ketoconazole	*Dasabuvir*	*Elvitegravir*	*Pomegranate juice[8]*
Posaconazole	*Ombitasvir*	*Indinavir*	
Voriconazole	*Paritaprevir*	*Lopinavir*	
	Telaprevir	*Ritonavir*	
		Saquinavir	
		Tipranavir	

Moderate CYP3A Inhibitors

- **When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce CALQUENCE dose to 100 mg QD[1]**

Examples[6,7,a]:

Antibiotic	*Antineoplastic*	*Antiemetic*	*Immuno-suppressant*
Ciprofloxacin	*Crizotinib*	*Aprepitant*	*Cyclosporine*
Erythromycin	*Imatinib*	*Ca Channel Blocker*	*SSRI/ Antianxiety*
Antifungal	*Antiarrhythmic*	*Verapamil*	*Fluvoxamine*
Clotrimazole	*Dronedarone*	*Diltiazem*	
Fluconazole		*Vasopressin Inhibitor*	
		Conivaptan[9]	

Strong CYP3A Inducers

- **Avoid co-administration with CALQUENCE[1]**
- **If a strong CYP3A inducer cannot be avoided, increase the CALQUENCE dose to 200 mg approx. Q12h[1]**

Examples[6,7,a]:

Androgen Receptor Inhibitor	*Antibiotic*	*Anticonvulsant*
Apalutamide	*Rifampin*	*Carbamazepine*
Enzalutamide	*Antineoplastic*	*Phenytoin*
	Mitotane	*Other*
		St. John's Wort

[a]*Does not represent all possible examples. Please cross-check all patient medication for possible interactions.*

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CALQUENCE® (acalabrutinib) 100 mg capsules

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CALQUENCE: Common Event Management

Headache in the LY-004 Trial[a]

Headache occurred in 39% of patients[1,10]

The majority of headache events (30/47) were Grade 1, and most patients (36/47) had only 1 event (47/124)[10]

Median time to onset was 5 days; median duration was 11 days[10]

Tips to Help Manage Headache

- Advise your patients about headache. Over-the-counter acetaminophen and caffeinated drinks may be helpful.[11] In the clinical trial, headache was mostly self-limiting and required no intervention
- If headache is severe, advise patients to seek emergency care for evaluation[12]

Diarrhea in the LY-004 Trial[a]

Overall incidence of diarrhea was 31%, all grades (38/124)[10]

The majority of diarrhea events (21/38) were Grade 1, and most patients (28/38) had only 1 event[10]

Tips to Help Manage Diarrhea

- Counsel patients on diarrhea, which frequently resolved over time with continued treatment in the clinical trial.[11] Offer these tips to patients[13]:
  - Drink clear liquids, such as water or oral rehydration drinks, and eat small, frequent meals
- Grade 1-2 diarrhea may be managed with standard care and over-the-counter medication[12]
- If diarrhea is recurrent, rule out infection; may need further evaluation[12]

Fatigue in the LY-004 Trial[a]

Fatigue was reported by 28% of patients (35/124)[1]

Tips to Help Manage Fatigue

- Discuss ways to alleviate fatigue. Suggestions may include[14]:
  - Getting adequate nighttime sleep and taking short naps
  - Relaxation and stress reduction through enjoyable activities or light exercise (advise patients to consult their doctor before any exercise plan)

Myalgia in the LY-004 Trial[a]

Myalgia was reported by 21% of patients (26/124)[1]

Tips to Help Manage Myalgia

- For myalgia, advise patients to take medications as prescribed and be prepared to discuss other treatments such as acupuncture, hypnosis, massage, or physical therapy[15]
- Educate patients on the benefits of mild stretching while positioned on their hands and knees[12]

[a]The safety data described in this section reflect exposure to CALQUENCE (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in the LY-004 trial. The median duration of treatment with CALQUENCE was 16.6 months (range: 0.1 to 26.6 months). As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Important Safety Information About CALQUENCE® (acalabrutinib) capsules (cont'd)

Hemorrhage

- Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.
- Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.
- Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

- Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies

- Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter

- Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

ADVERSE REACTIONS

- The most common adverse reactions (≥20%) of any grade in patients with MCL were anemia,* thrombocytopenia,* headache (39%), neutropenia,* diarrhea (31%), fatigue (28%), myalgia (21%), and bruising (21%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea (3.2%).
  - *Treatment-emergent decreases (all grades) of hemoglobin (46%), platelets (44%), and neutrophils (36%) were based on laboratory measurements and adverse reactions.
- Dosage reductions or discontinuations due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.
- Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

DRUG INTERACTIONS

- See opposite side for information on co-administration of CALQUENCE with CYP3A inhibitors, CYP3A inducers, and gastric acid reducing agents.

SPECIFIC POPULATIONS

- Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus.
- Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE.
- It is not known if CALQUENCE is present in human milk. Advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.
- Avoid administration of CALQUENCE in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment.

Please see accompanying full Prescribing Information, including Patient Information.

1. CALQUENCE® (acalabrutinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. 2. US National Library of Medicine. https://medlineplus.gov/ency/patientinstructions/000381.htm. Accessed February 4, 2020. 3. US National Library of Medicine. https://medlineplus.gov/ency/patientinstructions/000382.htm. Accessed February 4, 2020. 4. WebMD. https://www.webmd.com/heartburn-gerd/guide/treating-heartburn-over-counter-medicine. Accessed February 4, 2020. 5. Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma [article and supplementary information]. *Leukemia*. 2019;33(11):2762-2766. 6. US Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors, and inducers. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table1-2. Accessed February 4, 2020. 7. US National Library of Medicine. MedlinePlus. Accessed February 7, 2020. 8. Hidaka M, Okumura M, Fujita K, et al. Effects of pomegranate juice on human cytochrome p450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. *Drug Metab Dispos*. 2005;33(5):644-648. 9. DrugBank Database. February 7, 2020. 10. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391(10121):659-667. 11. Awan FT, Jurczak W. Use of acalabrutinib in patients with mantle cell lymphoma. *Expert Rev Hematol*. 2018;11(6):495-502. 12. Badillo M, Nava D, Dela Rosa M, Chen W, Wang M. Management of adherence and adverse events in patients with mantle cell lymphoma treated with acalabrutinib: the MD Anderson Cancer Center experience. Poster presented at: Pan Pacific Lymphoma Conference; July 16-20, 2018; Hawaii, USA. 13. National Cancer Institute. Side effects of cancer treatment: diarrhea. https://www.cancer.gov/about-cancer/treatment/side-effects/diarrhea. Accessed February 4, 2020. 14. American Cancer Society. Getting help for fatigue. 2017. https://www.cancer.org/content/dam/cancer-org/cancer-control/en/booklets-flyers/getting-help-for-fatigue.pdf. Accessed February 4, 2020. 15. National Cancer Institute. Pain in people with cancer. https://www.cancer.gov/about-cancer/treatment/side-effects/pain. Updated August 9, 2018. Accessed February 4, 2020.

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View the CALQUENCE Educational Video Series

CALQUENCE® (acalabrutinib) 100 mg capsules

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