PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr CALQUENCE®

acalabrutinib capsules

Capsules, 100 mg, Oral

Antineoplastic

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RECENT MAJOR LABEL CHANGES

Not Applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CALQUENCE (acalabrutinib) is indicated for:

- the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and those younger than 65 years. See WARNINGS AND PRECAUTIONS, Special Populations.

2 CONTRAINDICATIONS

CALQUENCE is contraindicated in patients who are hypersensitive to acalabrutinib or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING section of the Product Monograph.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with CALQUENCE should be initiated and supervised by a qualified physician experienced in the use of anticancer therapies.
- Concomitant use of CALQUENCE with a strong CYP3A inhibitor should be avoided (see DRUG INTERACTIONS).
- Serious Haemorrhage: Monitor for bleeding and manage appropriately (see WARNINGS AND PRECAUTIONS, Haemorrhage).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Avoid concomitant use with strong CYP3A4 inhibitors (see DRUG INTERACTIONS).
- Avoid concomitant use with strong CYP3A4 inducers (see DRUG INTERACTIONS).

- Avoid concomitant use with proton pump inhibitors (see DRUG INTERACTIONS).
- Consider the benefit-risk of withholding CALQUENCE for at least 3 days pre-and post-surgery.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose
The recommended dose of CALQUENCE is 100 mg twice daily (equivalent to a total daily dose of 200 mg). Doses should be separated by approximately 12 hours.

Treatment with CALQUENCE should continue until disease progression or unacceptable toxicity.

Dosage Adjustment
Recommended dose modifications of CALQUENCE for Grade ≥3 adverse reactions are provided in Table 1.

Table 1 Recommended Dose Adjustments for Adverse Reactions[a]

Adverse Reaction	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg twice daily)
Grade ≥3 non-haematologic toxicities, or Grade 3 thrombocytopenia with significant bleeding, or 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

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

Recommended dose modifications of CALQUENCE for use with CYP3A inhibitors or gastric acid reducing agents are provided in Table 2.

Table 2 Use with CYP3A Inhibitors or Gastric Acid Reducing Agents

	Co-administered Drug	Recommended CALQUENCE Use
CYP3A Inhibitors	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. Patients should be monitored for adverse reactions.
	Mild CYP3A inhibitor	No dose adjustment. Patients should be monitored for adverse reactions.
Gastric Acid Reducing Agents	Proton Pump Inhibitors	Avoid concomitant use.
	H2-Receptor Antagonists	Take CALQUENCE 2 hours before taking a H2-receptor antagonist.
	Antacids	Separate dosing by at least 2 hours.

Special Populations

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dose adjustment is necessary based on age (see ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: No dose adjustment is recommended in patients with mild to moderate renal impairment (eGFR ≥30 mL/min/1.73m^2 as estimated by MDRD (modification of diet in renal disease equation)).

The pharmacokinetics and safety of CALQUENCE in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end-stage renal disease have not been studied (see ACTION AND CLINICAL PHARMACOLOGY).

Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B, or total bilirubin between 1.5-3 times the upper limit of normal [ULN] regardless of aspartate aminotransferase [AST] levels).

The pharmacokinetics and safety of CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin 3-10 times ULN regardless of AST levels) have not been studied (see ACTION AND CLINICAL PHARMACOLOGY).

4.3 Administration

CALQUENCE should be swallowed whole with water at approximately the same time each day. CALQUENCE can be taken with or without food. The capsule should not be chewed, dissolved, or opened.

4.4 Missed Dose

If a patient misses a dose of CALQUENCE by more than 3 hours, instruct the patient to take the next dose at its regularly scheduled time. Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

5 OVERDOSAGE

There is no specific treatment for CALQUENCE overdose and symptoms of overdose have not been established. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	100 mg acalabrutinib capsule	Ammonium hydroxide, black iron oxide, colloidal silicon dioxide, FD&C Blue 2 (Indigotine/Indigo carmine), gelatine, magnesium stearate, microcrystalline cellulose, partially pregelatinized starch (maize), propylene glycol, shellac, sodium starch glycolate (Type A), titanium dioxide, and yellow iron oxide.

Description
Size 1 hard gelatine capsule with a yellow body and blue cap, marked in black ink with ‘ACA 100 mg’

Packaging
White high density polyethylene (HDPE) plastic bottle, capped with a child-resistant closure containing 60 capsules.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Cardiovascular
Atrial Fibrillation
In patients with haematologic malignancies (n=612) treated with CALQUENCE monotherapy, Grade 1 or 2 atrial fibrillation/flutter have been reported in 1.9% of patients, and Grade 3 in 1.0% of patients.

Haemorrhage
Serious haemorrhagic events, including fatal events, have been reported in patients with haematologic malignancies (n=612) treated with CALQUENCE monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2.0% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in 51.6% of patients with haematological malignancies.

The mechanism for the bleeding events is not well understood. Patients receiving antiplatelet or anticoagulant therapies may be at increased risk of haemorrhage and should be monitored for signs of bleeding (see DRUG INTERACTIONS, Drug-Drug Interactions, Anticoagulant and antiplatelet agents). Consider the benefit-risk of withholding CALQUENCE for at least 3 days pre- and post-surgery.

Carcinogenesis and Mutagenesis
Second Primary Malignancies
Second primary malignancies, including non-skin carcinomas, have been reported in patients with haematologic malignancies treated with CALQUENCE monotherapy. The most frequent second primary malignancy was skin cancer, reported in 6.5% of patients.

Driving and Operating Machinery
CALQUENCE has no or negligible influence on the ability to drive and use machines. However, during treatment with acalabrutinib fatigue and dizziness have been reported and patients who experience these symptoms should observe caution when driving or using machines.

Haematologic
Cytopenias
Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia and thrombocytopenia based on laboratory measurements, occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy (see Monitoring and Laboratory Tests).

Immune
Infections
Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, have been reported in patients with haematologic malignancies treated with CALQUENCE monotherapy. 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.

Monitoring and Laboratory Tests

- Monitor complete blood counts as per routine clinical practice.
- Monitor for atrial fibrillation and atrial flutter and manage as appropriate.
- Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Sexual Health
Fertility
There are no data on the effect of CALQUENCE on human fertility.

7.1 Special Populations

7.1.1 Pregnant Women

CALQUENCE should not be used during pregnancy and women of childbearing potential should be advised to avoid becoming pregnant while receiving CALQUENCE. There are very limited clinical data on CALQUENCE use in pregnant women. Based on findings from animal studies, there may be a risk to the foetus from exposure to acalabrutinib during pregnancy. Administration of acalabrutinib to pregnant rabbits at exposures 4-times the human exposure at the recommended dose was associated with reduced foetal growth (see NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is not known whether acalabrutinib is excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed infant or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. A risk to the suckling child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with CALQUENCE and for 2 weeks after receiving the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of CALQUENCE in children and adolescents aged less than 18 years have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): No dose adjustment is necessary based on age (see ACTION AND CLINICAL PHARMACOLOGY). Eighty (65%) of the 124 MCL patients in clinical trials of CALQUENCE were 65 years of age or older, and 32 patients (26%) were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and those younger than 65 years.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of CALQUENCE is based on data from 612 patients with haematologic malignancies receiving acalabrutinib monotherapy at doses ranging from 100 mg twice daily to 200 mg twice daily.

The most common (≥20%) adverse events (AEs) of any grade reported in patients receiving acalabrutinib were headache, diarrhea, fatigue, cough, nausea, contusion, and upper respiratory tract infection.

The majority of adverse events reported were Grade 1 or 2 in severity and generally did not lead to acalabrutinib discontinuation. The most frequently reported (≥2%) serious adverse events (SAEs) included pneumonia (6%) and pyrexia (3%).

Dose reductions and interruptions due to adverse events (AEs) were reported in 3% and 36% of patients, respectively. Discontinuation due to AEs were reported in 6.5% of the patients.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse event information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of CALQUENCE in patients with MCL has been studied in 124 patients at a dose of 100 mg twice daily in a single-arm Phase 2 trial (ACE-LY-004). The median dose intensity was 99%.

The frequencies of treatment-emergent adverse events reported (regardless of causality) in the ACE-LY-004 study have been included in Table 4. The median duration of acalabrutinib treatment in patients with MCL (ACE-LY-004) was 17.3 months.

Table 4 Treatment-emergent adverse events reported at ≥10% incidence (frequencies reported regardless of causality) in ACE-LY-004 Study (100 mg twice daily)

	CALQUENCE (N=124)	
System Organ Class Preferred Term[a]	**All CTCAE[b] Grades**	**CTCAE Grade ≥3[c]**
Blood and lymphatic system disorders		
Anaemia	13%	10%
Neutropenia	10%	10%
Gastrointestinal disorders		
Diarrhoea	36%	3%
Nausea	19%	2%
Constipation	15%	0%
Vomiting	15%	2%
Abdominal Pain[d]	15%	2%
General disorders and administration site conditions		
Asthenia	17%	2%
Fatigue	28%	2%
Pyrexia	16%	0%
Infections and infestations		
Sinusitis	12%	0%
Upper respiratory tract infection	10%	0%
Musculoskeletal and connective tissue disorders		
Myalgia	21%	2%
Nervous system disorders		
Headache	38%	2%
Dizziness	12%	0%
Respiratory, thoracic and mediastinal disorders		
Cough	22%	0%
Dyspnoea	10%	2%
Skin and subcutaneous tissue disorders		
Bruising[d]	21%	0%
Rash[d]	19%	2%

[a] Based on MedDRA version 20.1.
[b] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[c] All events were Grade 3, except one Grade 4 intracranial haemorrhage and one Grade 5 intracranial haematoma.
[d] AEs based on grouping of individual preferred terms (PTs)
Abdominal pain: Any PT containing 'abdominal pain'
Bruising: Any PT containing 'bruise', 'contusion', 'petechiae', or 'ecchymosis'
Rash: Any PT containing 'rash'

Contusion, a common finding in B cell malignancies, was reported at a lower rate in the ACE-LY-004 population (13%) than in the overall safety analysis (N=612) population (23%), while myalgia was reported at a higher rate in the ACE-LY-004 population (21%) than in the overall safety analysis (12.6%) population. Overall, the most commonly reported AEs were consistent between the ACE-LY-004 and overall safety analysis populations.

8.3 Less Common Clinical Trial Adverse Reactions

The following treatment-emergent adverse events (regardless of causality) have been reported in the ACE-LY-004 study (100 mg twice daily) in ≥5% and <10% of patients.

Eye disorders: lacrimation increased (6%), vision blurred (7%)

Gastrointestinal disorders: stomatitis (7%)

General disorders and administration site conditions: peripheral oedema (7%)

Infections and infestations: bronchitis (7%), nasopharyngitis (8%), pneumonia (7%)

Injury, poisoning and procedural complications: fall (6%)

Metabolism and nutrition disorders: decreased appetite (7%)

Musculoskeletal and connective tissue disorders: arthralgia (9%), back pain (9%), muscle spasms (7%), musculoskeletal pain (7%), pain in extremity (7%)

Nervous system disorders: paraesthesia (8%), memory impairment (7%)

Psychiatric disorders: insomnia (8%)

Respiratory, thoracic and mediastinal disorders: epistaxis (6%)

Skin and subcutaneous tissue disorders: erythema (6%)

Vascular disorders: haemorrhage/haematoma* (9%), hypotension (6%)

*AEs based on grouping of individual preferred terms: any preferred term containing 'haemorrhage' or 'haematoma'

8.4 Abnormal Laboratory Findings: Haematologic, Clinical Chemistry and Other Quantitative Data

Haematologic laboratory abnormalities are described in Table 5.

Table 5 Treatment-emergent haematological laboratory abnormalities in ACE-LY-004 Study (N=124)

Haematological Adverse Reaction[a]	All grades	Grade ≥3
Absolute neutrophil count decreased	36%	13%
Haemoglobin decreased	42%	6%
Platelets decreased	44%	11%

[a] Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

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 32% of patients in the ACE-LY-004 trial. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 6.7 weeks.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Serious Drug Interactions
Concomitant use of CALQUENCE with a strong CYP3A inhibitor should be avoided (see DOSAGE AND ADMINISTRATION, Concomitant use of CYP3A Inhibitors).

9.2 Overview

Co-administration of CALQUENCE with strong CYP3A inhibitors may increase acalabrutinib plasma concentrations. Consider alternative therapies that do not have strong inhibition of CYP3A activity in order to prevent an increased risk of toxicity with CALQUENCE.

Co-administration of CALQUENCE with strong CYP3A inducers decreases acalabrutinib plasma concentrations. Consider alternative therapies that do not strongly induce CYP3A activity in order to prevent a reduction of CALQUENCE activity.

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

Increase in gastric pH may decrease acalabrutinib concentrations. Avoid use with proton pump inhibitors. If antacids are used, it is recommended to separate dosing of CALQUENCE by 2 hours. CALQUENCE should be taken 2 hours before the administration of H2 receptor antagonists.

9.3 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Active substances that may increase acalabrutinib plasma concentrations
CYP3A Inhibitors
Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased the acalabrutinib C_{max} and AUC by 3.7-fold and 5.1-fold, respectively, in healthy subjects (N=17).

Consider alternative therapies that do not strongly inhibit CYP3A activity. Alternatively, if the strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, interrupt CALQUENCE.

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max}, and AUC by 2- to almost 3-fold. When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce the acalabrutinib dose to 100 mg once daily.

Active substances that may decrease acalabrutinib plasma concentrations
CYP3A Inducers
Co-administration of a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77%, respectively, in healthy subjects (N=24).

Strong inducers of CYP3A activity (e.g., phenytoin, rifampin, carbamazepine) should be avoided during treatment with CALQUENCE.

Gastric Acid Reducing Medications
Acalabrutinib solubility decreases with increasing pH. Co-administration of acalabrutinib 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%.

If treatment with an acid reducing agent is required, consider using an antacid (e.g., calcium carbonate) or an H2-receptor antagonist (e.g., ranitidine or famotidine). For use with antacids, separate dosing by at least 2 hours. For H2-receptor antagonists, CALQUENCE should be taken 2 hours before their administration.

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

Active substances whose plasma concentrations may be altered by CALQUENCE
CYP3A Substrates
Based on *in vitro* data and PBPK modelling, no interaction with CYP substrates is expected at the clinically relevant concentration (see ACTION AND CLINICAL PHARMACOLOGY).

BCRP Substrates
Based on *in vitro* data, clinically relevant drug-drug interactions with BCRP substrates via

inhibition of intestinal BCRP transport activity cannot be discounted (see ACTION AND CLINICAL PHARMACOLOGY).

Anticoagulant and antiplatelet agents
Use of CALQUENCE in patients receiving antiplatelet or anticoagulant therapies may increase the risk of bleeding (see WARNINGS AND PRECAUTIONS, Haemorrhage).

9.4 Drug-Food Interactions

In healthy subjects, administration of a single 75 mg dose of CALQUENCE from a developmental formulation 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, although C_{max} was decreased by 73% and T_{max} was delayed by 1-2 hours.

In healthy subjects, administration of acalabrutinib with acidic beverages such as orange juice and grapefruit juice decreased AUC by 40% and 17%, respectively, compared to when administered with water.

9.5 Drug-Herb Interactions

Avoid St. John's wort which may unpredictably decrease acalabrutinib plasma concentrations.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Acalabrutinib is a potent, highly selective small-molecule inhibitor of Bruton's tyrosine kinase (BTK), with minimal off-target kinase activity. Bruton's tyrosine kinase is a signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. Acalabrutinib was selected to exhibit high potency against BTK and few interactions with other kinases.

Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK (IC50 ≤ 5 nM) with minimal off-target interactions. In a screen of >380 mammalian wild-type kinases, the only additional kinase interactions at clinically relevant concentrations of acalabrutinib and ACP-5862 were with non-receptor tyrosine kinase (BMX) and erb-b2 receptor tyrosine kinase 4 (ERBB4), with 3- to 4-fold less potency than with BTK.

In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69, inhibited malignant B-cell proliferation and survival, and had minimal activity on other immune cells (T cells and NK cells).

10.2 Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg CALQUENCE 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
In a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover ECG assessment study, single dose administration of acalabrutinib 100 mg and 400 mg (4X maximum recommended single dose) was not demonstrated to have a clinically meaningful effect on the QTcF interval, the QRS duration, or the PR interval in healthy subjects (N=44).

10.3 Pharmacokinetics

The pharmacokinetics (PK) of acalabrutinib were studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits almost linear PK across a dose range of 75 to 250 mg and exhibits dose-proportionality. At the recommended dose of 100 mg twice daily in patients with MCL, the daily area under the plasma drug concentration over time curve (AUC) was 842 ng•h/mL and maximum plasma concentration (C_{max}) of acalabrutinib was 583 ng/mL. The PK of ACP-5862 has not been fully characterized.

Absorption: The absolute bioavailability of acalabrutinib was 25%. The median time to peak acalabrutinib plasma concentrations (T_{max}) was 0.75 hours.

Distribution: Reversible binding of acalabrutinib to human plasma protein was 97.5% and for ACP-5862 was 98.6%. The *in vitro* mean blood-to-plasma ratio was 0.7. The mean steady state volume of distribution (V_{ss}) was approximately 34 L.

Metabolism: *In vitro*, acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major 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.

In vitro, 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 or CYP3A4/5 *in vitro*. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4 mRNA; the active metabolite (ACP-5862) weakly induces CYP3A4.

In vitro, acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3. Acalabrutinib does not inhibit OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 at clinically relevant concentrations.

In vitro, acalabrutinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein BCRP, but does not inhibit P-gp. Acalabrutinib may inhibit intestinal BCRP transport activity (see DRUG INTERACTIONS).

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.

Following administration of a single 100 mg radiolabelled [^{14}C]-acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the faeces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted in urine as unchanged acalabrutinib.

Special Populations and Conditions
Based on population PK analysis, age, sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib.

Pediatrics: No pharmacokinetic studies were performed with acalabrutinib in patients under 18 years of age.

Geriatrics: Based on population pharmacokinetic analysis, age (42 to 90 years) did not have a clinically meaningful effect on the PK of acalabrutinib.

Hepatic Insufficiency: Acalabrutinib is metabolized in the liver. In a dedicated hepatic impairment study, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold and 1.5-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 difference was observed between subjects with mild (n=41) or moderate (n=3) hepatic impairment (total bilirubin between 1.5 to 3 times 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; see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Acalabrutinib undergoes minimal renal elimination. A PK study in patients with renal impairment has not been conducted. Based on population PK analysis, no clinically relevant PK difference was observed in 282 patients with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2 as estimated by MDRD), 86 patients with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2) relative to 226 patients with normal renal function (eGFR greater than or equal to 90 mL/min/1.73m^2). The pharmacokinetics of acalabrutinib is unknown in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical trials (see DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store CALQUENCE at room temperature, between 15°C-30°C, in original bottle.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

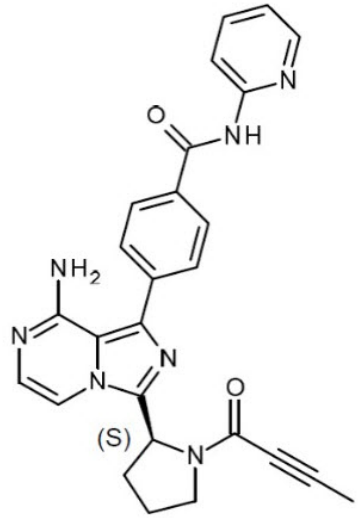
Drug Substance

Proper/Common name: Acalabrutinib

Chemical name: 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl)}-N-(pyridine-2-yl)benzamide

Molecular formula and molecular mass: $C_{26}H_{23}N_7O_2$; 465.51

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

Mantle Cell Lymphoma (MCL)

14.1 Trial Design and Study Demographics

The safety and efficacy of CALQUENCE in patients with MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients (Table 6).

Table 6 Summary of patient demographics for Study ACE-LY-004 (N=124)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ACE-LY-004	Open-label, multi-centre, single-arm Phase 2	100 mg orally twice daily until disease progression or unacceptable toxicity	124	68 (range 42 to 90) years	M: 80% F: 20%

In Study ACE-LY-004, 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 months and the median number of prior treatments was 2 (range 1 to 5), including 18% with prior stem cell transplant. The majority of patients (95%) had previously received rituximab as a single agent or part of a regimen. Common prior regimens included CHOP-based regimen (52%), cytarabine (34%), bendamustine and rituximab-based regimens (22%), and Hyper-CVAD (21%). At baseline, 24% and 76% of patients had refractory and relapsed disease, respectively, and 37% of patients had at least one tumour with a longest diameter ≥5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The Simplified MCL International Prognostic Index (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, and 75% of subject had Ann Arbor Stage IV disease.

Patients were to receive CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity. The median duration of treatment was 17.3 months and the median dose intensity was 98.7%. The median duration of follow-up was 26.3 months.

The trial did not include patients who received prior treatment with BTK inhibitors.

The primary endpoint was investigator-assessed overall response rate (ORR) per the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of Response (DoR) was an additional outcome measure.

14.2 Study Results

The efficacy analysis was conducted at a median follow-up of 26.3 months, and the results are summarized below and presented in Table 7. At time of analysis, 39.5% of patients remained on study. The ORR was 80.6% with a median time to documented response of 1.9 months and a median DoR of 25.7 months.

Table 7 Efficacy Results of Study ACE-LY-004 (N=124) in Patients with Mantle Cell Lymphoma Who Have Received At Least One Prior Therapy

Efficacy Parameter	Investigator Assessed[a] n (%) (95% CI[b])
Overall Response Rate (ORR)[c]	
Overall Response Rate	100 (80.6%) (72.6, 87.2)
Complete Response	53 (42.7%) (33.9, 51.9)
Partial Response	47 (37.9%) (29.3, 47.1)
Stable Disease	11 (8.9%) (4.5, 15.3)
Progressive Disease	10 (8.1%) (3.9, 14.3)
Duration of Response (DoR)	
Median (months)	25.7 (17.5, NE)

CI=Confidence Interval; NE=Not Estimable

[a] Per Lugano classification for non-Hodgkin's lymphoma (Cheson et al. 2014, J.Clin.Oncol.32:3059-3068)

[b] 95% exact binomial confidence interval.

[c] Non-Evaluable: 3 subjects were non-evaluable due to inadequate post-baseline disease assessment.

15 NON-CLINICAL TOXICOLOGY

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Genotoxicity/Mutagenicity

Acalabrutinib was not mutagenic in a bacterial reverse mutation assay, in an *in vitro* chromosome aberration assay, or in an *in vivo* mouse bone marrow micronucleus assay.

Repeat-dose toxicity

Daily oral administration of acalabrutinib for up to 6 months duration in rats and 9 months in dogs, was tolerated at exposure levels that exceed human therapeutic exposures at the recommended dose (4-fold in rats, 14-fold in dogs, based on AUC).

Kidney, liver and heart were identified as the target organs of toxicities in rats and dogs. In rats, liver and kidney findings were observed at exposures 7 times the total clinical exposures. More severe toxicities including cardiac findings were observed in both species at exposures ≥ 12 times the total clinical exposure. Reversibility was demonstrated for liver and kidney findings in both species. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the maximum tolerated dose (MTD).

Toxicology species were exposed to relevant metabolites of acalabrutinib, including the active metabolite ACP-5862.

Reproductive toxicology
No effects on fertility were observed in male or female rats at exposures 18 or 16 times the human AUC exposure at the recommended dose, respectively.

In a combined fertility and embryofoetal 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 embryofoetal 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 foetal rat plasma.

In an embryofoetal study in pregnant rabbits, acalabrutinib was administered orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Acalabrutinib produced no maternal toxicity and no evidence of teratogenicity or foetal development, growth, or survival at doses of 50 mg/kg/day (approximately equivalent to the human AUC exposure at the recommended dose). Decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity (doses ≥ 100 mg/kg/day), which were approximately 4-times greater than the human exposure levels at the recommended dose.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrCALQUENCE®

acalabrutinib capsules

Read this carefully before you start taking **CALQUENCE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CALQUENCE**.

Serious Warnings and Precautions

- Take CALQUENCE only under the care of a doctor who knows how to use anti-cancer drugs.
- **Haemorrhage (serious bleeding problems)** may occur when you take CALQUENCE. This can be bleeding a lot, or bleeding that is difficult to stop.

What is CALQUENCE used for?

CALQUENCE is used to treat patients with a kind of cancer called mantle cell lymphoma (MCL). It is only used in patients who received at least one other MCL therapy before using CALQUENCE.

How does CALQUENCE work?

CALQUENCE blocks a specific protein in the body that helps cancer cells live and grow. This protein is called “Bruton's Tyrosine Kinase.” By blocking this protein, CALQUENCE may help kill and reduce the number of cancer cells and slow the spread of the cancer.

What are the ingredients in CALQUENCE?

Medicinal ingredient: acalabrutinib

Non-medicinal ingredients: ammonium hydroxide, black iron oxide, colloidal silicon dioxide, FD&C Blue 2 (Indigotine/Indigo carmine), gelatine, magnesium stearate, microcrystalline cellulose, partially pregelatinized starch (maize), propylene glycol, shellac, sodium starch glycolate (Type A), titanium dioxide, and yellow iron oxide.

CALQUENCE comes in the following dosage forms:

Capsules:100 mg

Do not use CALQUENCE if:

- You are allergic to acalabrutinib or any other ingredients in CALQUENCE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CALQUENCE. Talk about any health conditions or problems you may have, 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.
- Have severe liver or kidney disease or are on dialysis.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby. Avoid getting pregnant while on CALQUENCE.
- 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.

New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin. Use sun protection when you are outside in sunlight.

Other warnings you should know about:
CALQUENCE is not for use in patients under the age of 18.

Driving and Using Machines: Before you do tasks which may require special attention, wait until you know how you respond to CALQUENCE. If you have blurred vision, feel tired or dizzy, do not drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Before you start any new medication, tell your doctor who prescribed CALQUENCE for you. You must not take CALQUENCE with certain medications. The combination can increase the amount of CALQUENCE in your blood. Your doctor can decide and tell you if it is safe to take the new medication while you are taking CALQUENCE.

The following may interact with CALQUENCE:
- Antibiotics used to treat bacterial infections (clarithromycin, erythromycin, rifampin).
- Medicines for fungal infections (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole).
- Medicines for HIV infection (indinavir, ritonavir).
- Medicines to treat low blood sodium levels (conivaptan).
- Medicines to treat hepatitis C (telaprevir).
- Medicines used to prevent seizures or to treat epilepsy or medicines used to treat a painful condition of the face called trigeminal neuralgia (carbamazepine, phenytoin).
- Medicines to treat acid reflux and stomach ulcers (omeprazole).
- Medicines to lower stomach acid (calcium carbonate, famotidine, ranitidine).
- Medicines used to treat cancer, rheumatoid arthritis and psoriasis (methotrexate).
- Medicines used to treat heart conditions or high blood pressure (diltiazem, verapamil).
- Medicines that may increase your risk of bleeding, including:
    - aspirin and anti-inflammatories such as ibuprofen or naproxen.
    - blood thinners such as warfarin, heparin or other medicines for blood clots such as dabigatran, rivaroxaban, apixaban.
    - supplements such as fish oil, vitamin E and flaxseed.

- An herbal medicine used for depression (St. John's Wort).

How to take CALQUENCE:
- Take it exactly as your healthcare provider tells you.
- If you are on 2 doses a day, take them about 12 hours apart.
- Take at about the same time each day.
- Take with or without food.
- Swallow whole with a glass of water. Do NOT chew, dissolve or open the capsules.

Usual Adult Dose: One capsule twice a day. Do not decrease, stop or change your dose on your own.

If you need to take other medications or develop certain side effects the doctor may tell you to reduce or stop your dose. Sometimes the stop is temporary.

If you need to take:
- **Antacid medicine (for example calcium carbonate):** take it either 2 hours before or 2 hours after you take CALQUENCE.
- **Certain other medicines called acid reducers (for example famotidine or ranitidine)**, take CALQUENCE 2 hours before the acid reducer medicine.

Overdose:

If you think you have taken too much CALQUENCE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
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 possible side effects from using CALQUENCE?
These are not all the possible side effects you may feel when taking CALQUENCE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- tiny red or purple spots on the skin, bruising
- watery eyes
- rash or redness of the skin
- constipation
- decreased appetite
- headache
- dizziness
- tiredness
- falls
- abdominal pain, muscle pain/aches, pain in the arms and legs, back pain
- tingling, pain, or numbness in hands, feet, legs
- sores in mouth
- trouble with falling asleep or staying asleep

- memory loss

CALQUENCE can cause abnormal blood test results. Your doctor may do blood tests before you start CALQUENCE and while you take it. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Infections (from bacteria, a virus or fungus): cough,infection in your nose (sinus infection), sore throat, fatigue, loss of appetite, fever, chills and flu-like symptoms.		√	
Anemia (low red blood cells): Being short of breath. Feeling very tired. Having pale skin. Fast heartbeat. Loss of energy, or weakness.		√	
Neutropenia (low white blood cells, neutrophils): Fever or infection. Fatigue. Aches and pains. Flu-like symptoms.		√	
Nausea and Vomiting: Severe, feeling sick. Severe, being sick or throwing up.	√		
Diarrhea: Increased number of bowel movements. Watery stool. Stomach pain and/or cramps.	√		
New cancers of skin and other types of cancer.		√	
COMMON			
Haemorrhage (serious bleeding problems): Blood in your stool or urine. Long-lasting headache. Feeling dizzy or confused. Nose bleeds. Coughing up blood. Increased bruising.		√	
Pneumonia, Bronchitis (infection in the lungs): Cough with or without mucus. Fever, chills. Shortness of breath that may only occur when you climb stairs. Difficult and painful breathing.		√	
Thrombocytopenia (low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself. Fatigue and weakness.		√	
Arrhythmia (heart rhythm problems): Racing or uncomfortable or irregular heartbeat. Flip-flop feeling in your chest. Feeling dizzy or confused.		√	
Hypotension (low blood pressure): Dizziness, fainting, lightheadedness		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature between 15 to 30°C in original bottle.

Keep out of reach and sight of children.

If you want more information about CALQUENCE:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.canada.ca/en/health-canada.html); the manufacturer's website (www.astrazeneca.ca), or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.

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