CALQUENCE: A BTKi for adult patients with MCL after at least one prior therapy

CONTINUOUS INHIBITION OF BTK THROUGH TWICE-DAILY DOSING[1]

CALQUENCE maintained median steady state BTK occupancy of ≥95% in peripheral blood over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval[1]

BTK OCCUPANCY OVER 12 HOURS

Does not represent actual capsule size.

One 100-mg capsule of **CALQUENCE** is taken orally twice daily

Take approximately every 12 hours until disease progression or unacceptable toxicity

CALQUENCE can be taken with or without food

Capsule should be swallowed whole with water, and should not be opened, broken, or chewed

✦ If a dose is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules should not be taken to make up for a missed dose[1]

BTKi=Bruton tyrosine kinase inhibitor; MCL=mantle cell lymphoma.

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.

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information.

CALQUENCE®
(acalabrutinib) 100 mg capsules

RECOMMENDED DOSE MODIFICATIONS FOR PATIENTS TAKING CONCOMITANT MEDICATIONS

- Co-administration of **CALQUENCE** with strong CYP3A inducers or inhibitors altered acalabrutinib plasma concentrations; moderate CYP3A inhibitors may increase acalabrutinib plasma concentrations. Please see below, and full Prescribing Information, for recommended adjustments[1]

USE WITH CYP3A INHIBITORS OR INDUCERS[1]

CYP3A	CO-ADMINISTERED DRUG	RECOMMENDED CALQUENCE USE
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to 7 days), interrupt **CALQUENCE**.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase **CALQUENCE** dose to 200 mg approximately every 12 hours.

- Avoid co-administration with proton pump inhibitors. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with **CALQUENCE**[1]
- Co-administration of **CALQUENCE** with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations, which may reduce **CALQUENCE** activity[1]
  - If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (eg, ranitidine or famotidine) or an antacid (eg, calcium carbonate)

USE WITH GASTRIC ACID REDUCING AGENTS[1]

GASTRIC ACID REDUCING AGENTS	CO-ADMINISTERED DRUG	RECOMMENDED CALQUENCE USE
	Proton pump inhibitors	Avoid co-administration.
	H2-receptor antagonists	Take **CALQUENCE** 2 hours before taking the H2-receptor antagonist.
	Antacids	Separate dosing by at least 2 hours.

Important Safety Information (Cont'd)

Hemorrhage (Cont'd)
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.

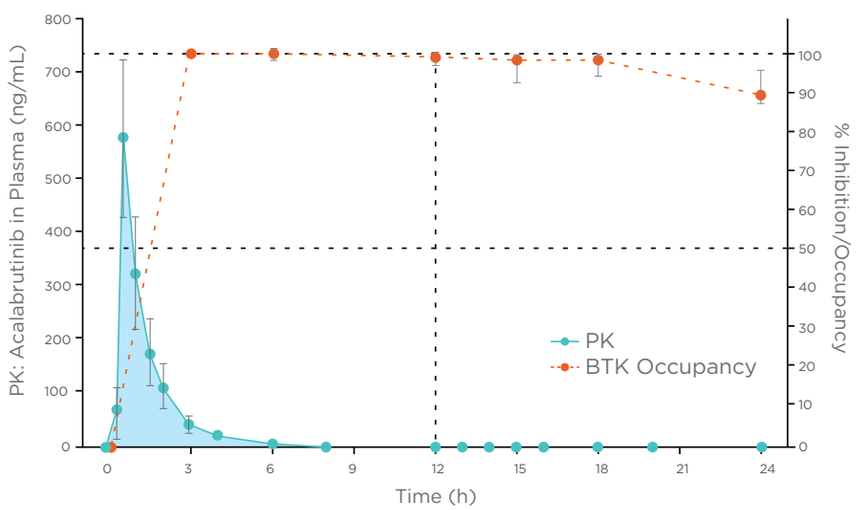
Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment.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

RECOMMENDED DOSE ADJUSTMENTS FOR ADVERSE REACTIONS GRADE ≥3[1]

EVENT	ADVERSE REACTION OCCURRENCE*	DOSE MODIFICATION (Starting dose=100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and second	Interrupt **CALQUENCE**. Once toxicity has resolved to Grade 1 or baseline level, **CALQUENCE** may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt **CALQUENCE**. Once toxicity has resolved to Grade 1 or baseline level, **CALQUENCE** may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue **CALQUENCE**.

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

CALQUENCE maintains median target occupancy over 12 hours at a single 100 mg dose[2]



- Acalabrutinib is a rapidly absorbed, irreversibly binding, covalent BTK inhibitor[2]
- A single oral dose of 100 mg reaches full target occupancy in healthy human subjects, as seen in the graph[2]

The mean acalabrutinib concentration in plasma (n=6; blue) is plotted with median BTK occupancy (n=4; orange).
Adapted from Barf T, Covey T, Izumi R, et al. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
This figure was published by ASPET under the CC BY-NC Attribution 4.0 International license.

References: 1. CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **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.** 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. **4.** Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. *Leukemia.* 2019;33(11):2762-2766. doi:10.1038/s41375-019-0575-9.

Important Safety Information (Cont'd)

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information.

CALQUENCE®
(acalabrutinib) 100 mg capsules

As seen in the LY-004 trial

STRONG EFFICACY OVER TIME IN R/R MCL PATIENTS

At median follow-up of 15.2 months[1,3,*]

- **80% ORR** (n=99/124) (95% CI: 72, 87)
- **40% CR** (n=49/124) (95% CI: 31, 49)
- **40% PR** (n=50/124) (95% CI: 32, 50)

At median follow-up of 26 months[4,†]

- **81% ORR** (n=100/124) (95% CI: 73, 87)
- **43% CR** (n=53/124) (95% CI: 34, 52)
- **38% PR** (n=47/124) (95% CI: 29, 47)
- **Median DoR** of more than 2 years (26 months) (95% CI: 17.5, NR)
- **Median PFS** of more than 1.5 years (20 months) (95% CI: 16.5, 27.7)

*Independent Review Committee-assessed per 2014 Lugano Classification.[1]
†Investigator-assessed per 2014 Lugano Classification. Median follow-up was 26 months (range: 0.3 to 35.1 months).[4]

LY-004 trial: a Phase 2, open-label, single-arm, multicenter trial in 124 patients (≥18 years) with MCL who had received ≥1 prior therapy. Patients received CALQUENCE 100 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was ORR; secondary endpoints included DoR, PFS, and OS.[1,3]

Continuous inhibition of BTK through twice-daily dosing

- CALQUENCE maintained median steady state BTK occupancy of ≥95% in peripheral blood over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval[1]

AFTER AT LEAST 1 PRIOR THERAPY, SELECT CALQUENCE AS YOUR BTKi THERAPY-OF-CHOICE FOR APPROPRIATE ADULT PATIENTS WITH MCL

CI=confidence interval; CR=complete response; DoR=duration of response; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory.

Important Safety Information (Cont'd)

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

Strong CYP3A Inhibitors: Avoid co-administration with a strong CYP3A inhibitor. If a strong CYP3A inhibitor will be used short-term, interrupt CALQUENCE.

Moderate CYP3A Inhibitors: When CALQUENCE is co-administered with a moderate CYP3A inhibitor, reduce CALQUENCE dose to 100 mg once daily.

Strong CYP3A Inducers: Avoid co-administration with a strong CYP3A inducer. If a strong CYP3A inducer cannot be avoided, increase the CALQUENCE dose to 200 mg approximately every 12 hours.

Gastric Acid Reducing Agents: If treatment with a gastric acid reducing agent is required, consider using an H2-receptor antagonist or an antacid. Take CALQUENCE 2 hours before taking an H2-receptor antagonist. Separate dosing with an antacid by at least 2 hours.

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

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.

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, either visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

AstraZeneca

CALQUENCE® (acalabrutinib) 100 mg capsules