CALQUENCE

Acalabrutinib

Capsules

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1. NAME OF THE MEDICINAL PRODUCT

CALQUENCE® (acalabrutinib), 100 mg, capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of CALQUENCE contains 100 mg acalabrutinib.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CALQUENCE is indicated 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 Posology 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 Lymphocytic Lymphoma (SLL)

The recommended dose of CALQUENCE for the treatment of CLL is 100 mg (1 capsule) twice daily, either as monotherapy or in combination with obinutuzumab. Administer CALQUENCE prior to obinutuzumab when given on the same day. Refer to the obinutuzumab product information for recommended obinutuzumab dosing information (for details of the combination regimen, see section 5.1 Pharmacodynamic properties).

Doses should be separated by approximately 12 hours.

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

Missed dose

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

Dose adjustments

Adverse reactions

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

Table 1 Recommended dose adjustments for adverse reactions[a]

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

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

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

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

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

	Co-administered medicines	Recommended CALQUENCE use
CYP3A inhibitor	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	Reduce CALQUENCE dose to 100 mg once daily.
CYP3A inducer	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg twice daily.
	Proton pump inhibitors	Avoid concomitant use.
Gastric acid reducing medicines	H2-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). 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 capsule should not be chewed, dissolved, or opened.

4.3 Contraindications

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

4.4 Special warnings and special 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
Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anaemia, and thrombocytopenia occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy and in combination with obinutuzumab. Monitor complete blood counts as medically indicated.

Second primary malignancies
Second primary malignancies, including non-skin cancers, occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy and in the combination with obinutuzumab. Skin cancer were commonly reported. Monitor patients for the appearance of skin cancers and advise protection from sun exposure.

Atrial fibrillation
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

Other medicinal products
Co-administration of strong CYP3A inhibitors with Calquence may lead to increased acalabrutinib exposure and consequently a higher risk for toxicity. On the contrary, coadministration of CYP3A inducers may lead to decreased acalabrutinib exposure and consequently a risk for lack of efficacy. Concomitant use with strong CYP3A inhibitors should be avoided. If these inhibitors will be used short term (such as anti-infectives for up to seven days), treatment with Calquence should be interrupted. Patients should be closely monitored for signs of toxicity if a moderate CYP3A inhibitor is used. Concomitant use with strong CYP3A4 inducers should be avoided due to risk for lack of efficacy

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 Interaction with other medicinal products and other forms of interaction

Acalabrutinib and its active metabolite are primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4), and both substances are substrates for P-gp and breast cancer resistance protein (BCRP).

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.

CYP3A/P-gp inhibitors
Concomitant use with strong CYP3A/P-gp inhibitors should be avoided. If the strong CYP3A/P-gp inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, treatment with Calquence should be interrupted.

CYP3A Inducers
Concomitant use with strong inducers of CYP3A activity (e.g., phenytoin, rifampicin, carbamazepine) should be avoided. Concomitant treatment with St. John's wort, which may unpredictably decrease acalabrutinib plasma concentrations, should be avoided.

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.

Gastric acid reducing medicinal products
Acalabrutinib solubility decreases with increasing pH. Co-administration of acalabrutinib with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43%.

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.

CYP3A substrates
Based on in vitro data, it cannot be excluded that acalabrutinib is an inhibitor of CYP3A4 at the intestinal level and may increase the exposure of CYP3A4 substrates sensitive to gut CYP3A metabolism. Caution should be exercised if co-administering acalabrutinib with CYP3A4 substrates with narrow therapeutic range administered orally (e.g. cyclosporine, ergotamine, pimozide).

Effect of acalabrutinib on CYP1A2 substrates
In vitro studies indicate that acalabrutinib induces CYP1A2. Co-administration of acalabrutinib with CYP1A2 substrates (e.g. theophylline, caffeine) may decrease their exposure

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. To minimise the potential for an interaction in the Gastrointestinal (GI) tract, oral narrow therapeutic range BCRP substrates such as methotrexate should be taken at least 6 hours before or after acalabrutinib

ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1. Patients taking concomitant medicinal products with disposition dependent upon MATE1 (e.g. metformin) should be monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Calquence

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

Effect of food on acalabrutinib

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are no data on the effect of Calquence on human fertility. In a non-clinical study of acalabrutinib in male and female rats, no adverse effects on fertility parameters were observed. 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 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.

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(PatientswithPreviouslyUntreatedCLL)

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

Table 6 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 7 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 8 and Table 9 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 8 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 9 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 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.

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

Table 10 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 11. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 11 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)

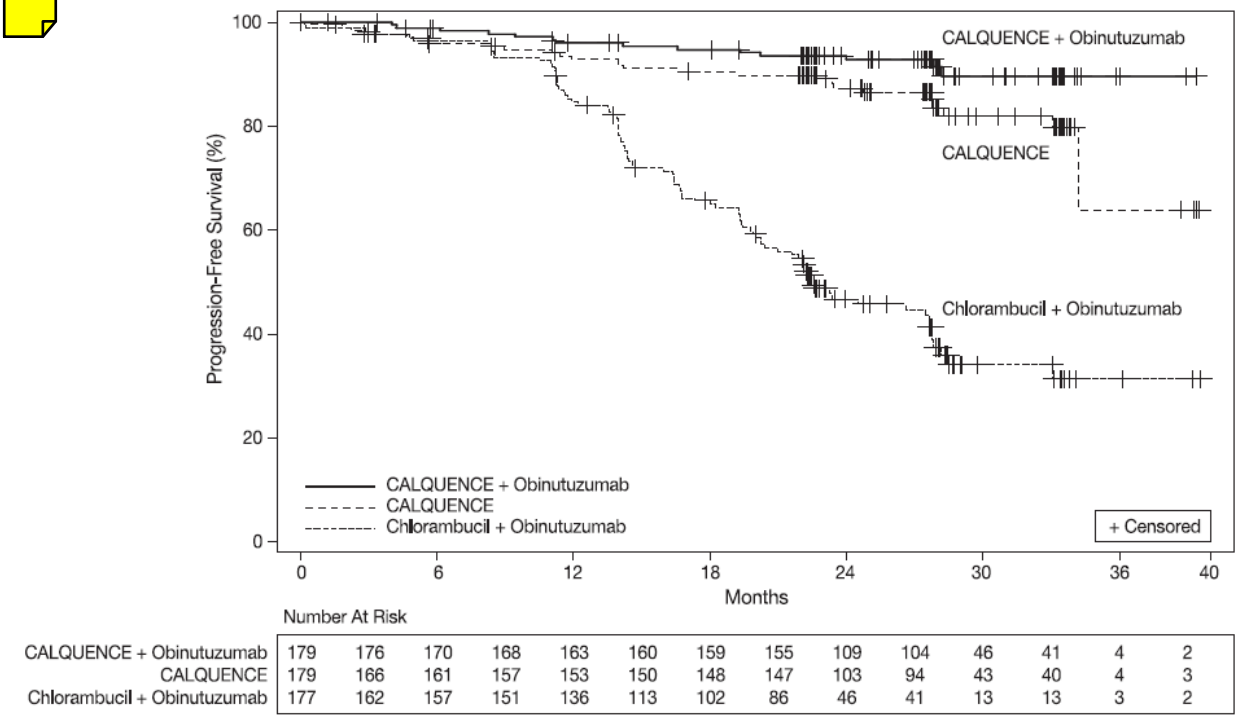
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)
HR† (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall Response Rate* (CR + CRi + nPR + PR)			
ORR, n (%) (95% CI)	168 (93.9) (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)



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.

Table 12. Subgroup analysis of PFS (Study ELEVATE-TN)

	Calquence monotherapy			**Calquence+G**		
	N	**Hazard Ratio**	**95% CI**	**N**	**Hazard Ratio**	**95% CI**
All subjects	179	0.20	(0.13, 0.30)	179	0.10	(0.06, 0.17)
Del 17P Yes No	 19 160	 0.20 0.20	 (0.06, 0.64) (0.12, 0.31)	 21 158	 0.13 0.09	 (0.04, 0.46) (0.05, 0.17)
TP53 mutation Yes No	 19 160	 0.15 0.20	 (0.05, 0.46) (0.12, 0.32)	 21 158	 0.04 0.11	 (0.01, 0.22) (0.06, 0.20)
Del 17P or/and TP53 mutation Yes No	 23 156	 0.10 0.10	 (0.03, 0.34) (0.05, 0.18)	 25 154	 (0.03, 0.34) (0.05, 0.18)	 (0.09, 0.48) (0.21, 0.61)

IGHV mutation						
Mutated	58	0.69	(0.31, 1.56)	74	0.15	(0.04, 0.52)
Unmutated	119	0.11	(0.07, 0.19)	103	0.08	(0.04, 0.16)
Del 11q						
Yes	31	0.07	(0.02, 0.22)	31	0.09	(0.03, 0.26)
No	148	0.26	(0.16, 0.41)	148	0.10	(0.05, 0.20)
Complex Karyotype						
Yes	31	0.10	(0.03, 0.33)	29	0.09	(0.03, 0.29)
No	117	0.27	(0.16, 0.46)	126	0.11	(0.05, 0.21)

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

Table 13 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 14. The Kaplan-Meier curve for PFS is shown in Figure 2.

Table 14 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

With long term data, the median follow-up was 22.1 months for Calquence and 21.9 months for the IR/BR. The median PFS was not reached in Calquence and was 16.8 months in IR/BR. The hazard ratio of INV-assessed PFS of Calquence compared with IR/BR was 0.27 [95% CI, 0.18 to 0.40] representing a 73% reduction in the risk of death or progression for patients in the Calquence arm. Efficacy results per Investigator Assessments (INV) are presented in Table 15.

Table 15 Long term follow-up efficacy results per INV assessments 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 (%)	35 (22.6)	90 (58.1)
PD, n (%)	23 (14.8)	79 (51)
Death events (%)	12 (7.7)	11 (7.1)
Median (95% CI), months	NR	16.8
HR† (95% CI)	0.27	
21 months estimate, % (95% CI)	79.1	45.3
Overall survival[a]		

Death events (%)	21	26
Hazard Ratio (95% CI) †	0.78	-
Best overall response rate* (CR + CRi + nPR + PR)**		
ORR, n (%)	124 (80)	130 (83.9)
P-value	0.3516	-
CR, n (%)	5 (3.2)	6 (3.9)
PR, n (%)	114	122 (78.7)
Duration of Response (DoR)		
Median (95% CI), months	NR	18 (11.9, 19.8)

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; PD=progressive disease

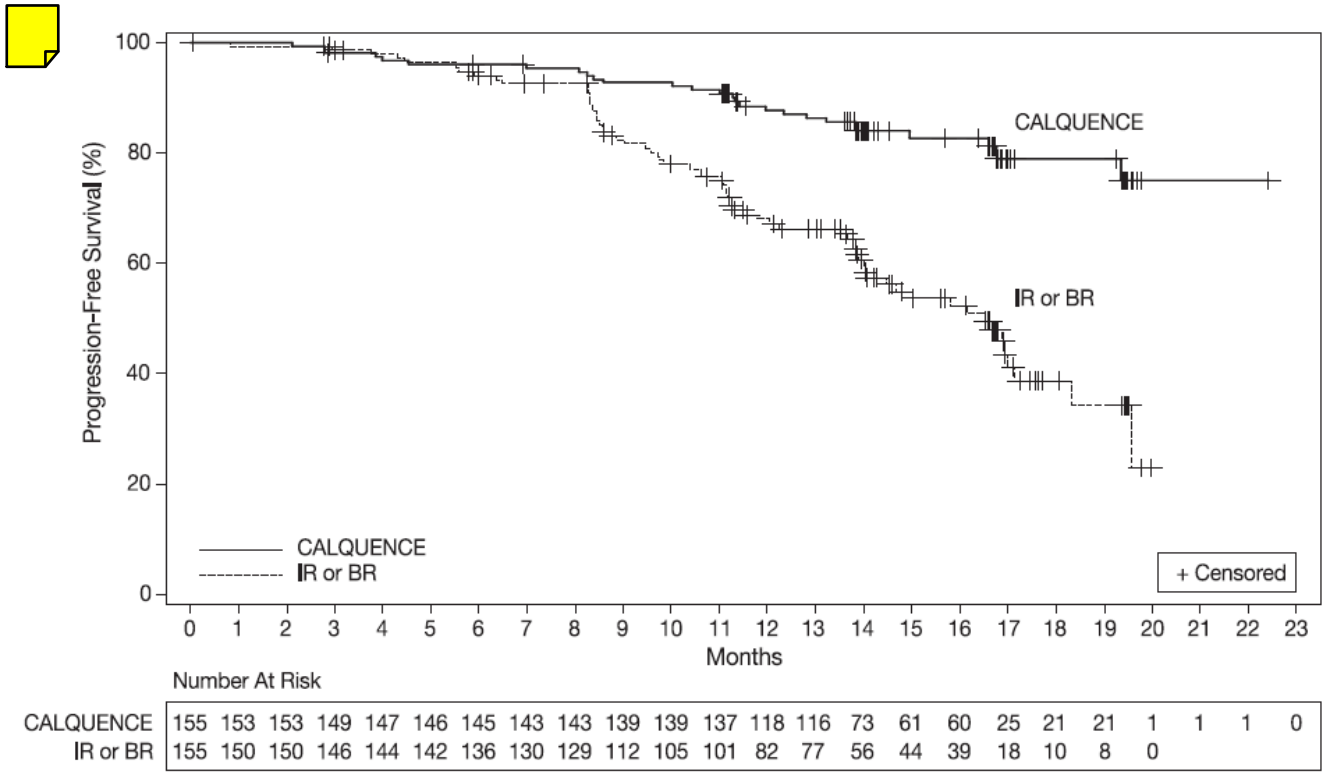
*Per INV assessment

[a] Median OS not reached for both arms P<0.4094 for OS.

**CRi and nPR have values of 2 and 5.

†Based on stratified Cox-Proportional-Hazards model

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



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)].

Table 16 Subgroup analysis of PFS (Study ASCEND)

	Calquence monotherapy		
	N	**Hazard Ratio**	**95% CI**
All subjects	155	0.27	(0.18, 0.40)
Del 17P Yes No	 28 127	 0.18 0.30	 (0.07, 0.43) (0.19, 0.47)
TP53 mutation Yes No	 39 113	 0.17 0.33	 (0.08, 0.37) (0.21, 0.52)
Del 17P or TP53 mutation Yes No	 45 108	 0.16 0.34	 (0.08, 0.34) (0.22, 0.55)
IGHV mutation Mutated Unmutated	 33 118	 0.30 0.28	 (0.12, 0.76) (0.18, 0.43)
Del 11q Yes No	 39 116	 0.35 0.26	 (0.16, 0.75) (0.16, 0.41)
Complex Karyotype Yes No	 50 97	 0.28 0.25	 (0.15, 0.53) (0.15, 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 (CLL), the geometric mean steady state daily area under the plasma drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) of acalabrutinib were 1893 ng•h/mL and 466 ng/mL, respectively, and for ACP-5862 were 4091 ng•h/mL and 420 ng/mL, respectively.

Absorption

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

Distribution

Reversible binding to human plasma protein was 97.5% for acalabrutinib and 98.6% for ACP-5862. The in

vitro mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The mean steady-state volume of distribution (Vss) was approximately 34 L for acalabrutinib.

Metabolism

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

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

Excretion

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life (t½) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The median t½ of the active metabolite, ACP- 5862, was 6.9 hours (range: 2.7 to 9.1) hours.

The mean apparent oral clearance (CL/F) was 70 L/hr for acalabrutinib and 13 L/hr for ACP-5862, with similar PK between patients and healthy subjects, based on population PK analysis.

Following administration of a single 100 mg radiolabelled [^{14}C]-acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the faeces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged acalabrutinib in urine and faeces.

Specific populations

Age, race, and body weight

Age (32 to 90 years), sex, race (Caucasian, African American), and body weight (40 to 149 kg) did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862, based on population PK analysis.

Renal impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 543 patients with mild or moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR <29 mL/min/1.73 m^2, MDRD) or renal impairment requiring dialysis.

Hepatic impairment

Acalabrutinib is metabolized in the liver. In hepatic impairment studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B) and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=651) hepatic function (total bilirubin and AST within ULN).

Drug interaction studies

Effect of CYP3A inhibitors on acalabrutinib

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

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib Cmax and AUC increased by 2- to almost 3-fold (see Section 4.5 Interactions with other medicines and other forms of interactions).

Effect of CYP3A inducers on acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects (see Section 4.5 Interactions with other medicines and other forms of interactions).

Gastric acid reducing medicines

Acalabrutinib solubility decreases with increasing pH. Co-administration with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43% (see Section 4.5 Interactions with other medicines and other forms of interactions).

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Genotoxicity/Mutagenicity/Phototoxicity

Acalabrutinib was not mutagenic in an *in vitro* bacterial reverse mutation assay, in an in vitro chromosome aberration assay or in an in vivo mouse bone marrow micronucleus assay. Acalabrutinib was found to have a possible phototoxic potential in an in vitro phototoxicity assay using 3T3 cell line.

Repeat-dose toxicity

In rats, microscopic findings of minimal to mild severity were observed in the pancreas (hemorrhage/pigment/inflammation/ fibrosis in islets) at all dose levels. Non-adverse findings of minimal to mild severity in the kidneys (tubular basophilia, tubular regeneration, and inflammation) were observed in studies of up to 6-month duration with a No Observed Adverse Effect level (NOAEL) of 30 mg/kg/day in rats. The mean exposures (AUC) at the NOAEL in male and female rats correspond to 0.6x and 1x, respectively, the clinical exposure at the recommended dose of 100 mg twice daily, respectively. The Lowest Adverse Observed Effect Level (LOAEL) at which reversible renal (moderate tubular degeneration) and liver (individual hepatocyte necrosis) findings were observed in the chronic rat study was 100 mg/kg/day and provided an exposure margin 4.2 times greater than the clinical exposure at the recommended dose of 100 mg twice daily. In studies of 9 months duration in dogs, the NOAEL was 10 mg/kg/day corresponding to an exposure 3x the clinical AUC at the recommended clinical dose. Minimal tubular degeneration in kidney, slight decreases in spleen weights and transient minimal to mild decreases in red cell mass and increases in ALT and ALP were observed at 30 mg/kg/day (9x the clinical AUC) in dogs. Cardiac toxicities in rats (myocardial haemorrhage, inflammation, necrosis) and dogs (perivascular/vascular inflammation) were observed only in animals that died during studies at doses above the maximum tolerated dose (MTD). The exposures in rats and dogs with cardiac findings was at least 6.8 times and 25 times the clinical AUC, respectively. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the MTD.

Reproductive toxicology
No effects on fertility were observed in male or female rats at exposures 10 or 9 times the clinical AUC at the recommended dose, respectively.

No effects on embryofoetal development and survival were observed in pregnant rats, at exposures approximately 9 times the AUC in patients at the recommended dose of 100 mg twice daily. In two rat reproductive studies, dystocia (prolonged/difficult labour) was observed at exposures >2.3 times the clinical exposure at 100mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma. Acalabrutinib and its active metabolite were present in the milk of lactating rats.

In an embryofoetal study in pregnant rabbits, decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity which were 2.4 times greater than the human AUC at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Silicified microcrystalline cellulose
Pregelatinised starch
Magnesium stearate (E572)
Sodium starch glycollate Type A.

Capsule
Shell:
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)

Ink:
Shellac
Iron oxide black (E172)
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
36 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Polyamide-aluminium-polyvinylchloride/aluminium blisters. Cartons of 56 capsules.

6.6 Instructions for use, handling and disposal
Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7. PACK SIZE
Box, 7 blisters @ 8 capsule, Reg No: DKI2151304101A1

HARUS DENGAN RESEP DOKTER

Manufactured and released by:

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi
Indonesia

DATE OF FIRST AUTHORISATION

10 December 2021

DATE OF REVISION OF THE TEXT

5 September 2023
ANGEL Doc ID: Doc ID-004277301

Leaflet Informasi Pasien
CALQUENCE
Acalabrutinib

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakanlah dokter, apoteker, atau perawat Anda
- Obat ini diresepkan khusus hanya untuk Anda. Jangan berikan pada orang lain. Obat ini dapat membahayakan mereka walaupun tanda-tanda penyakit yang mereka miliki sama dengan Anda.
- Jika Anda mengalami efek samping, beritahu dokter, apoteker, ataupun perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi terdapat pada leaflet ini. Lihat bagian 4.

Leaflet ini berisi informasi mengenai:

1. CALQUENCE dan kegunaannya

CALQUENCE adalah obat antikanker digunakan pada orang dewasa untuk mengobati:

- Leukemia limfositik kronis/leukemia limfositik kecil, yaitu tipe kanker darah yang menyerang limfosit (salah satu jenis sel darah putih) dan nodus limfa.

CALQUENCE mengandung zat aktif acalabrutinib, yang merupakan kelompok obat antikanker yang disebut penghambat Bruton Tirosin Kinase (BTK). BTK adalah protein di dalam tubuh yang membantu sel kanker untuk berkembang.

CALQUENCE bekerja dengan menghambat BTK yang akan membantu mengurangi jumlah sel kanker dan memperlambat penyebaran sel kanker.

Tanyakan dokter, perawat, atau apoteker Anda jika Anda memiliki pertanyaan tentang mengapa obat ini diresepkan untuk Anda.

Dokter Anda mungkin meresepkan ini untuk alasan yang lain.

Obat dapat digunakan hanya dengan resep dokter.

Belum ada informasi yang cukup untuk merekomendasikan penggunaan obat ini pada anak-anak maupun remaja di bawah 18 tahun.

DISETUJUI OLEH BPOM : 12/3/2026 ID : EREG10042212600040

2. Hal yang perlu diketahui sebelum menggunakan CALQUENCE.

Jangan gunakan apabila telah melewati tanggal kedaluwarsa yang tertera pada kemasan atau jika kemasannya robek atau menunjukkan tanda-tanda kerusakan. Jika telah kedaluwarsa atau rusak, kembalikan ke apotek atau rumah sakit Anda untuk dibuang.

Anda tidak boleh menggunakan CALQUENCE.

Jangan gunakan CALQUENCE jika Anda alergi (hipersensitif) terhadap obat yang mengandung acalabrutinib atau bahan lain yang terkandung dalam obat ini (baca bagian 6).
Beberapa gejala reaksi alergi diantaranya termasuk:

- Nafas yang pendek
- Mengi atau kesulitan dalam bernafas
- Bengkak pada wajah, bibir lidah, atau bagian tubuh lainnya
- Ruam, gatal-gatal pada kulit.

Beritahukan dokter jika Anda sedang hamil atau berencana untuk hamil. Anda tidak boleh CALQUENCE jika Anda sedang hamil, dan Anda tidak boleh hamil ketika menggunakan CALQUENCE. CALQUENCE dapat membahayakan bayi Anda yang belum lahir.

Beritahukan dokter Anda jika Anda menyusui atau berencana untuk menyusui. Anda tidak boleh menyusui ketika sedang dalam pengobatan menggunakan CALQUENCE.
Belum diketahui apakah CALQUENCE dapat masuk kedalam ASI Anda.
Jangan menyusui ketika melakukan pengobatan menggunakan CALQUENCE, setidaknya 2 minggu setelah dosis terakhir Anda.

Jika Anda tidak yakin apakah Anda harus mulai menggunakan obat ini, hubungi dokter, perawat, atau apoteker Anda.

Sebelum menggunakan CALQUENCE

Beritahukan dokter Anda jika Anda memiliki alergi terhadap obat lain, makanan, pengawet atau pewarna.
Beritahukan dokter Anda jika Anda memiliki atau pernah memiliki kondisi medis dibawah ini:

- Memar atau pendarahan yang tidak biasa, atau Anda memiki gangguan pendarahan.
- Infeksi (bakteri, virus dan/atau jamur)
- Gangguan hati
- Infeksi pada hati (Hepatitis B), sehingga dokter dapat mewaspadai tanda infeksi ini seperti demam, meriang, lemas, kebingungan, muntah, dan penyakit kuning (menguningnya bola mata dan kulit)
- Memiliki atau pernah memiliki gangguan irama jantung (seperti atrium fibrilasi)
- Atau kondisi medis lainnya.

Bicaralah dengan dokter Anda jika terdapat lesi baru atau perubahan tampilan pada suatu area di kulit, karena anda berisiko tinggi terkena kanker kulit, lihat bagian 4. Gunakan pelindung matahari dan lakukan pemeriksaan kulit secara teratur.

Dokter Anda akan memeriksa jumlah sel darah Anda sesuai kebutuhan selama perawatan.

Anak-anak dan remaja
Jangan berikan obat ini kepada anak-anak atau remaja berusia kurang dari 18 tahun. Karena belum adanya penelitan kelompok usia ini.

Beritahukan dokter jika Anda beru saja melakukan operasi atau berencana melakukan operasi atau tindakan medis lainnya.
Dokter Anda akan meminta untuk menghentikan penggunaan CALQUENCE sampai dengan 7 hari sebelum dan sesudah operasi atau tindakan medis lain yang dapat meningkatkan resiko pendarahan.

Jika Anda belum memberitahu dokter, perawat, atau apoteker Anda mengenai hal-hal diatas, segera beritahukan sebelum mulai menggunakan CALQUENCE.

Menggunakan obat-obatan lainnya

Beritahukan dokter, perawat, atau apoteker Anda jika Anda menggunakan obat-obatan lainnya, termasuk obat yang Anda gunakan tanpa resep dokter dari apotek, supermarket, atau toko obat.
CALQUENCE dapat membuat Anda mengalami pendarahan lebih mudah. Maka Anda harus memberitahukan dokter jika Anda menggunakan obat lain yang dapat meningkatkan resiko pendarahan. Hal ini termasuk:

- Obat-obatan yang digunakan untuk mengobati nyeri dan kondisi inflamasi (contohnya aspirin dan Anti Inflamasi Non-Steroid [AINS/NSAID] seperti ibuprofen).
- Obat-obatan yang digunakan untuk mencegah pembekuan darah, seperti antiplatelet atau pengencer darah (contohnya aspirin, warfarin).

Sebagai tambahan, beberapa obat dan CALQUENCE dapat saling mengganggu satu sama lain. Hal ini termasuk:

- antibiotik untuk infeksi bakteri – seperti clarithromycin
- ketoconazole – obat untuk sindrom cushing (suatu kondisi di mana tubuh memproduksi terlalu banyak hormon kortisol)
- rifampisin – antibiotik untuk infeksi bakteri (Tuberkulosis)
- obat untuk migrain – ergotamine
- obat untuk kadar natrium darah yang rendah – conivaptan
- obat untuk mencegah penolakan organ – siklosporin
- pimozide – obat yang digunakan untuk Tourette (kondisi yang menyebabkan gerakan tak terkendali dan keluarnya kata dan suara yang tak terkendali)
- teofilin – obat yang digunakan untuk mengi, sesak napas, dan dada sesak
- obat penurun asam lambung:
    - antasida – seperti kalsium karbonat: konsumsi Calquence 2 jam sebelum atau 2 jam setelah Anda minum obat ini
    - penghambat reseptor histamin-2 – seperti ranitidine dan famotidine: konsumsi Calquence 2 jam sebelum atau 10 jam setelah Anda minum obat ini
    - pompa proton – seperti omeprazole: hindari mengkonsumsi minum obat-obatan ini saat Anda menggunakan Calquence
- metotreksat – obat untuk penyakit seperti rheumatoid arthritis, psoriasis dan kolitis ulserativa, yang disebabkan oleh sistem kekebalan tubuh yang bekerja secara tidak seharusnya.
    - Obat ini harus diminum minimal 6 jam sebelum atau sesudah Calquence.
- Obat-obatan yang digunakan untuk mengontrol irama jantung (contohnya amiodaron, dtiazem, verapamil)

- Obat-obatan yang digunakan untuk mengobati infeksi jamur (contohnya fluconazole, posaconazole, ketoconazole, itraconazole, voriconazole)
- Obat-obatan yang digunakan untuk mengobati infeksi HIV (contohnya ritonavir, saquinavir, amprenavir, atazanavir, darunavir/ritonavir atau fosamprenavir)
- Obat-obatan yang digunakan untuk mengobati infeksi hepatitis C (contohnya telaprevir)
- Obat-obatan yang digunakan untuk mencegah kejang atau mengobati epilepsi (contohnya carbamazepine, phenytoin)
- *St. John's wort* – yaitu herbal yang digunakan untuk mengobati depresi
- Obat-obatan yang digunakan untuk mengontrol kadar gula darah pada pasien diabetes (contohnya metformin).

Obat-obatan ini dapat dipengaruhi oleh CALQUENCE atau dapat mempengaruhi seberapa baik obat ini bekerja. Anda mungkin membutuhkan jumlah obat yang berbeda atau Anda mungkin perlu menggunakan obat yang berbeda.

Kehamilan
Bicaralah dengan dokter Anda sebelum menggunakan Calquence jika Anda sedang hamil, berpikir Anda mungkin hamil, atau berencana memiliki bayi. Ini karena Calquence dapat membahayakan bayi Anda yang belum lahir.

Menyusui
Jangan menyusui selama pengobatan dengan Calquence dan selama 2 minggu setelah dosis terakhir Calquence Anda. Belum diketahui apakah Calquence dapat masuk ke dalam ASI.

Mengemudi dan menggunakan mesin
Calquence tidak berpotensi mempengaruhi kemampuan mengemudi dan menggunakan mesin. Namun, jika Anda merasa pusing, lemas atau lelah saat mengonsumsi Calquence, Anda tidak dianjurkan mengemudi atau menggunakan mesin.

Calquence mengandung natrium
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per dosis, dengan kata lain 'bebas natrium'.

Dokter, perawat, dan apoteker Anda memiliki informasi lebih mengenai obat yang harus dihindari ketika menggunakan obat ini.

3. Cara penggunaan CALQUENCE

Selalu gunakan obat ini sesuai dengan petunjuk dari dokter Anda. Periksa kembali dengan dokter atau apoteker Anda jika Anda tidak yakin.
Instruksi dapat berbeda dengan informasi yang terdapat di dalam leaflet ini.

Berapa yang harus digunakan

Dosis yang biasa digunakan yaitu satu kapsul 100 mg, dua kali sehari. Dosis ini harus digunakan dengan selang waktu 12 jam.

Bagaimana cara penggunaan

Telan kapsul secara utuh dengan air minum. Jangan dikunyah, dilarutkan, atau dibuka dari cangkang kapsulnya.

Kapan harus digunakan

Gunakan obat Anda pada waktu yang sama tiap harinya.
Penggunaan pada waktu yang sama tiap harinya dapat memberikan efek yang paling baik. Hal ini juga dapat membantu Anda mengingat kapan harus meminumnya.

Anda dapat memeriksa kapan terakhir kali Anda meminum CALQUENCE kapsul dengan melihat simbol matahari dan bulan pada kemasan blister. Simbol matahari (untuk pagi hari) dan simbol bulan (untuk malam hari). Simbol ini akan memberitahu apakah Anda telah meminum obat.

Anda dapat meminum CALQUENCE dengan atau tanpa makanan.

Penting agar Anda memberitahu dokter apakah Anda menggunakan obat-obatan yang disebutkan pada bagian "Menggunakan obat-obat lainnya", maka Anda perlu untuk:

- Menghindari penggunaan obat-obatan tertentu termasuk obat yang digunakan untuk mengobati infeksi fungi, atau untuk mengurangi asam lambung (PPI).
- Gunakan obat Anda pada waktu yang berbeda dengan CALQUENCE termasuk obat-obatan lainnya yang dapat mengurangi asam lambung.
- Dengan sementara meningkatkan atau menurunkan dosis CALQUENCE Anda, tergantung pada obat lain yang digunakan.

Berapa lama penggunaan

Lanjutkan penggunaan obat selama dokter meminta Anda untuk meminumnya. Jangan mengganti dosis atau berhenti menggunakannya.

Jika Anda lupa meminum

Jika Anda melewatkan dosis kurang dari 3 jam, segera minum obat. Gunakan dosis selanjutnya pada waktu biasa Anda meminumnya.

Jika Anda melewatkan dosis lebih dari 3 jam, lewati dosis obat yang terlupa. Gunakan dosis selanjutnya pada waktu biasa Anda meminumnya.

Jangan mengkonsumsi dosis ganda sekaligus untuk mengganti dosis yang terlupa.

Jika Anda tidak yakin apa yang harus dilakukan, tanyakan pada dokter, perawat, atau apoteker Anda.

Jika Anda memiliki kesulitan mengingat untuk minum obat, tanyakan pada perawat dan apoteker Anda untuk beberapa petunjuk.

Jika Anda meminum berlebih (*overdose*)

Segera telepon atau hubungi dokter untuk mendapatkan saran atau atau segera pergi ke instalasi gawat darurat rumah sakit terdekat, jika Anda atau orang lain mungkin meminum CALQUENCE berlebih. Lakukan hal ini meskipun tidak muncul rasa tidak nyaman atau tanda keracunan. Anda mungkin butuh tindakan medis segera. Bawa kapsul dan leaflet informasi pasien ini bersama Anda.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, Obat ini dapat menimbulkan efek samping, walaupun tidak setiap orang dapat mengalaminya.

Segera beritahukan dokter, perawat, atau apoteker Anda jika Anda merasa tidak nyaman di badan ketika menggunakan CALQUENCE.

Efek samping yang sering ditemui

Beritahukan pada dokter, perawat, dan apoteker, bila Anda merasakan hal dibawah ini:

- Infeksi, dengan gejala meliputi demam, meriang, atau gejala yang mirip seperti flu
- Sakit kepala
- Mual, muntah
- Pusing
- Nyeri pada perut
- Diare
- Konstipasi
- Ruam
- Gatal-gatal
- Pendarahan, termasuk mimisan
- Merasa sangat lelah (fatigue)
- Nyeri pada otot dan tulang
- Nyeri pada sendi
- Tekanan di area mata, hidung atau pipi (sinusitis)
- Sakit tenggorokan dan pilek (nasofaringitis)
- Infeksi saluran pernapasan atas
- Infeksi saluran kemih (nyeri atau rasa terbakar saat buang air kecil)
- Kanker baru, termasuk kanker kulit, dapat terjadi selama pengobatan dengan Calquence (lihat Bagian 2 “Hal yang perlu diketahui sebelum menggunakan CALQUENCE”)

Efek samping umum (dapat terjadi pada 1 dari 10 orang):

- bronkitis (tidak memerlukan tindakan segera)
- herpes

Efek samping yang jarang (dapat terjadi pada 1 dari 100 orang)

- kehilangan memori, kesulitan berpikir, kesulitan berjalan atau kehilangan penglihatan – hal ini mungkin merupakan tanda-tanda infeksi otak yang serius (*Progressive Multifocal Leukoencephalopathy* atau PML)
- demam, menggigil, lemah, bingung, sakit dan menguningnya kulit atau bola mata (*jaundice*) – ini mungkin merupakan tanda hepatitis B (infeksi hati) menjadi aktif kembali.
- limfositosis (jumlah limfosit yang lebih tinggi dari normal, yaitu sejenis sel darah putih dalam darah).

Berhenti minum Calquence dan hubungi dokter atau segera pergi ke unit gawat darurat terdekat jika Anda mengalami salah satu dari gejala berikut:

- Pendarahan. Gejala yang mungkin timbul yaitu feses hitam atau feses dengan darah, urin merah

muda atau coklat, mimisan, memar, pendarahan tak terduga, muntah atau batuk darah, pusing, lemah, kebingungan.
- Infeksi. Tanda yang mungkin timbul termasuk demam, menggigil, merasa lemah atau bingung, batuk, sesak napas [Pneumonia, **efek samping yang sangat umum** (dapat mempengaruhi lebih dari 1 dari 10 orang) atau infeksi Aspergillus, **efek samping yang tidak umum** (dapat mempengaruhi hingga 1 dari 100 orang)].

Efek samping serius yang umum (dapat terjadi pada 1 dari 10 orang)
- Detak jantung cepat, detak jantung tidak terjawab, denyut nadi lemah atau tidak merata, pusing, merasa ingin pingsan, rasa tidak nyaman di dada atau sesak napas (tanda-tanda permasalahan pada irama jantung yang dikenal sebagai fibrilasi atrium dan atrial flutter).

Efek samping serius yang jarang (dapat terjadi pada 1 dari 100 orang)
- demam, menggigil, mual, muntah, kebingungan, sesak napas, kejang, detak jantung tidak teratur, urin gelap atau keruh, kelelahan yang tidak biasa, atau nyeri otot atau sendi. Ini bisa menjadi gejala sindrom lisis tumor (TLS) – suatu kondisi yang disebabkan oleh kerusakan sel kanker yang cepat.

Beritahu dokter, perawat, atau apoteker jika Anda merasakan sesuatu yang membuat Anda merasa tidak enak badan.
Efek samping lain yang tidak terdaftar di atas dapat juga terjadi pada beberapa orang.

Seperti obat kanker lainnya, kanker baru seperti kanker kulit dapat diketahui dapat terjadi pada pasien yang menggunakan CALQUENCE.
Beberapa efek samping dapat ditemukan ketika dokter atau perawat Anda melakukan pemeriksaan darah rutin, diantaranya:
- Penurunan jumlah sel darah putih (neutropenia)
- Penurunan jumlah sel darah merah (anemia)
- Penurunan jumlah platelet yaitu sel yang membantu pembekuan darah (thrombocytopenia)
- Kondisi yang disebut *tumor lysis syndrome* (TLS), yaitu ketika terdapat zat kimia dalam kadar yang tidak seharusnya di dalam darah yang disebabkan oleh rusaknya sel kanker secara cepat yang terjadi selama pengobatan atau bahkan terkadang tanpa pengobatan. Gejala TLS diantaranya perubahan fungsi ginjal, detak jantung yang tidak normal, atau kejang.

Jangan khawatir dengan daftar efek samping diatas. Anda mungkin tidak akan mengalami efek samping tersebut.

Jika Anda memiliki pertanyaan, minta pada dokter, perawat, atau apoteker Anda untuk menjawab pertanyaan tersebut.

Pelaporan efek samping

Jika Anda mengalami efek samping, hubungi dokter, apoteker, atau perawat Anda, termasuk efek samping yang tidak tertera pada leaflet ini. Anda juga dapat melaporkan efek samping secara langsung dengan menghubungi PT. AstraZeneca Indonesia melalui nomor telepon +62 21 2997 9000. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara Penyimpanan CALQUENCE

Simpan kapsul pada tempat yang kering dimana suhu terjaga dibawah 30°C.

Jangan simpan CALQUENCE atau obat lainnya di kamar mandi atau dekat dengan pembuangan wastafel. Jangan simpan di dekat jendela atau di dalam mobil.
Panas dan lembab dapat merusak beberapa obat.

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

Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tertera pada blister foil dan karton (setelah EXP). Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.

Jangan membuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

CALQUENCE berupa 1 butir kapsul gelatin dengan badan kapsul berwarna kuning dan tutup kapsul berwarna biru, dengan tanda “ACA 100 mg” menggunakan tinta hitam.

Tiap kemasan karton berisi 7 blister @ 8 kapsul.

CALQUENCE mengandung:

- Zat aktif Acalabrutinib 100 mg
- Silicified microcrystalline cellulose
- Pregelatinized starch
- Magnesium stearate (E572)
- Sodium starch glycollate Type A
- Cangkang kapsul mengandung gelatin, titanium dioxide (E171), iron oxide yellow (E172) dan indigo carmine aluminium lake (E132) dengan tinta hitam (shellac, iron oxide black (E172) dan polypropyleneglycol)

HARUS DENGAN RESEP DOKTER

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