# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210259Orig1s000

# LABELING

## 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) capsules, 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)

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, 14)

**---------- DOSAGE AND ADMINISTRATION ----------**

- Recommended dose is 100 mg orally approximately every twelve hours; swallow whole with water and with or without food. (2 1)
- Advise patients not to break, open, or chew capsules. (2.1)
- Manage toxicities using treatment interruption, dose reduction, or discontinuation. (2.2)

**---------- DOSAGE FORMS AND STRENGTHS ----------**

Capsules: 100 mg. (3)

**---------- CONTRAINDICATIONS ----------**

None. (4)

**---------- WARNINGS AND PRECAUTIONS ----------**

- Hemorrhage: Monitor for bleeding and manage appropriately. (5.1)
- Infections: Monitor patients for signs and symptoms of infection and treat as needed. (5.2)
- Cytopenias: Monitor complete blood counts monthly during treatment. (5.3)
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers and other carcinomas. Advise patients to use sun protection. (5.4)
- Atrial Fibrillation and Flutter: Monitor for atrial fibrillation and atrial flutter and manage as appropriate. (5.5)

**---------- ADVERSE REACTIONS ----------**

Most common adverse reactions (reported in ≥ 20% of patients) were: anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. (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.**

**---------- DRUG INTERACTIONS ----------**

- CYP3A Inhibitors: Avoid co-administration with strong CYP3A inhibitors. Dose adjustments may be recommended. (2.2, 7, 12.3)
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers. Dose adjustments may be recommended. (2.2, 7, 12.3)
- Gastric Acid Reducing Agents: Avoid co-administration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids. (2.2, 7, 12.3)

**---------- USE IN SPECIFIC POPULATIONS ----------**

Lactation: Advise women not to breastfeed. (8.2)

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

**Revised: 10/2017**

**FULL PRESCRIBING INFORMATION: CONTENTS***



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

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

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)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dose of CALQUENCE is 100 mg taken orally approximately every twelve hours until disease progression or unacceptable toxicity.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. 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 capsules of CALQUENCE should not be taken to make up for a missed dose.

### 2.2 Dose Modifications

Adverse Reactions

Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 1.

**Table 1: Recommended Dose Modifications for Adverse Reactions**

| **Event** | **Adverse Reaction Occurrence** | **Dose Modification** (Starting dose = 100 mg twice daily) |
|---|---|---|
| Grade 3 or greater non-hematologic toxicities,<br>Grade 3 thrombocytopenia with bleeding,<br>Grade 4 thrombocytopenia or<br>Grade 4 neutropenia lasting longer than 7 days | First and Second | Interrupt CALQUENCE.<br>Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE therapy may be resumed at 100 mg twice daily. |
| | Third | Interrupt CALQUENCE.<br>Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE therapy may be resumed at 100 mg daily. |
| | Fourth | Discontinue CALQUENCE. |

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Dose Modifications for Use with CYP3A Inhibitors or Inducers

Recommended dose modifications are described below *[see Drug Interactions (7)]*.

| CYP3A | Co-administered Drug | Recommended CALQUENCE use |
|---|---|---|
| Inhibition | Strong CYP3A inhibitor | Avoid concomitant use.<br>If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE. |
| | Moderate CYP3A inhibitor | 100 mg once daily. |
| Induction | Strong CYP3A inducer | Avoid concomitant use.<br>If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg twice daily. |

Concomitant Use with Gastric Acid Reducing Agents

*Proton Pump Inhibitors*: Avoid concomitant use *[see Drug Interactions (7)]*.

*H2-Receptor Antagonists:* Take CALQUENCE 2 hours before taking a H2-receptor antagonist *[see Drug Interactions (7)]*.

*Antacids*: Separate dosing by at least 2 hours *[see Drug Interactions (7)]*.

## 3 DOSAGE FORMS AND STRENGTHS

100 mg capsules.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies.

The mechanism for the bleeding events is not well understood. CALQUENCE may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored 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.

### 5.2 Infection

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Consider prophylaxis in patients who are at increased risk for opportunistic infections.

Grade 3 or higher infections occurred in 18% of these patients. The most frequently reported Grade 3 or 4 infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) have occurred. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

### 5.3 Cytopenias

In the combined safety database of 612 patients with hematologic malignancies, patients treated with CALQUENCE monotherapy experienced Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (11%) and thrombocytopenia (8%) based on laboratory measurements. In the CALQUENCE clinical Trial LY-004, patients' complete blood counts were assessed monthly during treatment.

### 5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have occurred in 11% of patients with hematologic malignancies treated with CALQUENCE monotherapy in the combined safety database of 612 patients. The most frequent second primary malignancy was skin cancer, reported in 7% of patients. Advise protection from sun exposure.

### 5.5 Atrial Fibrillation and Flutter

In the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy, atrial fibrillation and atrial flutter of any grade occurred in 3% of patients, and Grade 3 in 1% of patients. Monitor for atrial fibrillation and atrial flutter and manage as appropriate.

## 6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infection *[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.

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