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

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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, 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 therapy may be resumed at 100 mg twice daily.
	Third	Interrupt CALQUENCE. 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.

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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. 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. 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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The safety data described in this section reflect exposure to CALQUENCE (100 mg twice daily) in 124 patients with previously treated MCL in Trial LY-004 *[see Clinical Studies (14)]*. The median duration of treatment with CALQUENCE was 16.6 (range 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

The most common adverse reactions (≥ 20%) of any grade were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Grade 1 severity for the non-hematologic, most common events were as follows: headache (25%), diarrhea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea.

Dose reductions or discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Tables 2 and 3 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 2: Non-Hematologic Adverse Reactions* in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General Disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin & subcutaneous tissue disorders		
Bruising†	21	-
Rash†	18	0.8
Vascular disorders		
Hemorrhage/Hematoma†	8	0.8
Respiratory, thoracic & mediastinal disorders		
Epistaxis	6	-

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Bruising: Includes all preferred terms (PTs) containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'
Rash: Includes all PTs containing 'rash'
Hemorrhage/hematoma: Includes all PTs containing 'hemorrhage' or 'hematoma'

Table 3: Hematologic Adverse Reactions Reported* in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03; based on laboratory measurements and adverse reactions.

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

7 DRUG INTERACTIONS

Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. • Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE *[see Dosage and Administration (2.2)]*.
Moderate CYP3A Inhibitors	
Clinical Impact	• Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	• When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.
Strong CYP3A Inducers	
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased acalabrutinib concentrations may reduce CALQUENCE activity.
Prevention or Management	• Avoid co-administration of strong CYP3A inducers with CALQUENCE. • If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily.

Gastric Acid Reducing Agents		
Clinical Impact	• Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased acalabrutinib concentrations may reduce CALQUENCE activity. • If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate).	
Prevention or Management	Antacids	Separate dosing by at least 2 hours *[see Dosage and Administration (2.2)]*.
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist *[see Dosage and Administration (2.2)]*.
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to pregnant rabbits during organogenesis resulted in reduced fetal growth at maternal exposures (AUC) approximately 4 times exposures in patients at the recommended dose of 100 mg twice daily (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 16-times the AUC in patients at the recommended dose of 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in

decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 4-times the AUC in patients at 100 mg twice daily.

8.2 Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

8.4 Pediatric Use

The safety and efficacy of CALQUENCE in pediatric patients have not been established.

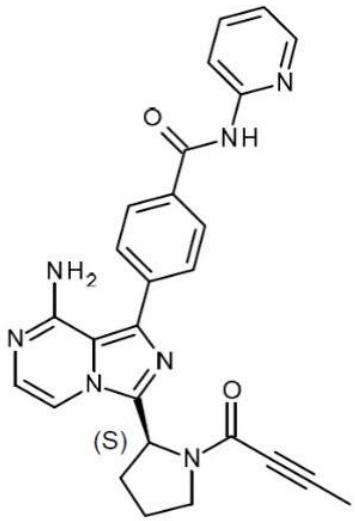
8.5 Geriatric Use

Eighty (64.5%) of the 124 MCL patients in clinical trials of CALQUENCE were 65 years of age or older, and 32 patients (25.8%) were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

11 DESCRIPTION

CALQUENCE (acalabrutinib) is an inhibitor of Bruton tyrosine kinase (BTK). The molecular formula for acalabrutinib is $C_{26}H_{23}N_7O_2$, and the molecular weight is 465.51. The chemical name is 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl)}-N-(pyridine-2-yl)benzamide.

The chemical structure of acalabrutinib is shown below:



Acalabrutinib is a white to yellow powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH values above 6.

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CALQUENCE capsules for oral administration contains 100 mg acalabrutinib and the following inactive ingredients: silicified microcrystalline cellulose, partially pregelatinized starch, magnesium stearate, and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2 and is imprinted with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acalabrutinib is a small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

12.2 Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg twice daily, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology

The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is the 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent (i.e., ≥ 10 ms).

12.3 Pharmacokinetics

The pharmacokinetics (PK) of acalabrutinib was studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits almost linear PK across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) and exhibits dose-proportionality. The daily area under the plasma drug concentration over time curve (AUC) was 1111 ng•h/mL and maximum plasma concentration (C_{max}) of acalabrutinib was 323 ng/mL.

Absorption

The geometric mean absolute bioavailability of acalabrutinib was 25%. Median time to peak acalabrutinib plasma concentrations (T_{max}) was 0.75 hours.

Effect of Food

In healthy subjects, administration of a single 75 mg dose of acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 73% and T_{max} was delayed 1-2 hours.

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Distribution

Reversible binding of acalabrutinib to human plasma protein was 97.5%. The *in vitro* mean blood-to-plasma ratio was 0.7. The mean steady-state volume of distribution (V_{ss}) was approximately 34 L.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was 6.9 hours.

Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/hr with similar PK between patients and healthy subjects, based on population PK analysis.

Metabolism

Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on *in vitro* studies. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

Excretion

Following administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted as unchanged acalabrutinib.

Specific Populations

Age, Race, and Body Weight

Age (42 to 90 years), sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib, based on population PK analysis.

Renal Impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 368 patients with mild or moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73m^2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment

Acalabrutinib is metabolized in the liver. In a hepatic impairment study, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by less than two-fold in subjects with mild (n=6) (Child-Pugh A) and moderate (n=6) (Child-Pugh B) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in

subjects with mild (n=41) or moderate (n=3) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=527) hepatic function (total bilirubin and AST within ULN). Acalabrutinib PK has not been evaluated in patients with severe hepatic impairment (Child-Pugh C or total bilirubin between 3 and 10 times ULN and any AST).

Drug Interaction Studies

Effect of CYP3A Inhibitors on Acalabrutinib

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased the acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects.

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max} and AUC increased by 2- to almost 3-fold *[see Drug Interactions (7)]*.

Effect of CYP3A Inducers on Acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects *[see Drug Interactions (7)]*.

Gastric Acid Reducing Agents

Acalabrutinib solubility decreases with increasing pH. Co-administration with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43% *[see Drug Interactions (7)]*.

In Vitro Studies

Metabolic Pathways

Acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, and CYP2D6. The active metabolite (ACP-5862) is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6 and CYP3A4/5.

Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; the active metabolite (ACP-5862) weakly induces CYP3A4.

Based on *in vitro* data and PBPK modeling, no interaction with CYP substrates is expected at clinically relevant concentrations.

Drug Transporter Systems

Acalabrutinib is a substrate of P-glycoprotein (P-gp) and BCRP. Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1, and OATP1B3.

Acalabrutinib does not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 at clinically relevant concentrations.

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with acalabrutinib.

Acalabrutinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat bone marrow micronucleus assay.

In a fertility study in rats, there were no effects of acalabrutinib on fertility in male rats at exposures 18-times, or in female rats at exposures 16-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

14 CLINICAL STUDIES

The efficacy of CALQUENCE was based upon Trial LY-004 titled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma" (NCT02213926). Trial LY-004 enrolled a total of 124 patients with MCL who had received at least one prior therapy.

The median age was 68 (range 42 to 90) years, 80% were male, and 74% were Caucasian. At baseline, 93% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 18% with prior stem cell transplant. Patients who received prior treatment with BTK inhibitors were excluded. The most common prior regimens were CHOP-based (52%) and ARA-C (34%). At baseline, 37% of patients had at least one tumor with a longest diameter ≥ 5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 44% and high in 17% of patients.

CALQUENCE was administered orally at 100 mg twice daily until disease progression or unacceptable toxicity. The median dose intensity was 98.5%. Tumor response was assessed according to the Lugano Classification for Non-Hodgkin's lymphoma (NHL). The major efficacy outcome of Trial LY-004 was overall response rate (ORR) and the median follow-up was 15.2 months.

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Table 4: Efficacy Results in Patients with MCL in Trial LY-004

	Investigator Assessed N=124	Independent Review Committee (IRC) Assessed N=124
Overall Response Rate (ORR)*		
Overall Response Rate (%) [95% CI]	81 [73, 87]	80 [72, 87]
Complete Response (CR) (%) [95% CI]	40 [31, 49]	40 [31, 49]
Partial Response (PR) (%) [95% CI]	41 [32, 50]	40 [32, 50]
Duration of Response (DoR)		
Median DoR in months [range]	NR [1+ to 20+]	NR [0+ to 20+]

*Per 2014 Lugano Classification.
CI= Confidence Interval; NR=Not Reached; + indicates censored observations

The median time to best response was 1.9 months.

Lymphocytosis

Upon initiation of CALQUENCE, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count (ALC) increased ≥ 50% from baseline and a post baseline assessment ≥ 5 x 10^9) in 31.5% of patients in Trial LY-004. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 6.7 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Pack Size	Contents	NDC Number
60-count bottle	Bottle containing 60 capsules 100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'	0310-0512-60

Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hemorrhage

Inform patients to report signs or symptoms of severe bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients to report signs or symptoms suggestive of infection *[see Warnings and Precautions (5.2)]*.

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE *[see Warnings and Precautions (5.3)]*.

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer. Advise patients to use sun protection *[see Warnings and Precautions (5.4)]*.

Atrial Fibrillation and Flutter

Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.5)]*.

Dosing Instructions

Instruct patients to take CALQUENCE orally twice daily, about 12 hours apart. CALQUENCE may be taken with or without food. Advise patients that CALQUENCE capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed *[see Dosage and Administration (2.1)]*.

Missed Dose

Advise patients that if they miss a dose of CALQUENCE, they may still take it up to 3 hours after the time they would normally take it. If more than 3 hours have elapsed, they should be instructed to skip that dose and take their next dose of CALQUENCE at the usual time. Warn patients they should not take extra capsules to make up for the dose that they missed *[see Dosage and Administration (2.1)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins and herbal products *[see Drug Interactions (7)]*.

Lactation

Advise women not to breastfeed during treatment with CALQUENCE and for at least 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

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PATIENT INFORMATION

CALQUENCE® (KAL-kwens)

(acalabrutinib)

capsules

What is CALQUENCE?

CALQUENCE is a prescription medicine used to treat adults with mantle cell lymphoma (MCL) who have received at least one prior treatment for their cancer.

It is not known if CALQUENCE is safe and effective in children.

What should I tell my healthcare provider before taking CALQUENCE?

Before taking CALQUENCE, tell your healthcare provider about all of your medical conditions, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop CALQUENCE for any planned medical, surgical, or dental procedure.
- have bleeding problems.
- have or had heart rhythm problems.
- have an infection.
- have or had hepatitis B virus (HBV) infection.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if CALQUENCE passes into your breast milk. Do not breastfeed during treatment with CALQUENCE and for 2 weeks after your final dose of CALQUENCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking CALQUENCE with certain other medications may affect how CALQUENCE works and can cause side effects. Especially tell your healthcare provider if you take a blood thinner medicine.

How should I take CALQUENCE?

- Take CALQUENCE exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking CALQUENCE unless your healthcare provider tells you to.
- Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking CALQUENCE if you develop certain side effects.
- Take CALQUENCE 2 times a day (about 12 hours apart).
- Take CALQUENCE with or without food.
- Swallow CALQUENCE capsules whole with a glass of water. Do not open, break, or chew capsules.
- If you need to take an antacid medicine, take it either 2 hours before or 2 hours after you take CALQUENCE.
- If you need to take certain other medicines called acid reducers (H-2 receptor blockers), take CALQUENCE 2 hours before the acid reducer medicine.
- If you miss a dose of CALQUENCE, take it as soon as you remember. If it is more than 3 hours past your usual dosing time, skip the missed dose and take your next dose of CALQUENCE at your regularly scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of CALQUENCE?

CALQUENCE may cause serious side effects, including:

- **Bleeding problems (hemorrhage)** may happen during treatment with CALQUENCE, and can be serious. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs or symptoms of bleeding, including:
  - blood in your stools or black stools (looks like tar)
  - pink or brown urine
  - unexpected bleeding, or bleeding that is severe or you cannot control
  - vomit blood or vomit that looks like coffee grounds
  - cough up blood or blood clots
  - dizziness
  - weakness
  - confusion
  - changes in your speech
  - headache that lasts a long time
- **Infections** can happen during treatment with CALQUENCE. These infections can be serious and may lead to death. Tell your healthcare provider right away if you have fever, chills, or flu-like symptoms.
- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with CALQUENCE, but can also be severe. Your healthcare provider should do monthly blood tests to check your blood counts.
- **Second primary cancers.** New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin. Use sun protection when you are outside in sunlight.
- **Heart rhythm problems (atrial fibrillation and atrial flutter)** have happened in people treated with CALQUENCE. Tell your healthcare provider if you have any of the following signs or symptoms:
  - your heartbeat is fast or irregular
  - feel lightheaded or dizzy
  - pass out (faint)
  - shortness of breath
  - chest discomfort

The most common side effects of CALQUENCE include:

- headache
- diarrhea
- tiredness
- muscle aches
- bruising

These are not all the possible side effects of CALQUENCE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CALQUENCE?

- Store CALQUENCE at room temperature between 68°F to 77°F (20°C to 25°C).

Keep CALQUENCE and all medicines out of the reach of children.

General information about the safe and effective use of CALQUENCE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CALQUENCE for a condition for which it was not prescribed. Do not give CALQUENCE to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about CALQUENCE that is written for health professionals.

What are the ingredients in CALQUENCE?

Active ingredient: acalabrutinib

Inactive ingredients: silicified microcrystalline cellulose, pregelatinized starch, magnesium stearate, and sodium starch glycolate.

Capsule shell contains: gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2, and black ink.

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For more information, go to www.CALQUENCE.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 10/2017