DOSING AND ADMINISTRATION GUIDELINES

Continuous BTK inhibition through twice-daily dosing

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

BTK=Bruton tyrosine kinase; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma.

INDICATION AND USAGE

CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

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

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

CALQUENCE®
(acalabrutinib) 100 mg capsules

How to take CALQUENCE

Continue dosing regimen until disease progression or unacceptable toxicity[1]

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

Take approximately every 12 hours

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.

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Dosing every 12 hours helps patients maintain consistent BTK inhibition during their treatment[1]

IMPORTANT SAFETY INFORMATION (Cont'd)

Hemorrhage (Cont'd)
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.

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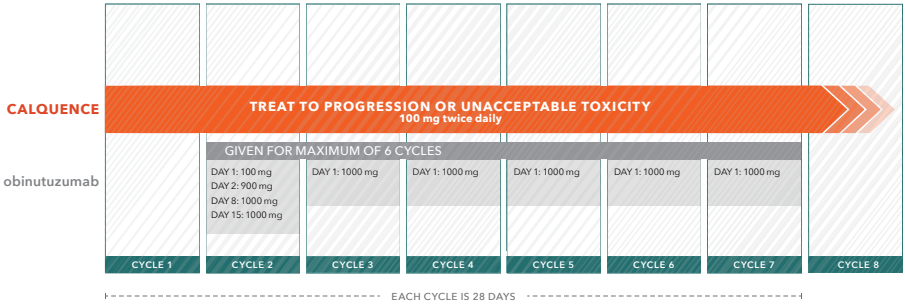
Taking CALQUENCE + obinutuzumab

If given on the same day, administer CALQUENCE prior to obinutuzumab.

In the ELEVATE-TN clinical trial, obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of six 28-day treatment cycles.[1]

CALQUENCE + OBINUTUZUMAB DOSING SCHEDULE[1]



ELEVATE-TN was a Phase 3, open-label, randomized, multicenter trial in patients with previously untreated CLL (N=535). Patients were randomized 1:1:1 into 3 arms to receive CALQUENCE + obinutuzumab, CALQUENCE monotherapy, or obinutuzumab + chlorambucil. Patients received CALQUENCE 100 mg every 12 hours until disease progression or unacceptable toxicity for either CALQUENCE + obinutuzumab or CALQUENCE monotherapy.[1,2]

Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2) and Days 8 and 15 of Cycle 2, followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.[1]

Refer to the obinutuzumab Prescribing Information for recommended obinutuzumab dosing information.

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.

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CALQUENCE® (acalabrutinib) 100 mg capsules

Dose modifications for adverse reactions

Recommended dose modifications for adverse reactions of 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).

IMPORTANT SAFETY INFORMATION (Cont'd)

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 (≥ 30%) of any grade in patients with CLL were anemia,* neutropenia, * thrombocytopenia,* headache, upper respiratory tract infection, and diarrhea.

*Treatment-emergent decreases (all grades) of hemoglobin, platelets, and neutrophils were based on laboratory measurements and adverse reactions.

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Dose modifications for patients taking concomitant medications

Concomitant 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

Concomitant use with gastric acid-reducing agents[1]

Gastric acid-reducing agents	Proton pump inhibitors*	Avoid concomitant use
	H2-receptor antagonists	Take CALQUENCE 2 hours before an H2-receptor antagonist
	Antacids	Separate dosing by at least 2 hours

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

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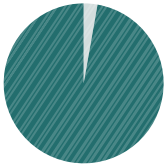
Discontinuation and dose reductions due to adverse events

Rates of discontinuation and dose reductions in both CALQUENCE arms of the ELEVATE-TN study[1]

For patients taking CALQUENCE monotherapy:

10%
discontinued therapy due to adverse reactions



4%
experienced dose reduction due to adverse reactions

For patients taking CALQUENCE + obinutuzumab:

11%
discontinued therapy due to adverse reactions

7%
experienced dose reduction due to adverse reactions

For more information, talk to your AstraZeneca representative

IMPORTANT SAFETY INFORMATION (Cont'd)

ADVERSE REACTIONS (Cont'd)

In patients with previously untreated CLL exposed to CALQUENCE, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE plus obinutuzumab arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (7% and 2.8%, respectively).

Adverse reactions led to CALQUENCE dose reduction in 7% and 4% of patients in the CALQUENCE plus obinutuzumab arm (N=178) and CALQUENCE monotherapy arm (N=179), respectively. Adverse events led to discontinuation in 11% and 10% of patients, respectively. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

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Learn more about CALQUENCE for CLL/SLL at **CALQUENCEhcp.com**

IMPORTANT SAFETY INFORMATION (Cont'd)

ADVERSE REACTIONS (Cont'd)

In patients with relapsed/refractory CLL exposed to CALQUENCE, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

Adverse reactions led to CALQUENCE dose reduction in 3.9% of patients (N=154), dosage interruptions in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and discontinuation in 10% of patients, most frequently due to second primary malignancies followed by infection. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 1.3% of patients who received CALQUENCE.

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 Important Safety Information throughout, and full Prescribing Information.

You may report side effects related to AstraZeneca products by clicking here.

References: 1. CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **2.** Elevate CLL TN: study of obinutuzumab + chlorambucil, acalabrutinib (ACP-196) + obinutuzumab, and acalabrutinib in subjects with previously untreated CLL. ClinicalTrials.gov identifier: NCT02475681. https://clinicaltrials.gov/ct2/show/NCT02475681. Updated October 14, 2019. Accessed November 14, 2019.

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