▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

CALQUENCE®
(acalabrutinib) capsules

1 NAME OF THE MEDICINE

acalabrutinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg acalabrutinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule, hard.

Size 1 hard gelatin capsule with a yellow body and blue cap, marked in black ink with 'ACA 100 mg'

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CALQUENCE is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

This indication is approved via the **provisional approval** pathway, based on overall response rate. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

CALQUENCE is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with CALQUENCE should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Recommended dosage (18 years and above)

Mantle Cell Lymphoma (MCL)

The recommended dose of CALQUENCE for the treatment of MCL is 100 mg (1 capsule) twice daily.

Chronic Lymphocytic Leukemia (CLL)

The recommended dose of CALQUENCE for the treatment of CLL is 100 mg (1 capsule) twice daily, either as monotherapy or in combination with obinutuzumab. Administer CALQUENCE

prior to obinutuzumab when given on the same day. Refer to the obinutuzumab product information for recommended obinutuzumab dosing information (for details of the combination regimen, see section 5.1 Pharmacodynamic properties).

Doses should be separated by approximately 12 hours.

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

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.

Dose adjustments

Adverse reactions

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

Table 1 Recommended dose adjustments for adverse reactions [a]

Event	**Adverse reaction occurrence**	**Dose modification** *(Starting dose = 100 mg twice daily)*
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with significant bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and second	Temporarily interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline (recovery) level, CALQUENCE therapy may be resumed at 100 mg twice daily.
	Third	Temporarily interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level (recovery), 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

Dose adjustments for use with CYP3A inhibitors or inducers, and gastric acid reducing medicines

Recommended dose adjustments are described in Table 2 below (see also Section 4.5 Interactions with other medicines and other forms of interactions).

Table 2 Use with CYP3A inhibitors or inducers, and gastric acid reducing medicines

	Co-administered medicines	**Recommended CALQUENCE use**
CYP3A inhibitor	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	Reduce CALQUENCE dose to 100 mg once daily.
CYP3A inducer	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg twice daily.
Gastric acid reducing medicines	Proton pump inhibitors	Avoid concomitant use.
	H_2-receptor antagonists	Take CALQUENCE 2 hours before taking a H2-receptor antagonist.

	Co-administered medicines	Recommended CALQUENCE use
	Antacids	Separate dosing by at least 2 hours.

Special patient populations

Renal impairment

No dose adjustment is recommended in patients with mild to moderate renal impairment (estimated Glomerular Filtration Rate (eGFR) ≥30 mL/min/1.73 m^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 <29 mL/min/1.73 m^2) or end-stage renal disease have not been studied (see Section 5.2 Pharmacokinetic properties).

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] and any AST). It is not recommended to administer CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN and any AST) (see Section 5.2 Pharmacokinetic properties).

Severe Cardiac Disease

Patients with severe cardiovascular disease were excluded from CALQUENCE clinical studies.

Use in the elderly

No dose adjustment is necessary based on age (see Section 5.2 Pharmacokinetic properties).

Paediatric use

The safety and efficacy of CALQUENCE in children and adolescents aged less than 18 years have not been established.

Method of 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.

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Serious haemorrhagic events, including fatal events, have occurred in the combined safety database of 1040 patients with hematologic malignancies treated with CALQUENCE monotherapy. Major haemorrhage (Grade 3 or higher bleeding events, serious, or any central nervous system events) occurred in 3.6% of patients, with fatalities occurring in 0.1% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in 46% of patients with haematological malignancies.

The mechanism for the bleeding events is not well understood. Use of antithrombotic agents concomitantly with CALQUENCE may increase the risk of haemorrhage . In CALQUENCE clinical trials, 3% of patients taking CALQUENCE without antithrombotic agents experienced major haemorrhage. The addition of antithrombotic agents increased the percentage to 4.3%.

Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. 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.

Infection

Serious infections (bacterial, viral or fungal), including fatal events have occurred in the combined safety database of 1040 patients with haematologic 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 higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

In the combined safety database of 1040 patients with haematologic malignancies, patients treated with CALQUENCE monotherapy experienced Grade 3 or 4 cytopenias, including neutropenia (21%), anaemia (10%) and thrombocytopenia (7%) based on laboratory measurements. Monitor complete blood counts as medically appropriate during treatment.

Second primary malignancies

Second primary malignancies, including non-skin cancers, occurred in 12% of patients with haematologic malignancies treated with CALQUENCE monotherapy in the combined safety database of 1040 patients. The most frequent second primary malignancy was skin cancer, which occurred in 7% of patients. Monitor patients for the appearance of skin cancers. Advise protection from sun exposure.

Atrial fibrillation and flutter

In the combined safety database of 1040 patients with haematologic malignancies treated with CALQUENCE monotherapy, Grade 3 atrial fibrillation and atrial flutter occurred in 1% of patients and Grade 1 or 2 in 3% of patients. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as appropriate.

Use in the elderly

Of the 1040 patients in clinical trials of CALQUENCE monotherapy, 41% were ≥65 years of age and less than 75 years of age, and 22% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger.

Paediatric use

The safety and efficacy of CALQUENCE in children and adolescents aged less than 18 years have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with CYP3A inhibitors and inducers, or gastric acid reducing medicines

The clinical impact and prevention or management of interactions with CYP3A inhibitors or inducers, or gastric acid reducing medicines are provided below in Table 3 and Table 4 respectively. See also Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties.

Table 3 Interactions with other medicines – CYP3A inhibitors and inducers

Strong CYP3A Inhibitors	
Clinical impact	Co-administration of CALQUENCE with a strong CYP3A inhibitor (e.g. itraconazole) increased acalabrutinib plasma concentrations. 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
Moderate CYP3A Inhibitors	
Clinical impact	Co-administration of CALQUENCE with a moderate CYP3A inhibitor (e.g. diltiazem, erythromycin, fluconazole) may increase acalabrutinib plasma concentrations. 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 (e.g. rifampin) decreased acalabrutinib plasma concentrations 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.

Table 4 Interactions with other medicines – Gastric acid reducing medicines

Clinical impact	Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations 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
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist
	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.

Effects of acalabrutinib and its active metabolite, ACP-5862, on CYP450 and UGT enzymes

In vitro data indicate no relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A2 or UGT2B7 by acalabrutinib or ACP-5862 at therapeutic concentrations. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; ACP-5862 weakly induces CYP3A4.

Effects of acalabrutinib and its active metabolite, ACP-5862, on drug transport systems

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

ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

In vitro, acalabrutinib and ACP-5862 are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3. ACP-5862 is not a substrate of OATP1B1 or OATP1B3. Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and MATE2-K at clinically relevant concentrations.

Effect of food on acalabrutinib

In healthy subjects, administration of a single 75 mg dose of acalabrutinib 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a fertility study in rats, there were no effects of acalabrutinib on fertility in male rats at exposures 16-times, or in female rats at exposures 14-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

Use in pregnancy – Category C

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 decreased fetal body weights and delayed skeletal ossification at maternal exposures (AUC) approximately 3.6 times exposures in patients at the recommended dose of 100 mg twice daily. This dose was maternotoxic. Dystocia was observed in a rat study (see below). Advise pregnant women of the potential risk to a fetus.

In a combined fertility and embryofetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting prior to mating through the period of organogenesis. No effects on embryofetal development or 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 a rat reproductive study involving dosing animals from implantation throughout gestation, parturition and lactation, dystocia (prolonged /difficult labour) was observed at ≥100 mg/kg/day, yielding exposures > 3.5-times the clinical exposure at 100 mg twice daily. Dystocia was not observed in rats at 50 mg/kg/day, associated with exposures approximately equivalent to the clinical exposure at 100 mg twice daily

Use in lactation

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Mantle Cell Lymphoma (MCL)

The safety data described in this section reflect exposure to CALQUENCE (100 mg twice daily) in 124 patients with previously treated MCL in ACE-LY-004 (see Section 5.1 Pharmacodynamic properties / *Clinical trials*). 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 anaemia, thrombocytopenia, headache, neutropenia, diarrhoea, fatigue, myalgia, and bruising. Grade 1 severity for the non-haematologic, most common events were as follows: headache (25%), diarrhoea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥3 non-haematological adverse reaction (reported in at least 2% of patients) was diarrhoea.

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

Table 5 and Table 6 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 5 Non-haematologic adverse reactions* in ≥5% (all grades) of patients with MCL in ACE-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		
Diarrhoea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General Disorders		
Fatigue	28	0.8

Body System Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥ 3 (%)
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin & subcutaneous tissue disorders		
Bruising†	21	-
Rash†	18	0.8
Vascular disorders		
Haemorrhage/Haematoma†	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'

† Haemorrhage/haematoma: Includes all PTs containing 'haemorrhage' or 'haematoma'

Table 6 Haematologic adverse reactions reported* in ≥20% of patients with MCL in ACE-LY-004

Haematologic Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥3 (%)
Haemoglobin 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.

Chronic Lymphocytic Leukemia (CLL)

The safety data described below reflect exposure to CALQUENCE (100 mg twice daily) in two randomized controlled clinical trials (ELEVATE-TN and ASCEND) in patients with CLL (see Section 5.1 Pharmacodynamic properties / *Clinical trials*).

The most common adverse reactions (≥ 20%) of any grade were infection, neutropenia, anaemia, thrombocytopenia, headache, diarrhoea, musculoskeletal pain, bruising, and nausea. The most commonly reported Grade ≥ 3 adverse reactions were infection, neutropenia, and anaemia.

ELEVATE-TN (Patients with Previously Untreated CLL)

The safety of CALQUENCE plus obinutuzumab (CALQUENCE+G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomized, multicentre, open-label, phase 3 study, in 526 patients with previously untreated CLL. Details of the study treatment are described in Section 5.1 (Pharmacodynamic properties / *Clinical trials*).

In the CALQUENCE+G arm, adverse events led to regimen discontinuation in 11% of patients and a dose reduction of CALQUENCE in 8% of patients. In the CALQUENCE monotherapy arm, adverse events led to discontinuation in 9% and dose reduction in 3% of patients. In the GClb arm, adverse events led to regimen discontinuation in 14% of patients and a dose reduction of chlorambucil in 28% of patients. There were no dose reductions for obinutuzumab.

The adverse reactions described below in Tables Table 7 and Table 8 reflect exposure to CALQUENCE in the CALQENCE+G and CALQUENCE monotherapy arms with a median duration of exposure of 27.7 months in patients with previously untreated CLL. The median duration of exposure in the GClb arm was 5.6 months.

Table 7 Non-Hematologic Adverse Reactions* in ≥ 5% (All Grades) of Patients with CLL in ELEVATE-TN

Body System Adverse Reaction	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders						
Leukopenia†	33	32	12	11	50	46
Nervous system disorders						
Headache	40	1	37	1	12	0
Dizziness	18	0	12	0	6	0
Gastrointestinal disorders						
Diarrhoea	39	5	35	1	21	2
Nausea	20	0	22	0	31	0
Constipation	14	0	11	0	10	1
Vomiting	14	1	12	1	11	1
Abdominal pain†	12	2	10	0	9	0
General disorders and administration site conditions						
Fatigue	28	2	18	1	17	1
Asthenia	10	1	5	0	6	1
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain†	37	2	32	1	16	2
Arthralgia	22	1	16	1	5	1
Infections and Infestations						
Infection†	69	21	65	14	44	8
Neoplasms benign, malignant and unspecified						
Second Primary Malignancy†	11	4	8	1	4	2
SPM excluding non-melanoma skin†	6	3	3	1	2	1
Non-Melanoma Skin Malignancy†	5	1	6	0	2	1
Skin and subcutaneous tissue disorders						
Bruising†	34	0	26	0	5	0
Rash†	22	2	19	1	7	1
Vascular disorders						
Haemorrhage/Hematoma†	13	1	9	1	4	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Includes multiple ADR terms

Table 8 Hematologic Adverse Reactions* in ≥ 20% of Patients with CLL in ELEVATE-TN

Hematologic Adverse Reactions	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Absolute Neutrophil Count decreased	53	35	24	13	76	50
Haemoglobin decreased	51	11	52	10	53	13
Platelets decreased	51	12	32	3	60	16

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

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) was reported in 2% of patients treated with CALQUENCE+G. No patients experienced TLS in the CALQUENCE monotherapy arm.

Atrial Fibrillation/Atrial Flutter

Atrial Fibrillation/Atrial Flutter was reported in patients treated with CALQUENCE+G and CALQUENCE monotherapy with an incidence of 3% and 4%, respectively, including 1% with ≥ Grade 3 atrial fibrillation/atrial flutter in the CALQUENCE+G arm. No patients experienced ≥ Grade 3 atrial fibrillation/atrial flutter in the CALQUENCE monotherapy arm.

Infusion related reaction

Infusion related reaction was reported in 14% and 40% of patients in the CALQUENCE+G and GClb arms, respectively.

ASCEND (Patients with CLL who received at least one prior therapy)

The safety of CALQUENCE versus investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab was evaluated in a randomized, multicentre, open-label, phase 3 study, in 307 patients with relapsed or refractory CLL. Details of the study treatment are described in Section 5.1 (Pharmacodynamic properties / *Clinical trials*).

In the CALQUENCE arm, adverse events led to discontinuation in 10% and dose reduction in 3% of patients. In patients receiving idelalisib plus rituximab, adverse events led to regimen discontinuation in 9% of patients and a dose reduction of idelalisib in 24%. In patients receiving bendamustine plus rituximab, adverse events led to regimen discontinuation in 9% of patients and a dose reduction of bendamustine in 14% of patients. There were no dose reductions of rituximab.

The adverse reactions described below in Tables Table 9 and Table 10 reflect exposure to CALQUENCE with a median duration of 15.7 months, exposure to idelalisib with a median duration of 11.5 months, exposure to rituximab with a median duration of 5.5 months, and exposure to bendamustine and a median duration of 5.6 months in patients with relapsed or refractory CLL.

Table 9 Non-Hematologic Adverse Reactions* in ≥ 5% (All Grades) of Patients with CLL in ASCEND

Body System Adverse Reaction	CALQUENCE N=154		Idelalisib plus Rituximab N=118		Bendamustine plus Rituximab N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders						
Leukopenia†	21	18	53	49	37	34
Cardiac disorders						
Atrial Fibrillation/Flutter†	5	1	3	1	3	3
Nervous system disorders						
Headache	22	1	6	0	0	0
Dizziness	6	0	3	0	0	0
Gastrointestinal disorders						
Diarrhoea	18	1	47	24	14	0
Nausea	7	0	13	1	20	0
Constipation	7	0	8	0	14	6
Abdominal pain†	8	0	9	1	3	0
General disorders and administration site conditions						
Fatigue	10	1	9	0	23	3
Asthenia	5	1	4	1	9	3
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain†	15	1	15	2	3	0
Arthralgia	8	1	6	0	3	0
Infections and Infestations						
Infection	57	15	65	28	49	11
Neoplasms benign, malignant and unspecified						
Second Primary Malignancy†	12	4	3	0	3	3
SPM excluding non-melanoma skin†	7	3	3	0	3	3
Non-Melanoma Skin Malignancy†	7	1	1	0	0	0
Skin and subcutaneous tissue disorders						
Bruising†	12	0	3	0	0	0
Rash†	7	0	16	3	9	0
Vascular disorders						
Haemorrhage/Hematoma†	13	1	4	1	6	3

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

†Includes multiple ADR terms

Table 10 Hematologic Adverse Reactions* in ≥ 20% of Patients with CLL in ASCEND

Hematologic Adverse Reactions	CALQUENCE N=154		Idelalisib plus Rituximab N=118		Bendamustine plus Ritixumab N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Absolute Neutrophil Count decreased	47	22	79	48	80	40
Haemoglobin decreased	47	15	44	8	57	17
Platelets decreased	33	6	40	13	54	6

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

Tumour Lysis Syndrome

TLS was reported in patients treated with CALQUENCE and idelalisib plus rituximab with an incidence of 1% in both arms. The one patient experiencing TLS treated with CALQUENCE had Grade 3 TLS and bulky disease.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of CALQUENCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Vascular disorders: hypertension

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific treatment for acalabrutinib 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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Acalabrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (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 signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical

studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and tumour growth in mouse xenograft models.

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).

Clinical trials

Mantle cell lymphoma (MCL)

The safety and efficacy of CALQUENCE in MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients. All patients received CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity. 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. Efficacy results are presented in Table 11.

The median age was 68 (range 42 to 90) years, 79.8% were male and 74.2% were Caucasian. At baseline, 92.8% 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 17.7% with prior stem cell transplant. The most common prior regimens were CHOP-based (51.6%) and ARA-C (33.9%). At baseline, 37.1% of patients had at least one tumour with a longest diameter ≥ 5 cm, 72.6% had extra nodal involvement including 50.8% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 43.5% and high in 16.9% of patients. The median dose intensity was 98.5%.

Table 11 Efficacy results in patients with MCL in ACE-LY-004

	Investigator Assessed N=124	**Independent Review Committee (IRC) Assessed N=124**
	n (%) (95% CI*)	**n (%) (95% CI*)**
Overall Response Rate (ORR)[a]		
Overall Response Rate	100 (80.6%) (72.6, 87.2)	99 (79.8%) (71.7, 86.5)
Complete Response	49 (39.5%) (30.9, 48.7)	49 (39.5%) (30.9, 48.7)
Partial Response	51 (41.1%) (32.4, 50.3)	50 (40.3%) (31.6, 49.5)
Stable Disease	11 (8.9%) (4.5, 15.3)	9 (7.3%) (3.4, 13.3)
Progressive Disease	10 (8.1%) (3.9, 14.3)	11 (8.9%) (4.9, 15.3)
Non-Evaluable†	3 (2.4%) (0.5, 6.9)	5 (4.0%) (1.3, 9.2)
Duration of Response (DoR)		
Median (months)	NR [1+ to 20+]	NR [0+ to 20+]

	Investigator Assessed N=124	Independent Review Committee (IRC) Assessed N=124
	n (%) (95% CI*)	n (%) (95% CI*)
Landmark DOR		
12 months estimate (%) (95% CI)	72.1 (61.6, 80.2)	72.3 (61.9, 80.2)
18 months estimate (%) (95% CI)	63.3 (49.4, 74.3)	56.0 (38.2, 70.6)

[a] *Per 2014 Lugano Classification.

CI=Confidence Interval; NR = Not Reached

*95% exact binomial confidence interval.

†Includes subjects without any adequate post-baseline disease assessment

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 ≥5x109) in 31.5% of patients in ACE-LY-004. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 6.7 weeks.

Chronic Lymphocytic Leukemia (CLL)

Patients with Previously Untreated CLL

The safety and efficacy of CALQUENCE in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. Patients received CALQUENCE plus obinutuzumab, CALQUENCE monotherapy, or obinutuzumab plus chlorambucil. Patients 65 years of age or older or between 18 and 65 years of age with coexisting medical conditions were included in ELEVATE-TN. The trial also allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

Patients were randomised in a 1:1:1 ratio into 3 arms to receive

- CALQUENCE plus obinutuzumab (CALQUENCE+G): CALQUENCE 100 mg was administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.
- CALQUENCE monotherapy: CALQUENCE 100 mg was administered twice daily until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was 28 days.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and geographic region (North America and Western Europe versus Other). After confirmed disease progression, 45 patients randomised on the GClb arm crossed over to CALQUENCE monotherapy. Table 12 summarizes the baseline demographics and disease characteristics of the study population.

Table 12 Baseline Patient Characteristics in (ELEVATE-TN) Patients with Previously Untreated CLL

Characteristic	CALQUENCE plus obinutuzumab N=179	CALQUENCE Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Age, years; median (range)	70 (41-88)	70 (44-87)	71 (46-91)
Male; %	62	62	59.9
Caucasian; %	91.6	95	93.2
ECOG performance status 0-1; %	94.4	92.2	94.4
Median time from diagnosis (months)	30.5	24.4	30.7
Bulky disease with nodes ≥ 5 cm; %	25.7	38	31.1
Cytogenetics/FISH Category; %			
17p deletion	9.5	8.9	9
11q deletion	17.3	17.3	18.6
TP53 mutation	11.7	10.6	11.9
Unmutated IGHV	57.5	66.5	65.5
Complex karyotype (≥ 3 abnormalities)	16.2	17.3	18.1
Rai stage; %			
0	1.7	0	0.6
I	30.2	26.8	28.2
II	20.1	24.6	27.1
III	26.8	27.9	22.6
IV	21.2	20.7	21.5

The primary endpoint was progression-free survival (PFS) of CALQUENCE+G arm versus GClb arm as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 28.3 months, PFS by IRC indicated a 90% statistically significant reduction in the risk of disease progression or death for previously untreated CLL patients in the CALQUENCE+G arm compared to the GClb arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 37 deaths: 9 (5%) in the CALQUENCE+G arm, 11 (6.1%) in the CALQUENCE monotherapy arm, and 17 (9.6%) in the GClb arm. Efficacy results are presented in Table 13. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 13 Efficacy Results in (ELEVATE-TN) Patients with CLL

	CALQUENCE plus obinutuzumab N=179	CALQUENCE Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Progression-Free Survival*			
Number of events (%)	14 (7.8)	26 (14.5)	93 (52.5)
PD, n (%)	9 (5)	20 (11.2)	82 (46.3)
Death events (%)	5 (2.8)	6 (3.4)	11 (6.2)
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)
HR† (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-

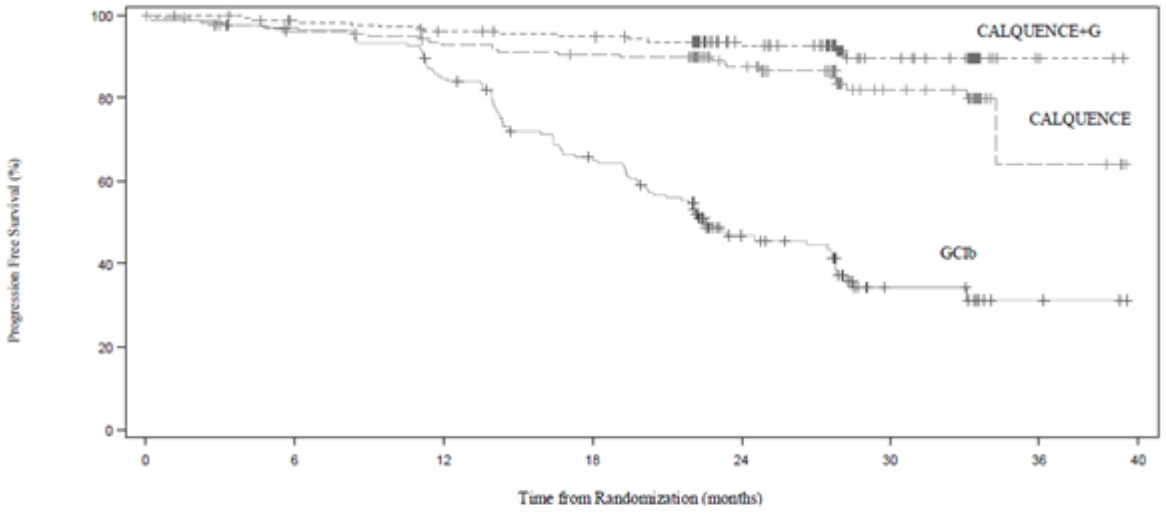
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall Response Rate* (CR + CRi + nPR + PR)			
ORR, n (%) (95% CI)	168 (93.9) (89.3, 96.5)	153 (85.5) (79.6, 89.9)	139 (78.5) (71.9, 83.9)
P-value	< 0.0001	0.0763	-
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)
CRi, n (%)	1 (0.6)	0	0
nPR, n (%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)
PRL, n (%)	0	2 (1.1)	0
SD, n (%)	4 (2.2)	8 (4.5)	15 (8.5)
PD, n (%)	0	3 (1.7)	0
Non-evaluable, n (%)	0	1 (0.6)	8 (4.5)
Unknown, n (%)	6 (3.4)	12 (6.7)	12 (6.8)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response; PRL=PR with lymphocytosis; SD=stable disease; PD=progressive disease

*Per IRC assessment

†Based on stratified Cox-Proportional-Hazards model

Figure 1 Kaplan-Meier Curve of IRC-Assessed PFS in (ELEVATE-TN) Patients with CLL (ITT Population)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
CALQUENCE	179	166	161	157	153	150	148	147	103	94	43	40	4	3
CALQUENCE+G	179	176	170	168	163	160	159	155	109	104	46	41	4	2
GCIb	177	162	157	151	136	113	102	86	46	41	13	13	3	2

PFS results for CALQUENCE with or without obinutuzumab were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV), the PFS HRs of CALQUENCE with or without obinutuzumab

versus obinutuzumab plus chlorambucil was 0.08 [95% CI (0.04, 0.15)] and 0.15 [95% CI (0.09, 0.25)], respectively.

Patients with CLL who received at least one prior therapy

The safety and efficacy of CALQUENCE in relapsed or refractory CLL were evaluated in a randomised, multi-centre, open-label phase 3 study (ASCEND) of 310 patients who received at least one prior therapy. Patients received CALQUENCE monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The trial allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

Patients were randomised 1:1 to receive either:
- CALQUENCE 100 mg twice daily until disease progression or unacceptable toxicity, or
- Investigator's choice:
  - Idelalisib 150 mg twice daily until disease progression or unacceptable toxicity in combination with ≤ 8 infusions of rituximab (375 mg/m2/500 mg/m2) on Day 1 of each 28-day cycle for up to 6 cycles
  - Bendamustine 70 mg/m2 (Day 1 and 2 of each 28-day cycle) in combination with rituximab (375 mg/m2/500 mg/m2) on Day 1 of each 28-day cycle for up to 6 cycles

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and number of prior therapies (1 to 3 versus ≥ 4). After confirmed disease progression, 35 patients randomised on investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab crossed over to CALQUENCE. Table 14 summarizes the baseline demographics and disease characteristics of the study population.

Table 14 Baseline Patient Characteristics in (ASCEND) Patients with CLL

Characteristic	**CALQUENCE monotherapy N=155**	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Age, years; median (range)	68 (32-89)	67 (34-90)
Male; %	69.7	64.5
Caucasian; %	93.5	91.0
ECOG performance status; %		
0	37.4	35.5
1	50.3	51.0
2	12.3	13.5
Median time from diagnosis (months)	85.3	79.0
Bulky disease with nodes ≥ 5 cm; %	49.0	48.4
Median number of prior CLL therapies (range)	1 (1-8)	2 (1-10)
Number of Prior CLL Therapies; %		
1	52.9	43.2
2	25.8	29.7
3	11.0	15.5
≥ 4	10.3	11.6
Cytogenetics/FISH Category; %		

17p deletion	18.1	13.5
11q deletion	25.2	28.4
TP53 mutation	25.2	21.9
Unmutated IGHV	76.1	80.6
Complex karyotype (≥3 abnormalities)	32.3	29.7
Rai Stage; %		
0	1.3	2.6
I	25.2	20.6
II	31.6	34.8
III	13.5	11.6
IV	28.4	29.7

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 16.1 months, PFS indicated a 69% statistically significant reduction in the risk of death or progression for patients in the CALQUENCE Arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 33 deaths: 15 (9.7%) in the CALQUENCE monotherapy arm and 18 (11.6%) in the investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab arm. Efficacy results are presented in Table 15. The Kaplan-Meier curve for PFS is shown in Figure 2.

Table 15 Efficacy Results in (ASCEND) Patients with CLL

	CALQUENCE monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-Free Survival*		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
15 months estimate, % (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
Overall Response Rate* (CR + CRi + nPR + PR)		
ORR, n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
P-value	0.2248	-
CR, n (%)	0	2 (1.3)
PR, n (%)	126 (81.3)	115 (74.2)
PRL, n (%)	11 (7.1)	3 (1.9)
SD, n (%)	9 (5.8)	12 (7.7)
PD, n (%)	2 (1.3)	1 (0.6)
Unknown, n (%)	7 (4.5)	22 (14.2)
Duration of Response (DoR)		

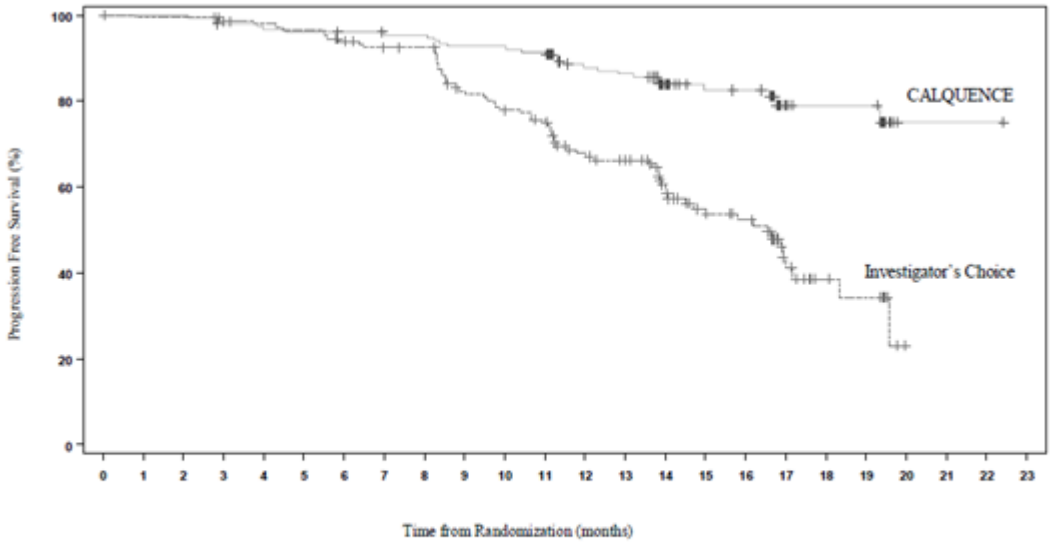
Median (95% CI), months	NR	13.6 (11.9, NR)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; PR=partial response; PRL=PR with lymphocytosis; SD=stable disease; PD=progressive disease

*Per IRC assessment

†Based on stratified Cox-Proportional-Hazards model

Figure 2 Kaplan-Meier Curve of IRC-Assessed PFS in (ASCEND) Patients with CLL (ITT Population)



Number of patients at risk																								
Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
CALQUENCE	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
Investigator's Choice	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			

PFS results for CALQUENCE were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV), the PFS HR was 0.27 [95% CI (0.17, 0.44)].

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862 were studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose). Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 does not differ significantly in patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including MCL and CLL), the geometric mean steady state daily area under the plasma drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (Cmax) of acalabrutinib were 1893 ng•h/mL and 466 ng/mL, respectively, and for ACP-5862 were 4091 ng•h/mL and 420 ng/mL, respectively.

Absorption

The median time to peak plasma concentrations (T_{max}) was 0.75 hours for CALQUENCE, and 1.0 hour for ACP-5862. The absolute bioavailability of CALQUENCE was 25%.

Distribution

Reversible binding to human plasma protein was 97.5% for acalabrutinib and 98.6% for ACP-5862. The in vitro mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The mean steady-state volume of distribution (Vss) was approximately 34 L for acalabrutinib.

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.

Acalabrutinib may inhibit intestinal BCRP substrates (see Section 4.5 Interactions with other medicines and other forms of interactions), while ACP-5862 may inhibit MATE1 (see Section 4.5 Interactions with other medicines and other forms of interactions) at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Excretion

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{½}$) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The median $t_{½}$ of the active metabolite, ACP-5862, was 6.9 hours (range: 2.7 to 9.1) hours.

The mean apparent oral clearance (CL/F) was 70 L/hr for acalabrutinib and 13 L/hr for ACP-5862, 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 2% of the dose excreted as unchanged acalabrutinib in urine and faeces.

Specific populations

Age, race, and body weight

Age (32 to 90 years), sex, race (Caucasian, African American), and body weight (40 to 149 kg) did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862, 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 543 patients with mild or moderate renal impairment (eGFR ≥30 mL/min/1.73 m^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/1.73 m^2, MDRD) or renal impairment requiring dialysis.

Hepatic impairment

Acalabrutinib is metabolized in the liver. In hepatic impairment studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B) and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=79) or moderate (n=6) 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=651) hepatic function (total bilirubin and AST within ULN).

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 Section 4.5 Interactions with other medicines and other forms of interactions).

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 Section 4.5 Interactions with other medicines and other forms of interactions).

Gastric acid reducing medicines

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 Section 4.5 Interactions with other medicines and other forms of interactions).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content: silicified microcrystalline cellulose, pregelatinised starch, magnesium stearate (E572), and sodium starch glycollate Type A.

Capsule: Shell: gelatin, titanium dioxide (E171), iron oxide yellow (E172) and indigo carmine aluminium lake (E132); Ink: shellac, iron oxide black (E172) and propylene glycol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Polyamide-aluminium-polyvinylchloride/aluminium blisters. Cartons of 56 capsules

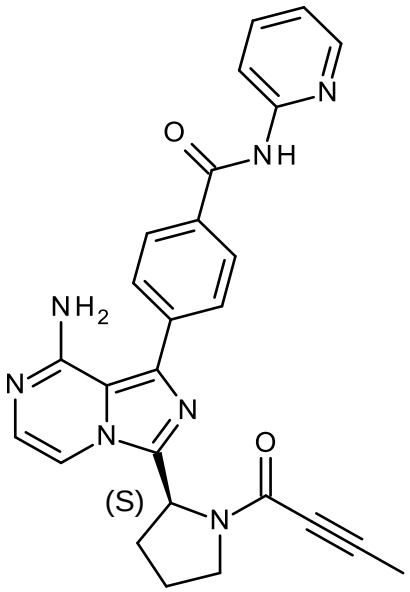
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Figure 3 Chemical structure of acalabrutinib



CAS number

CAS 1420477-60-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

21 November 2019

10 DATE OF REVISION

23 August 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of hypertension in post-marketing experience

CALQUENCE is a registered trade mark of the AstraZeneca group of companies.

© AstraZeneca, 2024

VV-RIM-01436838 v 5.0