

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CALQUENCE safely and effectively. See full prescribing information for CALQUENCE.

CALQUENCE® (acalabrutinib) tablets, for oral use  
Initial U.S. Approval: 2017

### INDICATIONS AND USAGE

CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. (1.1)  
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. (1.1, 14.1)
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). (1.2)

### DOSAGE AND ADMINISTRATION

- Recommended dose is 100 mg orally approximately every 12 hours; swallow whole with water and with or without food. (2.1)
- Advise patients not to chew, crush, dissolve, or cut tablets. (2.1)
- Manage toxicities using treatment interruption, dose reduction, or discontinuation. (2.2)
- Avoid CALQUENCE in patients with severe hepatic impairment. (8.6)

### DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Serious and Opportunistic Infections:** Monitor for signs and symptoms of infection and treat promptly. (5.1)

- Hemorrhage:** Monitor for bleeding and manage appropriately. (5.2)
- Cytopenias:** Monitor complete blood counts regularly. (5.3)
- Second Primary Malignancies:** Other malignancies have occurred, including skin cancers and other solid tumors. Advise patients to use sun protection. (5.4)
- Atrial Fibrillation and Flutter:** Monitor for symptoms of arrhythmias and manage. (5.5)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq$  30%) are: anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Strong CYP3A Inhibitors:** Avoid co-administration with CALQUENCE. (2.2, 7)
- Moderate CYP3A Inhibitors:** Reduce the dosage of CALQUENCE. (2.2, 7)
- Strong CYP3A Inducers:** Avoid co-administration with CALQUENCE. If co-administration is unavoidable, increase the dosage of CALQUENCE. (2.2, 7)

### USE IN SPECIFIC POPULATIONS

- Pregnancy:** May cause fetal harm and dystocia. (8.1)
- Lactation:** Advise not to breastfeed. (8.2)
- Severe Hepatic Impairment:** Avoid use of CALQUENCE. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Mantle Cell Lymphoma
- 1.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Recommended Dosage for Drug Interactions
- 2.3 Dosage Modifications for Adverse Reactions

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Serious and Opportunistic Infections
- 5.2 Hemorrhage
- 5.3 Cytopenias
- 5.4 Second Primary Malignancies
- 5.5 Atrial Fibrillation and Flutter

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

### 7 DRUG INTERACTIONS

- 7.1 Effect of Other Drugs on CALQUENCE

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

- 14.1 Mantle Cell Lymphoma
- 14.2 Chronic Lymphocytic Leukemia

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Mantle Cell Lymphoma

CALQUENCE is 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 [see [Clinical Studies \(14.1\)](#)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### 1.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

##### CALQUENCE as Monotherapy

For patients with MCL, CLL, or SLL, the recommended dosage of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

##### CALQUENCE in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dosage of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE prior to obinutuzumab when given on the same day.

Advise patients to swallow tablet whole with water. Advise patients not to chew, crush, dissolve, or cut the tablets. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

#### 2.2 Recommended Dosage for Drug Interactions

##### Dosage Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 [see [Drug Interactions \(7\)](#)].

**Table 1: Recommended Dosage Modifications for Use with CYP3A Inhibitors or Inducers**

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid co-administration. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE.
	Moderate CYP3A inhibitor	Reduce the CALQUENCE 100 mg every 12 hours dosage to 100 mg once daily.
Induction	Strong CYP3A inducer	Avoid co-administration. If co-administration is unavoidable, increase CALQUENCE dosage to 200 mg approximately every 12 hours.

**2.3 Dosage Modifications for Adverse Reactions**

Recommended dosage modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 2.

**Table 2: Recommended Dosage Modifications for Adverse Reactions**

Event	Adverse Reaction Occurrence	Dosage 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).

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

### 3 DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg acalabrutinib, orange, oval, film-coated, biconvex, debossed with 'ACA 100' on one side and plain on the other.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 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%) [see [Adverse Reactions \(6.1\)](#)]. 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 jirovecii* 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.

#### 5.2 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 [see [Adverse Reactions \(6.1\)](#)].

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 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

#### 5.3 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 [see [Adverse Reactions \(6.1\)](#)]. Monitor complete blood

counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted [see [Dosage and Administration \(2.3\)](#)].

#### 5.4 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 [see [Adverse Reactions \(6.1\)](#)]. 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.

#### 5.5 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 [see [Adverse Reactions \(6.1\)](#)]. 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.

### 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections [see [Warnings and Precautions \(5.1\)](#)]
- Hemorrhage [see [Warnings and Precautions \(5.2\)](#)]
- Cytopenias [see [Warnings and Precautions \(5.3\)](#)]
- Second Primary Malignancies [see [Warnings and Precautions \(5.4\)](#)]
- Atrial Fibrillation and Flutter [see [Warnings and Precautions \(5.5\)](#)]

#### 6.1 Clinical Trials Experience

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.

The data in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in  $\geq 30\%$  of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

##### Mantle Cell Lymphoma

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 Trial LY-004 [see [Clinical Studies \(14.1\)](#)]. The median duration of treatment with CALQUENCE was 16.6 (range: 0.1 to 26.6) months. A total of 91

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