Proposed packaging material		
Code	Calquence Tablet – PI-01.04	
Submission	☒NDA ☐Renewal ☐Variation change detail no.: RO-Primary Event-0002752-0044	
Code of previous version	N/A	
Changes	2022 NDA Calquence Tablet Submissions	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: AUS PI (Doc ID-005001474) ☒GRL approval: 6 Desember 2022
Name & Date	FTA (2 January 2025)	

CALQUENCE®

acalabrutinib (as maleate)

Tablets

1 NAME OF THE MEDICINE

Calquence, 100 mg, film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains acalabrutinib maleate equivalent to 100 mg of acalabrutinib.

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

3 PHARMACEUTICAL FORM

The CALQUENCE 100 mg film-coated tablet is an orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with 'ACA 100' on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CALQUENCE is indicated as:

- monotherapy or combination with obinutuzumab for the treatment of adult patients with previously untreated CLL / SLL
- monotherapy for the treatment of adult patients with relapsed or refractory CLL who have received at least one prior therapy.

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.

A baseline electrocardiogram should be obtained before treatment to monitor cardiac function.

Recommended dosage (18 years and above)

Chronic Lymphocytic Leukemia (CLL)/Small Lymphotic Lymphoma (SLL)

The recommended dose of CALQUENCE for the treatment of CLL/SLL is 100 mg (1 tablet) 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 tablets 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

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

	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.

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 (uncontrolled or untreated symptomatic arrhythmias, congestive heart failure, or myocardial infarction, or any Class 3 or 4 cardiac disease as defined by the NYHA Functional Classification, or corrected QT interval (QTc)> 480 msec) 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 tablet should not be chewed, crushed, dissolved, or divided.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4 HYPERSENSITIVITY TO THE ACTIVE SUBSTANCE OR TO ANY OF THE EXCIPIENTS.SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Major haemorrhagic events, including central nervous system and gastrointestinal haemorrhage, some fatal outcome, have occurred in patients with hematologic malignancies treated with CALQUENCE monotherapy and in combination with obinutuzumab. These events have occurred in patients both with and without thrombocytopenia. 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. Patients receiving antithrombotic agents may be at increase the risk of haemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Warfarin or other vitamin K antagonists should not be administered concomitantly with Calquence. Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery.

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.

Viral reactivation

Cases of hepatitis B reactivation have been reported in patients receiving Calquence. Hepatitis B virus (HBV) status should be established before initiating treatment with Calquence. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of Calquence within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in

patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected, then appropriate diagnostic evaluations should be undertaken and treatment with Calquence should be suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. 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

Atrial fibrillation/flutter occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with obinutuzumab. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated. In patients who develop atrial fibrillation on therapy with Calquence, a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk for thromboembolic disease, tightly controlled treatment with anticoagulants and alternative treatment options to Calquence should be considered

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

The clinical impact and prevention or management of interactions with CYP3A inhibitors or inducers are provided below in Table 3 . 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.

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 100 mg dose of acalabrutinib tablet 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 54% and T_{max} was delayed 1-2 hours.

Gastric Acid Reducing Medications

Acalabrutinib tablets can be co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids).

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. Clinical trials with acalabrutinib were studied with the acalabrutinib capsule formulation.

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 4 and Table 5 reflect exposure to CALQUENCE in the CALQUENCE+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 4 **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 5 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 6 and Table 7 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 6 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 7 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.

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:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Telepon: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

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.

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

Clinical trials with acalabrutinib were studied with the acalabrutinib capsule formulation.

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 8 summarizes the baseline demographics and disease characteristics of the study population.

Table 8 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 9. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 9 Efficacy Results in (ELEVATE-TN) Patients with CLL

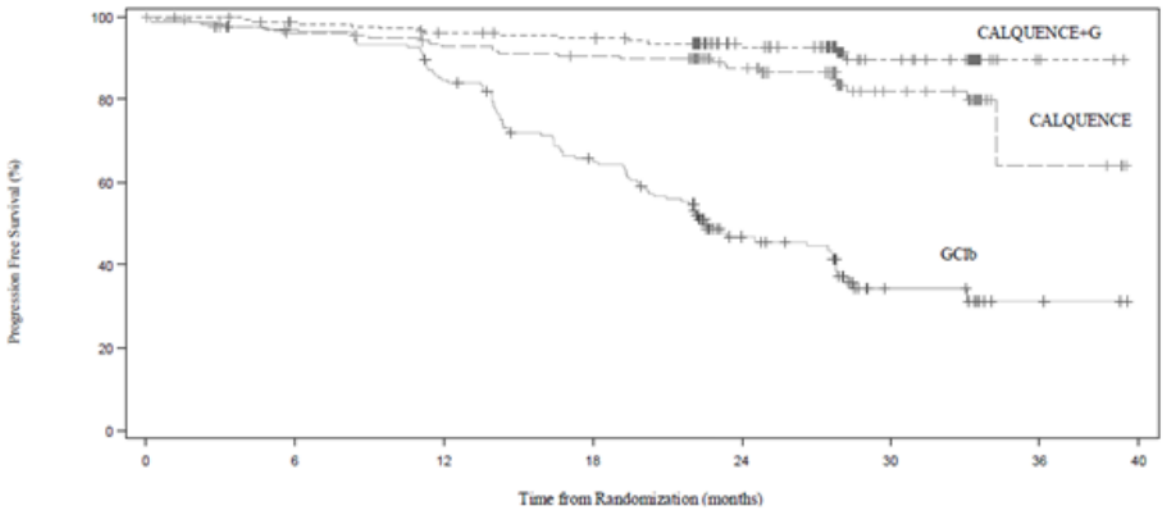
	CALQUENCE plus obinutuzumab N=179	**CALQUENCE Monotherapy N=179**	**Obinutuzumab plus Chlorambucil N=177**
Progression-Free Survival*			
Number of events (%)	14 (7.8)	26 (14.5)	93 (52.5)
PD, n (%)	9 (5)	20 (11.2)	82 (46.3)
Death events (%)	5 (2.8)	6 (3.4)	11 (6.2)
Median (95% CI), months	NR	NR (34.2, 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 10 summarizes the baseline demographics and disease characteristics of the study population.

Table 10 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 11. The Kaplan-Meier curve for PFS is shown in Figure 2.

Table 11 Efficacy Results in (ASCEND) Patients with CLL

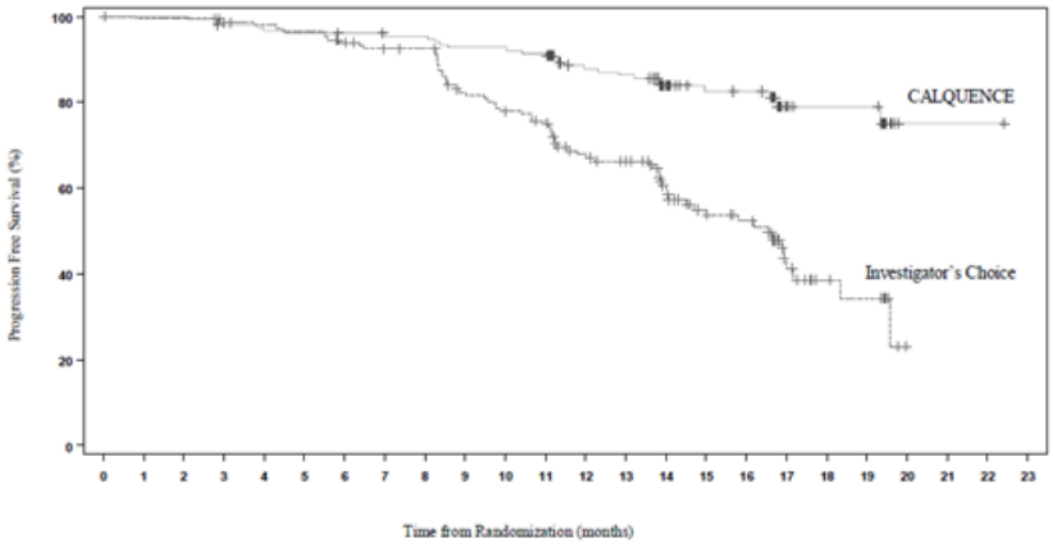
	CALQUENCE monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-Free Survival*		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† (95% 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 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.

CALQUENCE tablets and CALQUENCE capsules have been demonstrated to be bioequivalent. Geometric mean PK exposures (Cmax and AUClast or AUCinf) of acalabrutinib and ACP-5862 were similar (< 4% difference) between the tablet and capsule, with the 90% confidence intervals for geometric mean ratios within the pre-defined bioequivalence margin of 80% and 125%.

Absorption

The median (min-max) time to peak plasma concentrations (T_{max}) was 0.5 (0.2, 3.0) hours for acalabrutinib, and 0.75 (0.5, 4.0) hours for ACP-5862, following administration of acalabrutinib

tablet. The absolute bioavailability of CALQUENCE was 25% following oral administration of acalabrutinib capsule.

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 tablet, the median terminal elimination half-life ($t_{½}$) of acalabrutinib was 1.3 (range: 0.8 to 9.0) hours. The median $t_{½}$ of the active metabolite, ACP-5862, was 7.3 hours (range: 2.5 to 10.1) 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

Co-administration of acalabrutinib tablet with a proton pump inhibitor (20 mg rabeprazole, twice daily for 3 days) increased AUC by 17% (up to 31% increase, based on upper limit of 90% confidence interval) and decreased Cmax by 24% (up to 45% decrease, based on lower limit of 90% confidence interval), with a delay in Tmax (up to 1 hour, approximately).

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

Tablet core: mannitol, microcrystalline cellulose, hyprolose, and sodium stearylfumarate.

Tablet coating: hypromellose, copovidone, titanium dioxide, macrogol 3350, medium chain triglycerides, iron oxide yellow, iron oxide red.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

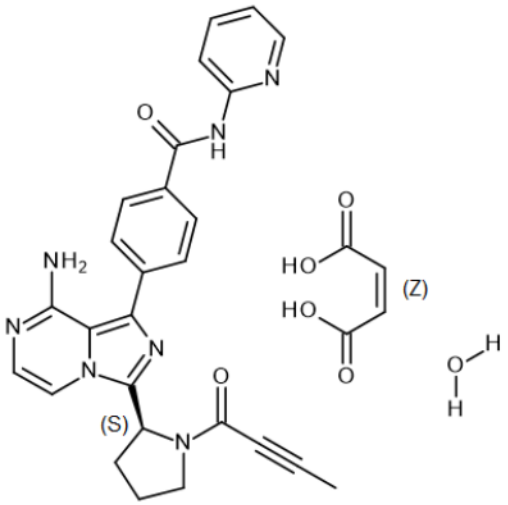
6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure

The chemical name is 4-{8-Amino-3-[(2*S*)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-*a*]pyrazin-1-yl}-*N*-(pyridin-2-yl)benzamide (2*Z*)-2-butenedioic acid hydrate (1:1:1).

Figure 3 Chemical structure of acalabrutinib maleate



Molecular formula: $C_{26}H_{23}N_7O_2.C_4H_4O_4.H_2O$

Molecular weight: 599.59

CAS number

CAS 2641500-53-8

7 PACK SIZE

Box, 7 blisters @ 8 tablets, Reg No: DKIXXXXXXXXXXXXX

Golongan Obat Keras

HARUS DENGAN RESEP DOKTER

Manufactured and released by:

AstraZeneca AB

Gärtunavägen Södertälje

Sweden

Imported by:

PT AstraZeneca Indonesia

Cikarang, Bekasi

Indonesia

DATE OF FIRST AUTHORISATION

2024

DATE OF REVISION OF THE TEXT

2 January 2025

ANGEL Doc ID: Doc ID-005039606

Proposed packaging material		
Code	Calquence Tablet – PIL-01.03	
Submission	☒NDA ☐Renewal ☐Variation change detail no.: TBC	
Code of previous version	N/A	
Changes	2022 NDA Calquence Tablet Submissions	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: AUS CMI (Doc ID-004692079 v1.0) ☒GRL approval: 6 Desember 2022
Name & Date	FTA (2 January 2025)	

CALQUENCE®

acalabrutinib (as maleate)

Tablet Salut Selaput

Brosur ini memberikan informasi penting tentang penggunaan CALQUENCE. Anda bisa menghubungi dokter atau apoteker jika ingin mendapatkan informasi lebih lanjut atau jika Anda memiliki kekhawatiran atau pertanyaan tentang penggunaan CALQUENCE.

Mencari informasi di dalam brosur ini:

1. Mengapa saya mengonsumsi CALQUENCE?

Tablet CALQUENCE mengandung bahan aktif acalabrutinib maleate

CALQUENCE termasuk ke dalam kelompok obat antikanker yang bernama inhibitor Bruton tyrosine kinase (BTK). BTK adalah protein dalam tubuh yang membantu pertumbuhan sel kanker.

CALQUENCE bekerja dengan menghalangi BTK yang dapat membantu mengurangi jumlah sel kanker dan dapat memperlambat penyebaran kanker.

CALQUENCE digunakan untuk mengobati:

Leukemia limfositik kronis (CCL, *Chronic Lymphocytic Leukaemia*) atau limfoma limfositik kecil (SSL, *Small Lymphocytic Lymphoma*) adalah sejenis kanker darah yang menyerang limfosit (salah satu jenis sel darah putih) dan kelenjar getah bening.

- Calquence digunakan secara tunggal ataupun dikombinasi dengan obinutuzumab untuk terapi pasien dewasa dengan Leukomia limfositik kronis atau limfoma limfositik kecil yang sebelumnya belum diobati;
- Calquence digunakan secara tunggal untuk pasien dengan Leukomia Limfositik Kronis yang kambuh atau yang telah menerima setidaknya satu terapi.

2. Apa yang harus saya ketahui sebelum mengonsumsi CALQUENCE?

Jangan gunakan CALQUENCE jika:

- Anda sedang hamil atau sedang merencanakan kehamilan
- Anda sedang menyusui
- Anda alergi terhadap acalabrutinib atau terhadap salah satu bahan yang tercantum di bagian akhir brosur ini.

Beberapa gejala reaksi alergi termasuk:

sesak napas; kesulitan bernapas; pembengkakan di wajah, bibir, lidah, atau bagian tubuh lainnya; ruam atau gatal-gatal kulit.

Tidak terdapat informasi yang cukup untuk merekomendasikan penggunaan obat ini untuk anak-anak atau remaja di bawah usia 18 tahun.

Konsultasikan dengan dokter jika Anda:

- memiliki alergi terhadap obat lain, makanan, pengawet, atau pewarna
- memiliki kondisi medis lain seperti:
    - mengalami memar atau pendarahan yang tidak biasa atau memiliki gangguan pendarahan
    - mengalami infeksi (bakteri, virus, dan/atau jamur);
    - memiliki gangguan fungsi hati
    - memiliki infeksi hati (Hepatitis B) sehingga dokter Anda dapat mengawasi tanda-tanda kambuhnya infeksi tersebut seperti demam, menggigil, lemas, pusing, muntah, dan penyakit kuning (warna kulit dan mata menjadi kuning)
    - mengalami atau pernah mengalami gangguan irama jantung (seperti fibrilasi atrium)
    - memiliki kondisi medis lainnya.
- sedang mengonsumsi obat untuk kondisi medis lain
- baru menjalani operasi atau akan menjalani operasi atau prosedur medis atau gigi.

Selama perawatan, Anda berisiko mengalami efek samping tertentu. Penting untuk memahami risiko dan cara memantaunya. Lihat informasi tambahan di Bagian 6. Apakah terdapat efek samping?

Kehamilan dan menyusui

Konsultasikan dengan dokter jika Anda sedang merencanakan kehamilan.

Anda dilarang mengonsumsi CALQUENCE jika sedang hamil dan Anda tidak boleh hamil saat sedang mengonsumsi CALQUENCE.

CALQUENCE dapat membahayakan bayi Anda yang belum lahir.

Konsultasikan dengan dokter jika Anda sedang menyusui atau berencana untuk menyusui.

Anda dilarang menyusui selama mengonsumsi CALQUENCE.

Belum diketahui apakah CALQUENCE dapat masuk ke dalam ASI Anda. Dilarang menyusui selama Anda sedang dalam pengobatan dengan mengonsumsi CALQUENCE dan setidaknya 2 minggu setelah dosis akhir CALQUENCE.

3. Bagaimana jika saya sedang mengonsumsi obat lain?

Informasikan dokter, perawat, atau apoteker jika Anda sedang mengonsumsi obat lain, termasuk obat, vitamin, atau suplemen apa pun yang Anda beli tanpa resep dari apotek, pasar swalayan, atau toko makanan kesehatan.

Beberapa obat dapat mengganggu CALQUENCE dan memengaruhi cara kerjanya.

- Obat-obatan yang digunakan untuk mengontrol gangguan irama jantung (misalnya amiodaron, diltiazem, verapamil)
- Antibiotik untuk mengobati infeksi bakteri (misalnya klaritromisin, eritromisin, telitromisin, siprofloksasin, rifampisin)
- Obat-obatan untuk infeksi jamur (misalnya flukonazol, posakonazol, ketokonazol, itrakonazol, vorikonazol)
- Obat-obatan untuk infeksi HIV (misalnya ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, darunavir/ritonavir, atau fosamprenavir)
- Obat yang untuk infeksi hepatitis C (misalnya telaprevir)
- Obat-obatan untuk mencegah kejang atau untuk mengobati epilepsi (misalnya karbamazepin, fenitoin)
- St. John's Wort - obat herbal untuk mengobati depresi
- Metotreksat, obat untuk mengobati kanker lainnya atau untuk mengobati gangguan kekebalan tubuh seperti artritis reumatoid atau psoriasis.
- Obat-obatan untuk mengontrol gula darah pasien penderita diabetes (misalnya metformin)

CALQUENCE dapat membuat Anda lebih mudah berdarah. Artinya, Anda harus menginformasikan dokter jika Anda menggunakan obat lain yang meningkatkan risiko pendarahan, termasuk:

- Obat-obatan untuk mengobati rasa sakit dan peradangan (misalnya aspirin dan antiinflamasi nonsteroid [NSAID] seperti ibuprofen)
- Obat-obatan untuk mencegah penggumpalan darah, seperti terapi antiplatelet atau pengencer darah (misalnya aspirin, warfarin).

Konsultasikan dengan dokter atau apoteker jika Anda tidak yakin dengan obat, vitamin, atau suplemen yang Anda konsumsi dan apakah akan memengaruhi kerja CALQUENCE.

4. Bagaimana cara mengonsumsi CALQUENCE?

Dokter telah meresepkan tablet salut selaput CALQUENCE untuk Anda. Mohon diperhatikan jika CALQUENCE juga tersedia dalam bentuk kapsul 100 mg dan tidak boleh ditukar dengan tablet salut selaput CALQUENCE.

Pengobatan dengan CALQUENCE harus diinisiasi dan diawasi oleh dokter yang berpengalaman dalam terapi antikanker. Data terkait Elektrokardiogram harus diketahui sebelum pengobatan dimulai untuk memantau aktivitas jantung

Berapa banyak yang dikonsumsi

- Dosis biasa adalah satu tablet 100 mg dua kali sehari.

Ikuti petunjuk yang diberikan dan gunakan CALQUENCE hingga dokter memberi tahu Anda untuk berhenti. Tanyakan kepada dokter, perawat, atau apoteker jika Anda tidak yakin.

Instruksi mungkin berbeda dari informasi yang diberikan di dalam brosur ini.

Kapan meminum CALQUENCE

- Tablet CALQUENCE harus diminum dengan selang waktu sekitar 12 jam.
- Minum obat pada waktu yang sama setiap hari.
  Meminumnya pada waktu yang sama setiap hari akan memberikan efek terbaik. Cara ini juga akan membantu Anda mengingat kapan harus meminumnya.
  Anda dapat mengetahui kapan terakhir kali meminum tablet CALQUENCE dengan melihat simbol matahari dan bulan di kemasan. Terdapat simbol matahari (untuk pagi hari) dan bulan (untuk malam hari). Simbol tersebut memberi tahu apakah Anda telah meminum dosis Anda.

Penting untuk menginformasikan dokter bahwa Anda mengonsumsi salah satu obat yang disebutkan di bagian 'Mengonsumsi obat lainnya' karena Anda mungkin perlu:

- menghindari untuk mengonsumsi obat-obatan tertentu termasuk obat-obatan yang digunakan untuk mengobati infeksi jamur
- minum obat Anda yang lain pada waktu yang berbeda dengan waktu meminum CALQUENCE
- tambah atau kurangi dosis CALQUENCE Anda untuk sementara waktu tergantung obat lainnya yang sedang Anda konsumsi.

Cara mengonsumsi/meminum CALQUENCE

- Telan tablet secara utuh dengan air. Jangan mengunyah, melarutkan, membagi, atau menghancurkan tablet.
- Anda dapat meminum CALQUENCE dengan atau tanpa makanan.

Jika Anda lupa meminum CALQUENCE

CALQUENCE harus dikonsumsi secara teratur pada waktu yang sama setiap hari.

Jika Anda melewatkan satu dosis lebih dari 3 jam, lewati dosis yang terlewat dan minum dosis selanjutnya sesuai dengan waktunya.

Jangan meminum dosis ganda untuk mengganti dosis yang terlewat.

Jika Anda terlalu banyak mengonsumsi CALQUENCE

Jika Anda merasa telah mengonsumsi terlalu banyak CALQUENCE, Anda memerlukan perhatian medis segera.

Anda harus segera:

- hubungi dokter, atau
- pergi ke Unit Gawat Darurat di rumah sakit terdekat.

Anda perlu melakukan tindakan tersebut meskipun tanpa tanda-tanda ketidaknyamanan atau keracunan.

5. Apa yang harus saya ketahui saat mengonsumsi CALQUENCE

Hal-hal yang harus Anda lakukan

- Anda harus berhati-hati untuk melindungi diri dari sinar matahari.
- Jika Anda akan melakukan pengobatan baru, ingatkan dokter, perawat, dan apoteker bahwa Anda sedang mengonsumsi CALQUENCE.
- Jika Anda akan menjalani operasi, informasikan ahli bedah atau anestesi bahwa Anda sedang mengonsumsi obat ini.
- Jika Anda akan melakukan tes darah, informasikan dokter dan perawat bahwa Anda sedang mengonsumsi obat ini.
- Simpan semua janji pertemuan dengan dokter sehingga kemajuan Anda dapat diperiksa.

Segera hubungi dokter jika Anda:

- hamil saat sedang mengonsumsi obat ini,

Ingatkan dokter, perawat, dokter gigi, atau apoteker yang Anda kunjungi bahwa Anda sedang mengonsumsi CALQUENCE.

Hal-hal yang tidak boleh Anda lakukan

- Jangan berhenti mengonsumsi obat ini atau mengubah dosisnya tanpa terlebih dahulu memeriksakan diri ke dokter.
- Jangan memberikan obat ini kepada orang lain, meskipun mereka memiliki kondisi yang sama dengan Anda.
- Jangan meminum obat ini setelah melewati tanggal kedaluwarsa yang tercetak di kemasan atau jika kemasan sobek atau terdapat tanda-tanda kerusakan. Jika sudah kedaluwarsa atau kemasannya rusak, kembalikan ke apoteker untuk dibuang

Mengemudi atau menggunakan mesin

Berhati-hatilah sebelum mengemudi atau menggunakan mesin atau alat apa pun sampai Anda tahu bagaimana CALQUENCE dapat memengaruhi Anda.

CALQUENCE dapat menyebabkan pusing, lemas, atau rasa lelah untuk beberapa orang.

Makanan dan minuman

Anda dapat meminum CALQUENCE dengan atau tanpa makanan.

6. Apakah terdapat efek samping?

Semua obat dapat memiliki efek samping. Jika Anda merasakannya, sebagian besar efek samping hanya bersifat ringan dan sementara. Namun, beberapa efek samping mungkin memerlukan perhatian medis.

Lihat informasi di bawah ini dan, jika perlu, tanyakan kepada dokter atau apoteker jika Anda memiliki pertanyaan lebih lanjut tentang efek samping.

Efek samping yang tidak terlalu serius

Efek samping yang tidak terlalu serius	**Apa yang harus dilakukan**
• Infeksi, tanda-tandanya termasuk demam, menggigil, atau gejala mirip flu • sakit kepala • mual, muntah • pusing • sakit perut • diare • sembelit • ruam • memar • berdarah, termasuk mimisan • merasa sangat lelah (keletihan) • nyeri otot dan tulang • nyeri sendi • kanker baru, termasuk kanker kulit Daftar di atas mencakup efek samping yang lebih umum dari obat Anda.	**Konsultasikan dengan dokter jika Anda mengalami efek samping yang tidak terlalu serius tersebut dan Anda merasa khawatir.**

Efek samping yang serius

Efek samping yang serius	**Apa yang harus dilakukan**
• tanda atau gejala pendarahan serius, seperti darah di tinja atau urine atau pendarahan yang	**Segera hubungi dokter atau segera pergi ke Unit Gawat**

berlangsung lama atau tidak dapat dikendalikan. • tanda atau gejala infeksi (jamur, virus, atau bakteri, misalnya pneumonia dan aspergilosis) seperti demam, menggigil, nyeri badan, gejala pilek atau flu, merasa lelah atau sesak napas. • tanda dan gejala masalah jantung (misalnya fibrilasi atrium) seperti rasa tidak nyaman di dada, sesak napas, atau jantung berdebar/perubahan ritme (berdenyut atau berdebar kencang). Daftar di atas mencakup efek samping serius yang mungkin memerlukan perhatian medis.	**Darurat di rumah sakit terdekat jika Anda mengalami salah satu dari efek samping serius tersebut.**

Informasikan dokter atau apoteker jika Anda mengalami kondisi lainnya yang mungkin membuat Anda merasa tidak enak badan.

Efek samping lainnya yang tidak tercantum dapat dialami oleh beberapa orang.

Seperti obat kanker lainnya, kanker baru seperti kanker kulit dapat dialami oleh pasien yang mengonsumsi CALQUENCE.

Beberapa efek samping juga dapat ditemukan saat dokter atau perawat melakukan pemeriksaan darah secara rutin. Efek sampingnya termasuk:

- penurunan jumlah sel darah putih (neutropenia).
- penurunan jumlah sel darah merah (anemia).
- penurunan jumlah trombosit yang merupakan sel yang membantu darah Anda menggumpal (trombositopenia).
- kondisi yang disebut dengan sindrom lisis tumor (TLS) yang diakibatkan oleh tingkat bahan kimia di dalam darah yang tidak biasa akibat hancurnya sel kanker secara cepat yang terjadi selama pengobatan kanker dan bahkan dapat terjadi saat tidak menerima pengobatan. Tanda-tanda TLS adalah perubahan fungsi ginjal, detak jantung yang tidak normal, atau kejang.

Melaporkan efek samping

Setelah mendapatkan saran medis untuk setiap efek samping yang dialami, Anda dapat melaporkan efek samping tersebut ke tenaga kesehatan. Dengan melaporkan efek samping tersebut, Anda membantu memberikan lebih banyak informasi tentang keamanan obat ini.

Selalu pastikan Anda berkonsultasi dengan dokter atau apoteker sebelum Anda memutuskan untuk berhenti mengonsumsi obat apa pun.

7. Rincian Produk

Seperti apa bentuk CALQUENCE

Tablet salut selaput CALQUENCE 100 mg berwarna oranye, 7,5 x 13 mm, oval, tablet bikonveks, dengan tulisan 'ACA 100' di satu sisi dan polos di sisi lainnya.

CALQUENCE tersedia dalam dus berisi 7 blister yang masing-masing berisi 8 tablet (total 56 tablet dalam dus).

Apa yang terkandung dalam CALQUENCE

Bahan aktif **(bahan utama)**	acalabrutinib maleate
Bahan-bahan lainnya **(bahan tidak aktif)**	mannitol microcrystalline cellulose hyprolose

	sodium stearylfumarate hypromellose copovidone titanium dioxide macrogol 3350 lemak jenuh rantai sedang besi oksida kuning besi oksida merah air yang dimurnikan

Jangan mengonsumsi obat ini jika Anda alergi terhadap salah satu bahan.

Obat ini tidak mengandung laktosa, sukrosa, gluten, tartrazin, atau pewarna azo lainnya.

Penyimpanan

Simpan di tempat kering dan sejuk dengan suhu di bawah 30 °C. Hindari menyimpan CALQUENCE di tempat lembap, panas, atau terkena sinar matahari langsung; misalnya, jangan menyimpannya di:

- di kamar mandi atau di dekat wastafel, atau
- di dalam mobil atau di ambang jendela.

Simpan di tempat yang tidak dapat dijangkau oleh anak-anak.

Membuang obat yang tidak diperlukan

Jika Anda tidak perlu lagi mengonsumsi obat atau jika obat sudah kedaluwarsa, bawa obat ke apotek untuk dibuang secara aman.

Jangan mengonsumsi obat ini setelah tanggal kedaluwarsa.

Golongan Obat Keras

HARUS DENGAN RESEP DOKTER

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