

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Calquence 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of acalabrutinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Yellow body, blue cap, size 1 (20 mm) hard capsule, marked with “ACA 100 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose is 100 mg acalabrutinib twice daily (equivalent to a total daily dose of 200 mg). Refer to obinutuzumab prescribing information for recommended obinutuzumab dosing information.

The dose interval is approximately 12 hours.

Treatment with Calquence should be continued until disease progression or unacceptable toxicity.

Dose adjustments

Adverse reactions

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

Table 1. Recommended dose adjustments for adverse reactions*

Adverse reaction	Adverse reaction occurrence	Dose modification (Starting dose = 100mg approximately every 12 hours)
Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia Or Grade 4 neutropenia lasting longer than 7 days Grade 3 or greater non-hematological toxicities	First and second	Interrupt Calquence Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at 100mg approximately every 12 hours
	Third	Interrupt Calquence Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at a reduced frequency of 100mg once daily
	Fourth	Discontinue Calquence

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

Interactions

Recommendations regarding use of Calquence with CYP3A inhibitors or inducers and gastric acid reducing agents are provided in Table 2 (see section 4.5).

Table 2. Use with CYP3A inhibitors or inducers and gastric acid reducing agents

	Co-administered medicinal product	Recommended Calquence use
CYP3A inhibitors	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt Calquence.
	Moderate CYP3A inhibitor	No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors.
	Mild CYP3A inhibitor	No dose adjustment.
CYP3A inducers	Strong CYP3A inducer	Avoid concomitant use.
Gastric acid reducing agents	Proton pump inhibitors	Avoid concomitant use.
	H2-receptor antagonists	Take Calquence 2 hours before (or 10 hours after) taking a H2-receptor antagonist.
	Antacids	The interval between taking the medicinal products should be at least 2 hours.

Missed dose

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

Special populations

Elderly

No dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

Renal impairment

No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in Calquence clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained, and serum creatinine levels monitored periodically. Calquence should be administered to patients with severe renal impairment (< 30 mL/min creatinine clearance) only if the benefit outweighs the risk and these patients should be monitored closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

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). However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity. It is not recommended to use Calquence in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN and any AST) (see section 5.2).

Severe cardiac disease

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

Paediatric population

The safety and efficacy of Calquence in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration

Calquence is for oral use. The capsules should be swallowed whole with water at approximately the same time each day, with or without food (see section 4.5). The capsules should not be chewed, dissolved or opened as this may affect the absorption of the medicinal product into the body.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhage

Major haemorrhagic events including central nervous system and gastrointestinal haemorrhage, some with fatal outcome, have occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with obinutuzumab. These events have occurred in patients both with and without thrombocytopenia. Overall, the bleeding events were less severe events including bruising and petechiae (see section 4.8).

The mechanism for the bleeding events is not well understood.

Patients receiving antithrombotic agents may be at increased 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 at least 3 days pre- and post-surgery.

Infections

Serious infections (bacterial, viral or fungal), including fatal events have occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with obinutuzumab. These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Infections due to hepatitis B virus (HBV) and herpes zoster virus (HZV) reactivation, aspergillosis and progressive multifocal leukoencephalopathy (PML) have occurred (see section 4.8).

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 (see section 4.8).

Second primary malignancies

Second primary malignancies, including skin and non-skin cancers, occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with obinutuzumab. Skin cancers were commonly reported. Monitor patients for the appearance of skin cancers and advise protection from sun exposure (see sections 4.8 and 5.3).

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 (see sections 4.5 and 4.2). 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, co-administration 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 (see sections 4.2 and 4.5). Concomitant use with strong CYP3A4 inducers should be avoided due to risk for lack of efficacy.

Calquence contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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).

Active substances that may increase acalabrutinib plasma concentrations

CYP3A/P-gp inhibitors

Co-administration with a strong CYP3A/P-gp inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.9-fold and 5.0-fold in healthy subjects (N=17), respectively.

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 (see section 4.2).

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A inducers

Co-administration of a strong CYP3A inducer (600 mg rifampicin once daily for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77% in healthy subjects (N=24), respectively.

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.

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%.

If treatment with an acid reducing agent is required, consider using an antacid (e.g., calcium carbonate), or an H₂-receptor antagonist (e.g., ranitidine or famotidine). For use with antacids, the interval between taking the medicinal products should be at least 2 hours (see section 4.2). For H₂-receptor antagonists, take Calquence should be taken 2 hours before (or 10 hours after) taking the H₂-receptor antagonist. Due to the long-lasting effect of proton pump inhibitors, separation of doses with proton pump inhibitors may not eliminate the interaction with Calquence and therefore concomitant use should be avoided (see section 4.2).

Active substances whose plasma concentrations may be altered by Calquence

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, pimozone).

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 medicinal product transport systems

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Calquence.

Pregnancy

There are no or limited amount of data from the use of acalabrutinib in pregnant women. Based on findings from animal studies, there may be a risk to the foetus from exposure to acalabrutinib during pregnancy. Dystocia (difficult or prolonged labour) was observed in the rat and administration to pregnant rabbits was associated with reduced foetal growth (see section 5.3).

Calquence should not be used during pregnancy unless the clinical condition of the woman requires treatment with acalabrutinib.

Breast-feeding

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

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 (see section 5.3).

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 be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Of the 1040 patients treated with Calquence monotherapy, the most common ($\geq 20\%$) adverse drug reactions (ADRs) of any grade reported in patients were infection (66.7%), headache (37.8%), diarrhoea (36.7%), bruising (34.1%), musculoskeletal pain (33.1%), nausea (21.7%), fatigue (21.3%), cough (21%) and rash (20.3%). The most commonly reported ($\geq 5\%$) Grade ≥ 3 adverse drug reactions were infection (17.6%), leukopenia (14.3%), neutropenia (14.2%), and anaemia (7.8%).

Of the 223 patients treated with Calquence combination therapy, the most common ($\geq 20\%$) ADRs of any grade reported in patients were infection (74%), musculoskeletal pain (44.8%), diarrhoea (43.9%), headache (43%), leukopenia (31.8%), neutropenia (31.8%), cough (30.5%), fatigue (30.5%), arthralgia (26.9%), nausea (26.9%), dizziness (23.8%), and constipation (20.2%). The most commonly reported ($\geq 5\%$) Grade ≥ 3 adverse drug reactions were leukopenia (30%), neutropenia (30%), infection (21.5%), thrombocytopenia (9%) and anaemia (5.8%).

Tabulated list of adverse reactions

The following adverse drug reactions (ADRs) have been identified in clinical studies with patients receiving Calquence as treatment for haematological malignancies. The median duration of Calquence treatment across the pooled dataset was 26.2 months.

Adverse drug reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are sorted by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is defined as: very common ($\geq 1/10$); common ($> 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib monotherapy (n=1040)

MedDRA SOC	MedDRA Term	Overall Frequency (all CTCAE grades)	Frequency of CTCAE Grade ≥ 3 [†]
Infections and infestations	Upper respiratory tract infection	Very common (22%)	0.8%
	Sinusitis	Very common (10.7%)	0.3%
	Pneumonia	Common (8.7%)	5.1%
	Urinary tract infection	Common (8.5%)	1.5%
	Nasopharyngitis	Common (7.4%)	0%
	Bronchitis	Common (7.6%)	0.3%
	Herpes viral infections [†]	Common (5.9%)	0.7%
	Aspergillus infections [†]	Uncommon (0.5%)	0.4%
	Hepatitis B reactivation	Uncommon (0.1%)	0.1%

Neoplasms benign, malignant and unspecified	Second Primary Malignancy [†] Non-melanoma skin malignancy [†] SPM excluding non-melanoma skin [†]	Very common (12.2%) Common (6.6%) Common (6.5%)	4.1% 0.5% 3.8%
Blood and lymphatic system disorders	Neutropenia [†]	Very common (15.7%)	14.2%
	Anaemia [†]	Very common (13.8%)	7.8%
	Thrombocytopenia [†]	Common (8.9%)	4.8%
	Lymphocytosis	Uncommon (0.3%)	0.2%
Metabolism and nutrition disorders	Tumour Lysis Syndrome [±]	Uncommon (0.5%)	0.4%
Nervous system disorders	Headache	Very common (37.8%)	1.1%
	Dizziness	Very common (13.4%)	0.2%
Cardiac disorders	Atrial fibrillation/Flutter [†]	Common (4.4%)	1.3%
Vascular disorders	Bruising [†] Contusion Petechiae Ecchymoses	Very common (34.1%) Very Common (21.7%) Very Common (10.7%) Common (6.3%)	0% 0% 0% 0%
	Haemorrhage/haematoma [†] Gastrointestinal haemorrhage Intracranial haemorrhage	Very common (12.6%) Common (2.3%) Common (1%)	1.8% 0.6% 0.5%
	Epistaxis	Common (7%)	0.3%
	Gastrointestinal disorders	Diarrhoea	Very common (36.7%)
Nausea		Very common (21.7%)	1.2%
Constipation		Very common (14.5%)	0.1%
Vomiting		Very common (13.3%)	0.9%
Abdominal pain [†]		Very common (12.5%)	1%
Skin and subcutaneous tissue disorders	Rash [†]	Very common (20.3%)	0.6%
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain [†]	Very common (33.1%)	1.5%
	Arthralgia	Very common (19.1%)	0.7%
General disorders and administration site conditions	Fatigue	Very common (21.3%)	1.7%
	Asthenia	Common (5.3%)	0.8%
	Haemoglobin decreased [§]	Very common (42.6%)	10.1%

Investigations[¶] (Findings based on test results)	Absolute neutrophil count decreased [§]	Very common (41.8%)	20.7%
	Platelets decreased [§]	Very common (31.1%)	6.9%

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

[†]Includes multiple ADR term.

[±]One case of drug-induced Tumour Lysis Syndrome was observed in acalabrutinib arm in the ASCEND Study.

[§]Represents the incidence of laboratory findings, not of reported adverse events.

[¶]Presented as CTCAE grade values.

Table 4. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib combination therapy (n=223)

MedDRA SOC	MedDRA Term	Overall Frequency (all CTCAE grades)	Frequency of CTCAE Grade ≥ 3 [†]
Infections and infestations	Upper respiratory tract infection	Very common (31.4%)	1.8%
	Sinusitis	Very common (15.2%)	0.4%
	Nasopharyngitis	Very common (13.5%)	0.4%
	Urinary tract infection	Very common (13%)	0.9%
	Pneumonia	Very common (10.8%)	5.4%
	Bronchitis	Common (9.9%)	0%
	Herpes viral infections [†]	Common (6.7%)	1.3%
	Progressive multifocal leukoencephalopathy	Uncommon (0.4%)	0.4%
	Hepatitis B reactivation	Uncommon (0.9%)	0.1%
	Aspergillus infections [†]	Very rare (0%)	0%
Neoplasms benign, malignant and unspecified	Second primary malignancy [†]	Very common (13%)	4.0%
	Non-melanoma skin malignancy [†]	Common (7.6%)	0.4%
	SPM excluding non-melanoma skin [†]	Common (6.3%)	3.6%
Blood and lymphatic system disorders	Neutropenia [†]	Very common (31.8%)	30%
	Thrombocytopenia [†]	Very common (13.9%)	9%
	Anaemia [†]	Very common (11.7%)	5.8%
	Lymphocytosis	Uncommon (0.4%)	0.4%
Metabolism and nutrition disorders	Tumour lysis syndrome [±]	Uncommon (1.8%)	1.3%

Nervous system disorders	Headache	Very common (43%)	0.9%
	Dizziness	Very common (23.8%)	0%
Cardiac disorders	Atrial fibrillation/flutter [†]	Common (3.1%)	0.9%
Vascular disorders	Bruising [†]	Very common (38.6%)	0%
	Contusion	Very common (27.4%)	0%
	Petechiae	Very common (11.2%)	0%
	Ecchymoses	Common (3.1%)	0%
	Haemorrhage/haematoma [†]	Very common (17.5%)	1.3%
	Gastrointestinal haemorrhage	Common (3.6%)	0.9%
	Intracranial haemorrhage	Uncommon (0.9%)	0%
	Epistaxis	Common (8.5%)	0%
Gastrointestinal disorders	Diarrhoea	Very common (43.9%)	4.5%
	Nausea	Very common (26.9%)	0%
	Constipation	Very common (20.2%)	0%
	Vomiting	Very common (19.3%)	0.9%
	Abdominal pain [†]	Very common (14.8%)	1.3%
Skin and subcutaneous tissue disorders	Rash [†]	Very common (30.9%)	1.8%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain [†]	Very common (44.8%)	2.2%
	Arthralgia	Very common (26.9%)	1.3%
General disorders and administration site conditions	Fatigue	Very common (30.5%)	1.8%
	Asthenia	Common (7.6%)	0.4%
Investigations[¶] (Findings based on test results)	Absolute neutrophil count decreased [§]	Very common (57.4%)	35%
	Platelets decreased [§]	Very common (46.2%)	10.8%
	Haemoglobin decreased [§]	Very common (43.9%)	9%

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

[†]Includes multiple ADR term.

[±]One case of drug-induced Tumour Lysis Syndrome was observed in the acalabrutinib arm in the ASCEND Study.

[§]Represents the incidence of laboratory findings, not of reported adverse events.

[¶]Presented as CTCAE grade values.

Description of selected adverse reactions

Discontinuation and dose reduction due to adverse reactions

Of the 1,040 patients treated with Calquence monotherapy, discontinuation due to adverse reactions were reported in 9.3% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 4.2% of patients. These main adverse reactions included hepatitis B reactivation, sepsis, and diarrhoea.

Of the 223 patients treated with Calquence combination, discontinuation due to adverse reactions were reported in 10.8% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 6.7% of patients. These main adverse reactions included neutropenia, diarrhoea and vomiting.

Elderly

Of the 1,040 patients in clinical studies of Calquence monotherapy, 41% were greater than 65 years 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.

Of the 223 patients in clinical studies of Calquence in combination of obinutuzumab therapy, 47% were greater than 65 years and less than 75 years of age and 26% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients and ≥ 65 years and younger.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

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

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE51.

Mechanism of action

Acalabrutinib is a selective inhibitor of Bruton tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis.

Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK with minimal off-target interactions

Pharmacodynamic effects

In patients with B-cell malignancies dosed with acalabrutinib 100 mg twice daily, median steady-state BTK occupancy of $\geq 95\%$ 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 46 healthy male and female subjects in a randomised, double-blind thorough QT study with placebo and positive controls. At a suprathreshold dose, 4-times the maximum recommended dose, Calquence did not prolong the QT/QTc interval to any clinically relevant extent (e.g., not greater than or equal to 10 ms) (see sections 4.4, 4.8 and 5.3).

Clinical efficacy and safety

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, 27.9% patients had a CrCl of < 60 mL/min. Of the patients who were < 65 years of age, 16.1% had a median CIRS-G score of 8. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.

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 1,000 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 1,000 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 1,000 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 1,000 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 5 summarises the baseline demographics and disease characteristics of the study population.

Table 5. 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. Efficacy results are presented in Table 6. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 6. Efficacy results per IRC Assessments 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 Survival^a			
Death events (%)	9 (5)	11 (6.1)	17 (9.6)
Hazard Ratio (95% CI) [†]	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	-
Best 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)

	Calquence plus obinutuzumab N=179	Calquence monotherapy N=179	Obinutuzumab plus chlorambucil N=177
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)

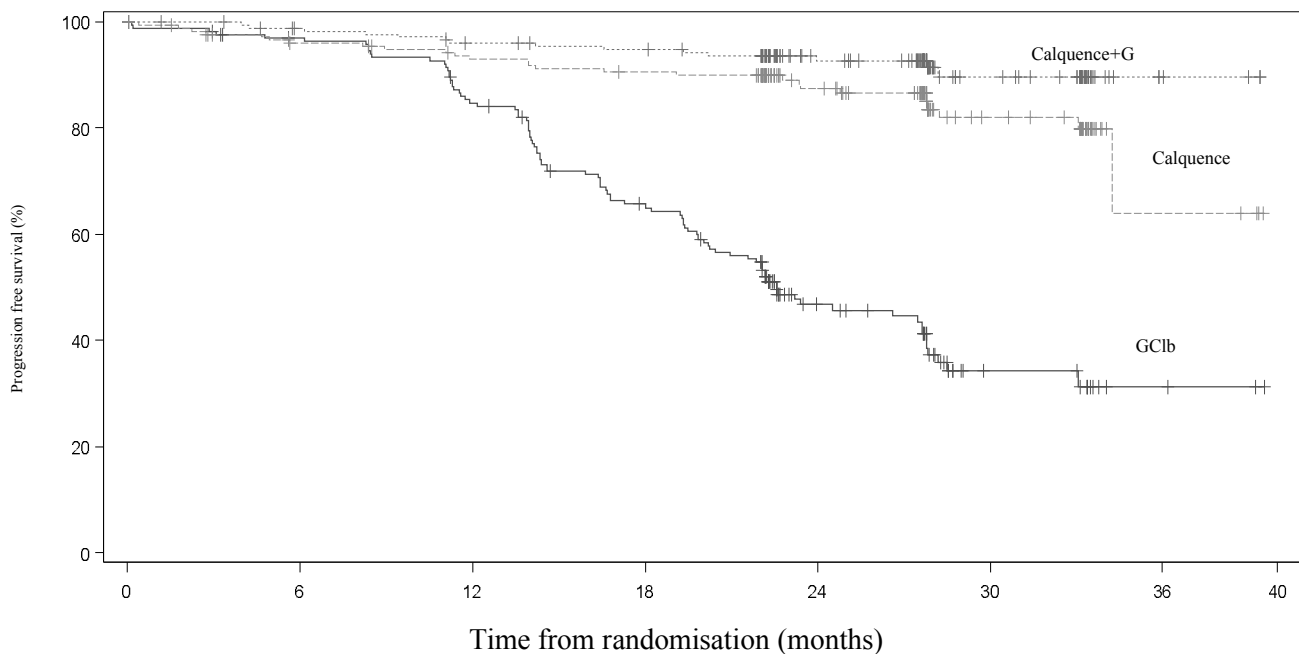
CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response;;

*Per IRC assessment

†Based on stratified Cox-Proportional-Hazards model

^a Median OS not reached for both arms.

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
GClb	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 or 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 0.13 [95% CI (0.08, 0.21)], respectively.

Table 7. Subgroup analysis of PFS (Study ELEVATE-TN)

	Calquence monotherapy			Calquence+G		
	N	Hazard	95% CI	N	Hazard	95% CI

		Ratio			Ratio	
All subjects	179	0.20	(0.13, 0.30)	179	0.10	(0.06, 0.17)
Del 17P						
Yes	19	0.20	(0.06, 0.64)	21	0.13	(0.04, 0.46)
No	160	0.20	(0.12, 0.31)	158	0.09	(0.05, 0.17)
TP53 mutation						
Yes	19	0.15	(0.05, 0.46)	21	0.04	(0.01, 0.22)
No	160	0.20	(0.12, 0.32)	158	0.11	(0.06, 0.20)
Del 17P or/and TP53 mutation						
Yes	23	0.10	(0.03, 0.34)	25	(0.03, 0.34)	(0.09, 0.48)
No	156	0.10	(0.05, 0.18)	154	(0.05, 0.18)	(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 not including BCL-2 inhibitors or B-cell receptor inhibitors. Patients received Calquence monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.

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 in combination with rituximab 375 mg/m² IV on Day 1 of the first cycle, followed by 500 mg/m² IV every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions
 - 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 8 summarizes the baseline demographics and disease characteristics of the study population.

Table 8. 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. Efficacy results are presented in Table 9. The Kaplan-Meier curve for PFS is shown in .

Table 9. Efficacy results per IRC 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 (%)	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 survival^a		
Death events (%)	15 (9.7)	18(11.6)
Hazard Ratio (95% CI) [†]	0.84 (0.42, 1.66)	-
Best 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)
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; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response; PD=progressive disease

*Per IRC assessment

^a Median OS not reached for both arms. P<0.6089 for OS.

**CRi and nPR have values of 0.

[†]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 10.

Table 10. 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)

	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Median (95% CI), months	NR	16.8 (14.1, 22.4)
HR [†] (95% CI)	0.27 (0.18, 0.40)	
21 months estimate, % (95% CI)	79.1 (71.5, 84.8)	45.3 (36.9, 53.4)
Overall survival^a		
Death events (%)	21 (13.5)	26 (16.8)
Hazard Ratio (95% CI) [†]	0.78 (0.44, 1.40)	-
Best overall response rate* (CR + CRi + nPR + PR)**		
ORR, n (%) (95% CI)	124 (80) (73, 85.5)	130 (83.9) (77.3, 88.8)
P-value	0.3516	-
CR, n (%)	5 (3.2)	6 (3.9)
PR, n (%)	114 (73.5)	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

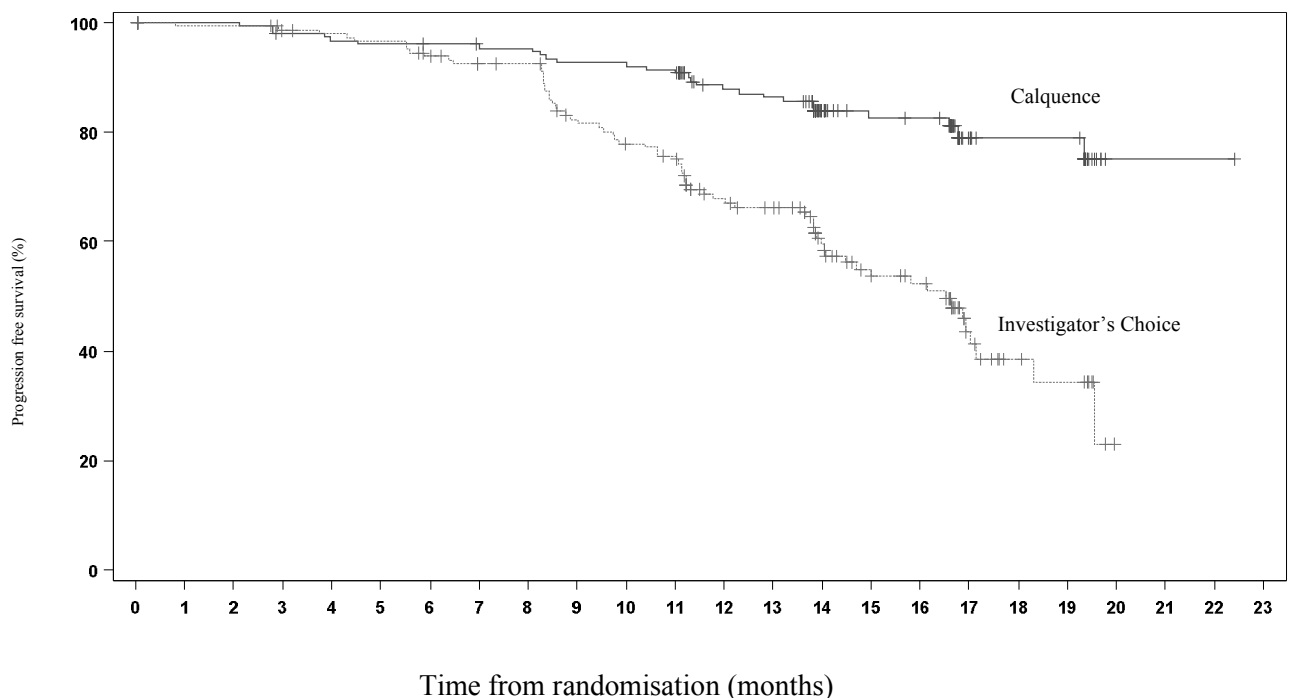
*Per INV assessment

^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)



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 0.25 [95% CI (0.16, 0.38)].

Table 11. 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	28	0.18	(0.07, 0.43)
No	127	0.30	(0.19, 0.47)
TP53 mutation			
Yes	39	0.17	(0.08, 0.37)
No	113	0.33	(0.21, 0.52)
Del 17P or TP53 mutation			
Yes	45	0.16	(0.08, 0.34)
No	108	0.34	(0.22, 0.55)
IGHV mutation			
Mutated	33	0.30	(0.12, 0.76)
Unmutated	118	0.28	(0.18, 0.43)
Del 11q			
Yes	39	0.35	(0.16, 0.75)
No	116	0.26	(0.16, 0.41)
Complex Karyotype			
Yes	50	0.28	(0.15, 0.53)
No	97	0.25	(0.15, 0.44)

Paediatric population The European Medicines Agency has waived the obligation to submit the results of studies with Calquence in all subsets of the paediatric population in CLL (for information on paediatric use, see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and in 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. Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 is similar across 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 concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1679 ng•h/mL and 438 ng/mL, respectively, and for ACP-5862 were 4166 ng•h/mL and 446 ng/mL, respectively.

Absorption

The time to peak plasma concentrations (T_{max}) was 0.5-1.5 hours for acalabrutinib, and 1.0 hour for ACP-5862. The absolute bioavailability of Calquence was 25%.

Effect of food on acalabrutinib

In healthy subjects, administration of a single 75 mg dose of acalabrutinib with a high fat, high calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 69% and T_{max} was delayed 1-2 hours.

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 (V_{ss}) was approximately 34 L for acalabrutinib.

Biotransformation/Metabolism

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

In vitro studies indicate that acalabrutinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1 or UGT2B7 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.

In vitro studies indicate that ACP-5862 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1 or UGT2B7 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.

Interactions with transport proteins

In vitro studies indicate that acalabrutinib and ACP-5862 are P-gp and BCRP substrates. Co-administration with BCRP inhibitors is however unlikely to result in clinically relevant drug interactions. Co-administration with an OATP1B1/1B3 inhibitor (600 mg rifampin, single dose) resulted in an increase in acalabrutinib C_{max} and AUC by 1.2-fold and 1.4-fold (N=24, healthy subjects), respectively, which is not clinically relevant.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and MATE2-K at clinically relevant concentrations. Acalabrutinib may inhibit intestinal BCRP, while ACP-5862 may inhibit MATE1 at clinically relevant concentrations (see section 4.5). Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the terminal elimination half-life ($t_{1/2}$) of acalabrutinib was) 1 to 2 hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was approximately 7 hours .

The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862 in patients with B-cell malignancies.

Following administration of a single 100 mg radiolabelled [¹⁴C]-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.

Special populations

Based on population PK analysis, age (>18 years of age), sex, race (Caucasian, African American) and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Paediatric population

No pharmacokinetic studies were performed with Calquence in patients under 18 years of age.

Renal Impairment

Acalabrutinib undergoes minimal renal elimination. A pharmacokinetic study in patients with renal impairment has not been conducted.

Based on population PK analysis, no clinically relevant PK difference was observed in 408 subjects with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m² as estimated by MDRD), 109 subjects with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m²) relative to 192 subjects with normal renal function (eGFR greater than or equal to 90 mL/min/1.73m²). The pharmacokinetics of acalabrutinib has not been characterised in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m²) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical studies (see section 4.2).

Hepatic impairment

Acalabrutinib is metabolised in the liver. In dedicated hepatic impairment (HI) 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. Subjects in the moderate HI group were however not significantly affected in markers relevant for the elimination capacity of drugs, so the effect of moderate hepatic impairment was likely underestimated in this study. Based on a population PK analysis, no clinically relevant difference was observed between subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST) relative to subjects with normal (n=613) hepatic function (total bilirubin and AST within ULN) (see section 4.2).

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Genotoxicity/Mutagenicity/Phototoxicity

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

Acalabrutinib was found to have a possible phototoxic potential in an *in vitro* phototoxicity assay using 3T3 cell line (see section 4.4).

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

Microcrystalline cellulose
Colloidal anhydrous silica

Partially pregelatinised maize starch
Magnesium stearate (E470b)
Sodium starch glycollate

Capsule shell

Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Indigo carmine (E132)

Printing ink

Shellac
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blisters with sun/moon symbols containing 6 or 8 hard capsules. Cartons of 56 or 60 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1479/001
EU/1/20/1479/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 November 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtnavägen
SE-151 85 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Calquence 100 mg hard capsules
acalabrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg of acalabrutinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
56 hard capsules
60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1479/001 56 hard capsules
EU/1/20/1479/002 60 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

calquence

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

CALQUENCE 100 mg capsules
acalabrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Sun/Moon symbol

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Calquence 100 mg hard capsules acalabrutinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Calquence is and what it is used for
2. What you need to know before you take Calquence
3. How to take Calquence
4. Possible side effects
5. How to store Calquence
6. Contents of the pack and other information

1. What Calquence is and what it is used for

What Calquence is

Calquence is a medicine used to treat cancer.

- Calquence contains the active substance acalabrutinib.
- It belongs to a group of medicines called Bruton tyrosine kinase (BTK) inhibitors.

What Calquence is used for

Calquence is used to treat adults with chronic lymphocytic leukaemia (CLL).

CLL is a cancer of white blood cells called B-lymphocytes (or B-cells). These cells are part of the immune system (the body's defences).

How Calquence works

Calquence works by blocking BTK, a protein in the body that helps these cancer cells grow and survive. By blocking BTK, Calquence helps to kill and can reduce the number of cancer cells which can slow down the worsening of the disease.

If you have any questions about how Calquence works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Calquence

Do not take Calquence if:

- you are allergic to acalabrutinib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before taking Calquence.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Calquence if you:

- have ever had unusual bruising or bleeding or are on any medicines that increase your risk of bleeding (see section 4 ‘Possible side effects’).
- have an infection (see section 4 ‘Possible side effects’)
- have recently had an operation or are about to have one. Your doctor may stop treatment with Calquence before and after a medical, surgical or dental procedure.
- have ever had hepatitis B (a liver infection) – this is because Calquence could cause hepatitis B to become active again and so that your doctor will look out for signs of this infection coming back (see section 4 ‘Possible side effects’).
- have or ever had irregular heart beat (see section 4 ‘Possible side effects’).

Talk to your doctor if you develop a new lesion or any change in the appearance of an area on the skin as you are at a high risk of developing skin cancer, see section 4. Use sun protection and make regular skin examination.

Your doctor will check your blood cell counts as needed during treatment.

Children and adolescents

Do not give this medicine to children or adolescents aged less than 18 years. This is because it has not been studied in this age group.

Other medicines and Calquence

Tell your doctor, pharmacist or nurse if you are taking or have recently taken or might take any other medicines, especially if you take any of the following:

- antibiotics for bacterial infections – such as clarithromycin
- medicines for fungal infections – such as posaconazole, itraconazole, voriconazole
- ketoconazole – a medicine for Cushing’s syndrome (a condition in which the body produces too much of the hormone cortisol)
- medicines for HIV infections – such as indinavir and ritonavir
- medicines for hepatitis C – such as telaprevir
- rifampicin – an antibiotic for bacterial infections (Tuberculosis)
- medicine for migraines – ergotamine
- medicine for low blood sodium – conivaptan
- medicine for high blood sugars – metformin
- medicine to prevent organ rejection – cyclosporine
- medicines for fits (seizures) or epilepsy – such as carbamazepine and phenytoin
- pimozide – a medicine used for Tourette (condition which causes uncontrolled movements and outbursts of words and sounds)
- St. John’s wort – a herbal medicine for depression
- theophylline – medicine used for wheezing, shortness of breath, and chest tightness
- medicines for reducing Stomach acid :

- antacids – such as calcium carbonate
 - Take Calquence 2 hours before or 2 hours after you take these medicines
- histamine-2 receptor blockers – such as ranitidine and famotidine
 - Take Calquence 2 hours before or 10 hours after you take these medicines
- proton pump inhibitors – such as omeprazole
 - Avoid taking these medicines while you are taking Calquence
- methotrexate – a medicine for diseases such as rheumatoid arthritis, psoriasis and ulcerative colitis, which are caused by the immune system working incorrectly.
 - This medicine should be taken at least 6 hours before or after Calquence.

Medicines that increase your risk of bleeding

Calquence may make you bleed more easily. Tell your doctor, pharmacist, or nurse if you take other medicines that increase your risk of bleeding:

- Antiplatelets (medicines that act against blood clotting) such as acetylsalicylic acid and clopidogrel.
- Anticoagulants (blood thinners) such as warfarin or enoxaparin.

Pregnancy

Talk to your doctor before taking Calquence if you are pregnant, think you may be pregnant, or are planning on having a baby. This is because Calquence may harm your unborn baby.

Breast-feeding

Do not breast-feed during treatment with Calquence and for 2 days after your last dose of Calquence. It is not known if Calquence passes into your breast milk.

Driving and using machines

Calquence is unlikely to affect the ability to drive and use machines. However, if you feel dizzy, weak or tired while taking Calquence, you must not drive or use machines.

Calquence contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to take Calquence

Calquence will only be prescribed to you by a doctor with experience in the use of medicines for cancer. Always take Calquence exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take

- The usual dose is one capsule (100 mg) twice a day. Take doses about 12 hours apart.

How to take

- Swallow the capsule whole with water at about the same time each day.
- Do not chew, dissolve or open the capsules as this may change how quickly the medicine gets into your body.
- You can take Calquence with food or between meals.
- You can check when you last took a capsule of Calquence by looking on the blister. Pictures on the blister will help you to take your dose at the right time — the sun for the morning dose and the moon for the evening dose.

If you take more Calquence than you should

If you have taken more Calquence than you should, see a doctor or go to the nearest hospital straight away. Take the capsules and this leaflet with you.

If you forget to take a dose

- If less than 3 hours have passed after your usual time for taking a dose, take the missed dose right away. Take the next dose at your usual time.
- If more than 3 hours have passed after your usual time for taking a dose, skip the missed dose. Take the next dose at your usual time.
- Do not take a double dose of Calquence to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Calquence and contact a doctor or go to your nearest emergency department immediately if you experience any of the following symptoms:

- Bleeding. Symptoms may be black stools or stools with blood, pink or brown urine, nosebleeds, bruising, unexpected bleeding, vomiting or coughing up blood, dizziness, weakness, confusion.
- Infections. Signs may include fever, chills, feeling weak or confused, cough, shortness of breath [Pneumonia, a **very common side effect** (may affect more than 1 in 10 people) or Aspergillus infections, an **uncommon side effect** (may affect up to 1 in 100 people)].

Common serious side effects (may affect up to 1 in 10 people)

- fast heart rate, missed heart beats, weak or uneven pulse, dizziness, feeling faint, chest discomfort or shortness of breath (signs of heart rhythm problems known as atrial fibrillation and atrial flutter).

Uncommon serious side effects (may affect up to 1 in 100 people)

- fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, or muscle or joint pain. This can be symptoms of tumor lysis syndrome (TLS) – a condition caused by the fast breakdown of cancer cells.

Other side effects:**Very common** (may affect more than 1 in 10 people):

- muscle or joint pain
- headache
- rash
- feeling tired (fatigue), weakness or lack of energy
- feeling sick to your stomach (nausea), vomiting, stomach pain, constipation (infrequent or hard to pass stool), diarrhoea (frequent or loose stools)
- decreased number of red blood cells, decreased number of neutrophils (a type of white blood cells) or decreased number of cells that help blood clot (platelets).
- dizziness
- headache, pressure in the eyes, nose or cheek area (sinusitis)
- sore throat and runny nose (nasopharyngitis)
- upper respiratory tract infection

- urinary tract infection (pain or burning feeling when passing urine).
- new cancers, including cancers of the skin, may happen during treatment with Calquence (see Section 2 ‘What you need to know before you take Calquence’)

Common (may affect up to 1 in 10 people):

- bronchitis (does not require immediate action)
- herpes

Uncommon side effects (may affect up to 1 in 100 people)

- memory loss, trouble thinking, difficulty walking or sight loss – these may be signs of a serious brain infection (Progressive Multifocal Leukoencephalopathy or PML)
- fever, chills, weakness, confusion, being sick and yellowing of the skin or eyeballs (jaundice) –these may be signs of hepatitis B (a liver infection) becoming active again.
- lymphocytosis (a higher than normal amount of lymphocytes, a type of white blood cells, in the blood).

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Calquence

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister foil and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Calquence contains

The active substance is acalabrutinib. Each hard capsule contains 100 mg of acalabrutinib.

The other ingredients are:

- Capsule content: microcrystalline cellulose, colloidal anhydrous silica, partially pregelatinised maize starch, magnesium stearate (E470b) and sodium starch glycolate (see section 2 “Calquence contains sodium”).
- Capsule shell: gelatine, titanium dioxide (E171), yellow iron oxide (E172) and indigo carmine (E132).
- Printing ink: shellac, black iron oxide (E172), propylene glycol (E1520) and ammonium hydroxide.

What Calquence looks like and contents of the pack

Calquence is a hard gelatine capsule with a yellow body, blue cap, 20 mm hard capsule, marked with “ACA 100 mg” in black.

Calquence is supplied in aluminium blisters containing either 6 or 8 hard capsules. Each carton contains either 56 or 60 hard capsules.

Not all pack sizes may be marketed.

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>