▼ 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 [1]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.

[2]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

[3]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.

4.2 [4]DOSE AND METHOD OF ADMINISTRATION

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

[1] 3.2.P.1

[2] 3.2.P.1

[3] As per TGA provisional determination; in line with US PI indication

[4] US PI text or inline with US PI text (note – special populations text located in different sections of the US PI)

Recommended dosage (18 years and above)

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.

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.
	Proton pump inhibitors	Avoid concomitant use.

	Co-administered medicines	Recommended CALQUENCE use
Gastric acid reducing medicines	H_2-receptor antagonists	Take CALQUENCE 2 hours before taking a H2-receptor antagonist.
	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). The pharmacokinetics and safety of CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin 3-10 times ULN and any AST) have not been studied (see Section 5.2 Pharmacokinetic properties).

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 [5]CONTRAINDICATIONS

None.

4.4 [6]SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Serious haemorrhagic events, including fatal events, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported

[5] US PI

[6] The majority of the warnings and precautions text is from the US PI or in line with US PI text. Please note that the safety database numbers differ to the clinical overview/clinical summary documents (and the Core Data Sheet) as they are based on the US 90 Day safety update report (see Module 2.7.4, 90 Day safety update)

in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with haematological malignancies.

The mechanism for the bleeding events is not well understood. CALQUENCE may further increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infection

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

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

Cytopenias

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

Second primary malignancies

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

Atrial fibrillation and flutter

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

Use in the elderly

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

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 [7]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.

[7] US PI text or in line with US PI text

Effects of acalabrutinib on drug transport systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g. methotrexate) by inhibition of intestinal BCRP (see Section 5.2 Pharmacokinetic properties).

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 [8]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 18-times, or in female rats at exposures 16-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

Use in pregnancy – Category C[9]

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

In a combined fertility and embryo-foetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-foetal 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 embryo-foetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased foetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 4-times the AUC in patients at 100 mg twice daily.

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

[8] US PI with Australian pregnancy categorisation.

[9] Australian Pregnancy Category C proposed as while there is evidence of decreased fetal body weight and delayed skeletal ossification, there is no evidence of fetal malformations.

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)

[10]Clinical trials experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The 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 or 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	-

[10] US PI; Module 2.5, Module 2.7.4 and Module 5.3.5.2 Clinical study report (CSR) ACE-LY-004

Body System Adverse Reactions	**CALQUENCE 100 mg twice daily N=124**	
	All Grades (%)	**Grade ≥ 3 (%)**
Vomiting	13	1.6
General Disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin & subcutaneous tissue disorders		
Bruising[†]	21	-
Rash[†]	18	0.8
Vascular disorders		
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.

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

[11]Mechanism of action

Acalabrutinib is a small-molecule inhibitor of Bruton 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 survival.

[12]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).

[13]Clinical trials

[14]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 7.

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),

[11] US PI

[12] US PI

[13] In line with US PI

[14] Module 2.5, Module 2.7.3 and Module 5.3.5.2 CSR ACE-LY-004

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 7 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+]
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.

5.2 [15]PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of acalabrutinib was studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits almost linear PK across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) and exhibits dose-proportionality. At the recommended dose of 100 mg twice daily, the daily area under the plasma drug concentration over time curve (AUC) was 1111 ng•h/mL and maximum plasma concentration (C_{max}) of acalabrutinib was 323 ng/mL.

[15] US PI text, or text consistent with the US PI

Absorption

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

Distribution

Reversible binding of acalabrutinib to human plasma protein was 97.5%. The in vitro mean blood-to-plasma ratio was 0.7. The mean steady-state volume of distribution (Vss) 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.

Interactions with transport proteins

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.

Effects of acalabrutinib on P-gp and BCRP

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

Elimination

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 $t_{½}$ 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 as unchanged acalabrutinib.

[16]Specific populations

Age, race, and body weight

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

Renal impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 368 patients with mild or moderate renal impairment (eGFR ≥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 a hepatic impairment study, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by less than two-fold in subjects with mild (n=6) (Child-Pugh A) and moderate (n=6) (Child-Pugh B) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=41) or moderate (n=3) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=527) hepatic function (total bilirubin and AST within ULN). Acalabrutinib PK has not been evaluated in patients with severe hepatic impairment (Child-Pugh C or total bilirubin between 3 and 10 times ULN and any AST).

Drug interaction studies

Effect of CYP3A inhibitors on acalabrutinib

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

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

[16] US PI

5.3 [17]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 [18]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 [19]SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 [20]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.

[17] US PI

[18] Module 3.2.P.1 with Australian Approved Name (AAN) terminology

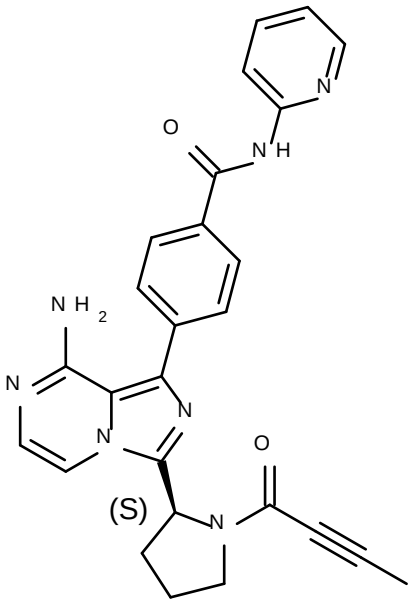
[19] Module 3.2.P.8.1

[20] Module 3.2.P.7

6.7 PHYSICOCHEMICAL PROPERTIES

[21]Chemical structure

Figure 1 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
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9 DATE OF FIRST APPROVAL

21 November 2019

10 DATE OF REVISION

Not applicable.

[21] Module 3.2.S.1.2

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product

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