Calquence©

100 mg, hard capsules
100 mg, film-coated tablets

Summary of the Risk Management Plan (RMP) for Calquence® (acalabrutinib / acalabrutinib maleate)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Calquence® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Calquence® in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. AstraZeneca AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Calquence®.

1. THE MEDICINE AND WHAT IT IS USED FOR

CALQUENCE is authorised for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL) (see SmPC for full indications). CALQUENCE contains acalabrutinib as the active substance and it is given orally by capsule or tablet.

Further information about the evaluation of CALQUENCE's benefits can be found in CALQUENCE's SwissPAR, including in its plain-language summary, available on the Swissmedic website.

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of CALQUENCE, together with measures to minimise such risks and the proposed studies for learning more about the risks of CALQUENCE, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of CALQUENCE is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing information

Important risks of CALQUENCE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CALQUENCE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 1 List of Important Risks and Missing Information

Important Identified Risks	Haemorrhage with or without association with thrombocytopenia Serious infections with or without association with neutropenia Second primary malignancy Atrial fibrillation/flutter
Important Potential Risks	Cerebrovascular events Hepatotoxicity
Missing Information	Long-term safety Use in patients with moderate to severe cardiac impairment

2.2 Summary of important risks

Table 2 Important Identified Risks

Important Identified Risk: Haemorrhage with or without association with thrombocytopenia	
Evidence for linking the risk to themedicine	Based on evidence that BTK inhibition is associated with platelet aggregation, there is a plausible mechanism of action for how CALQUENCE may lead to haemorrhage. Furthermore, the reported rates of haemorrhage of any grade and Grade ≥ 3 for patients in the CALQUENCE monotherapy, ABR combination therapy, and AG combination therapy populations were very common and common, respectively (per CIOMS-defined frequencies). Additionally, haemorrhage has been described with other BTK inhibitors. Infections due to hepatitis B virus reactivation and opportunistic infections have been reported. Also, progressive multifocal leukoencephalopathy has been reported in the CLL combination setting.
Risk factors and risk groups	**Patient factors** Advanced age, comorbid medical conditions (eg, cerebrovascular disease, hepatic or renal disease, and diabetes mellitus), a history of bleeding (especially in the GI tract), and anaemia are predictive of subsequent bleeding complications (Shoeb and Fang 2013). Lower levels of von Willebrand factor activity, and factor VIII (Lipsky et al 2015) are also risks.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section(s): “Warnings and Precautions” and “Undesirable effects” **Additional risk minimisation measures**: None

Important Identified Risk: Serious infections with or without association with neutropenia	
Evidence for linking the risk to the medicine	There is a plausible mechanism of action between BTK and infections, based on nonclinical evidence examining the role of BTK in XLA patients. Furthermore, the reported rates of infections (both any grade and Grade ≥3) for patients in the CALQUENCE monotherapy, ABR combination therapy, and AG combination therapy populations were very common (per CIOMS-defined frequencies). Additionally, infection has been described with other BTK inhibitors.
Risk factors and risk groups	General risk factors not specific to CALQUENCE are divided into those that are host-associated and those that are treatment-associated. Host-associated factors include underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, psychological stress (Zembower 2014), and the underlying haematological malignancy. Treatment-associated factors include surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s): "Warnings and Precautions" and "Undesirable effects" **Additional risk minimisation measures:** None

Important Identified Risk: Second Primary Malignancy	
Evidence for linking the risk to the medicine	Based on evidence that eliminating B cells, as with BTK inhibitors, may potentially promote cancer progression, there is a plausible mechanism of action for how CALQUENCE may lead to SPM. In the CALQUENCE monotherapy, ABR combination therapy, and AG

	combination therapy populations, the reported rates of SPM were very common (per CIOMS-defined frequencies). Results from 2 pivotal Phase III studies for CLL (ACE-CL-007 and ACE-CL-309) demonstrated higher incidence rates of SPM (skin and non-skin) in the CALQUENCE monotherapy arm as compared with rates in the comparator arms. In the pivotal study for previously untreated MCL (ACE-LY-308), the incidence rate of SPMs was slightly higher in the ABR arm than in the PBR comparator arm, and the incidence rate excluding non-melanoma skin SPMs in the ABR arm was similar to the incidence rate in the PBR comparator arm. It has been reported in the literature that the incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population (Bond et al 2019). Additionally, SPM has been described with other BTK inhibitors.
Risk factors and risk groups	**Patient factors** Age is a risk factor for secondary malignancy (Andre et al 2004, Moser et al 2006). Incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population (Bond et al 2019). **Additive or synergistic factors** Use of any type of chemotherapy alone was associated with higher risk for secondary malignant neoplasms. A similar result was observed in the sub-analysis on patients treated only with alkylating agents, while the pooled relative risk of secondary malignant neoplasms for patients who underwent treatment with CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [oncovin], and prednisolone), or CHOP-like or radiotherapy alone, was raised but not statistically significant. A

	combined modality of treatment was significantly associated with the risk for overall secondary malignant neoplasms but not for solid tumours (Pirani et al 2011).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s): "Warnings and Precautions" and "Undesirable effects" **Additional risk minimisation measures:** None

Important Identified Risk: Atrial Fibrillation/Flutter	
Evidence for linking the risk to the medicine	The mechanism underlying atrial fibrillation/flutter events is currently unknown. In 2 Phase III pivotal studies for CLL (ACE-CL-007 and ACE-CL-309), the incidence of atrial fibrillation/flutter events was higher in the CALQUENCE monotherapy arm as compared with the comparator arm. Similarly, in the pivotal study for ABR combination therapy in previously untreated MCL (ACE-LY-308), the incidence of atrial fibrillation/flutter events was higher in the ABR group as compared with the PBR group. Furthermore, the reported rates of atrial fibrillation/flutter for patients in the CALQUENCE monotherapy, ABR combination therapy, and AG combination therapy populations were common (per CIOMS-defined frequencies). Additionally, atrial fibrillation/flutter has been described with other BTK inhibitors.
Risk factors and risk groups	General risk factors not specific to CALQUENCE include advancing age, male sex, diabetes mellitus, hypertension, valvular disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, hypoxia, hypercapnia, acidosis, electrolyte disturbances, autonomic dysfunction, and PR-interval prolongation (Ferreira et al 2015, Rienstra et al 2012). In recent years, increasing data have been reported supporting the notion that atrial fibrillation/flutter in the general population is heritable (Rienstra et al 2012). Several classes of cancer chemotherapeutic agents appear to be associated with cardiac arrhythmias like anthracyclines (rate of 2% to 10% of cases), melphalan (rate of 7% to 12% of cases), and interleukin 2 (IL 2) (Guglin et al 2009).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s): “Warnings and Precautions” and “Undesirable effects” **Additional risk minimisation measures**: None

ABR = acalabrutinib + bendamustine + rituximab; AG = acalabrutinib + obinutuzumab; BTK = Bruton tyrosine kinase; CHOP = cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), and prednisolone; CIOMS = Council for International Organizations of Medical Sciences; CLL = chronic lymphocytic leukaemia; GI = gastrointestinal; IL-2 = interleukin 2; MCL = mantle cell lymphoma; PBR = placebo + bendamustine + rituximab; SmPC = Summary of Product Characteristics; SPM = second primary malignancy; XLA = X-linked agammaglobulinaemia.

Table 3 Important Potential Risks

Important Potential Risk: Cerebrovascular events	
Evidence for linking the risk to themedicine	Cerebrovascular events have been observed with ibrutinib but are not considered causally associated (not listed in section “Undesirable effects” of SmPC). Cerebrovascular events have been observed with CALQUENCE however a causal relationship seems unlikely, since in most cases other significant confounding factors were present as well as the long time to event onset in some cases.
Risk factors and risk groups	Many risk factors for cerebrovascular events have been described, some of them are biological traits such as age and sex, some of them are physiological or pathological characteristics such as high blood pressure, serum cholesterol and fibrinogen and some are behavioural such as smoking, diet, alcohol consumption, and physical inactivity; some are social characteristics such as education, social class and ethnicity; and some are environmental factors that may be physical (temperature, altitude), geographical, or psychosocial. In addition, medical factors including previous TIA or stroke, ischemic heart disease, atrial fibrillation, and glucose intolerance, all increase the risk of stroke. Overall, atrial fibrillation (an important identified risk for CALQUENCE) may be associated with higher risk of cardiovascular events.
Risk minimisation measures	None

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to themedicine	The mechanism underlying hepatotoxicity events is currently unknown. Following a comprehensive review of hepatotoxicity events in the CALQUENCE clinical program, there was insufficient evidence to establish an association between hepatotoxicity and CALQUENCE due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with transaminase elevations. There is limited evidence regarding hepatotoxicity from literature for other BTK inhibitors. In the pivotal study for previously untreated MCL (ACE-LY-308), a slight imbalance was noted between arms for transaminase elevations (ALT/AST increased). These transaminase elevations were not accompanied by symptoms and signs of liver injury or clinically significant increases of serum bilirubin. There is insufficient evidence that these transaminase elevations are associated with overt liver injury.
Risk factors and risk groups	Risk factors for the development of hepatotoxicity that are non-specific to CALQUENCE include increasing age, the female gender, chronic hepatitis B and C, and HIV. Additional risk factors include the daily dose and metabolism of the offending drug and the potential to develop toxic reactive metabolites secondary to hepatic metabolism (Chalasani and Bjornsson 2010). Chronic alcohol consumption, underlying nonalcoholic fatty liver disease, and concomitant medication use, such as some nonsteroidal anti-inflammatory drugs, antibiotics, and seizure medications may increase the risk for a patient to develop hepatotoxicity (Sandhu and Navarro 2020).

Risk minimisation measures	**Routine risk communication:** SmPC section(s): " Dosage/Administration"

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BTK = Bruton tyrosine kinase; SmPC = Summary of Product Characteristics; TIA = transient ischaemic attack.

Table 4 Missing Information

Missing Information: Long-term Safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ACE-CL-007 This utilisation will be further characterised from routine pharmacovigilance activities and from results of an ongoing Study ACE-CL-007 a randomized, multicenter, open-label, 3 arm phase 3 study of obinutuzumab in combination with chlorambucil, ACP-196 in combination with obinutuzumab, and ACP-196 monotherapy in subjects with previously untreated chronic lymphocytic leukemia. The primary objective of this study is to evaluate the efficacy and safety of CALQUENCE in treatment naïve CLL patients (as monotherapy or combination therapy with Obinutuzumab).
Missing Information: Use in Patients with Moderate to Severe Cardiac Impairment	
Risk minimisation measures	**Routine risk communication:** SmPC section(s): " Dosage/Administration"

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** D8223C00016 This utilisation will be further characterised from routine pharmacovigilance activities and from results of Study D8223C00016, which is a Multicentre, Open-Label, Randomized, Phase IV Study to Investigate Acalabrutinib Monotherapy Compared to Investigator's Choice of Treatment in Adults (> 18 Years) with Chronic Lymphocytic Leukemia and Moderate to Severe Cardiac Impairment in approximately 60 subjects with moderate to severe cardiac impairment. All subjects are required to have a left ventricular ejection fraction assessed by ECHO <50%. Safety assessments will include AEs, serious adverse events (SAEs), events of clinical interest, adverse events of special interest, laboratory parameters (haematology, clinical chemistry, urinalysis, and others as clinically indicated), physical examinations and vital signs, cardiac assessments (ECG, Holter, echocardiography, cardiac biomarkers, and cardiac MRI) and other tests deemed critical to the safety evaluation of the study treatment.

AE = adverse event; AESI = adverse event of special interest; CLL = chronic lymphocytic leukaemia; ECG = electrocardiogram; ECI = event of clinical interest; MRI = magnetic resonance imaging; SAE = serious adverse event.

3. POST-AUTHORISATION DEVELOPMENT PLAN

3.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligations of CALQUENCE.

3.2 Other studies in post-authorisation development plan

ACE-CL-007

Study short name and title

A Randomized, Multicenter, Open Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP 196 in Combination with Obinutuzumab, and

ACP 196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia

Rationale

This randomised controlled Phase III study in previously untreated patients with CLL is designed to determine whether treatment with CALQUENCE in combination with obinutuzumab (Arm B) results in a clinically significant improvement in progression-free survival (PFS) as compared with treatment with obinutuzumab in combination with chlorambucil (Arm A), and whether treatment with CALQUENCE monotherapy (Arm C) results in a clinically significant improvement in PFS as compared with treatment with Arm A.

Study objectives

- Primary objective: To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with CALQUENCE in combination with obinutuzumab (Arm B), based on independent review committee (IRC) assessment of PFS per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria, in subjects with previously untreated CLL.
- Secondary objectives:
    - To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus CALQUENCE monotherapy (Arm C) based on IRC assessment of PFS per IWCLL 2008 criteria.
    - To compare obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib plus obinutuzumab (Arm B), and obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) in terms of:
        - IRC- assessed objective response rate (ORR) per IWCLL 2008 criteria;
        - TTNT (defined as the time from randomization to institution of non protocol specified treatment for CLL); and
        - Overall survival.
- Safety objective: Incidence of AEs including AEs, events of clinical interest (ECIs), and adverse events of special interest (AESIs), and SAEs and changes in laboratory measurements.
- This study was amended from a duration of 4.5 years to up to 10 years in order to collect additional long-term safety information. The results from this ongoing study ACE-CL-007 will be used to further characterise the missing information of long-term safety in subjects treated with CALQUENCE.

D8223C00016

Study short name and title

Acalabrutinib Monotherapy vs Investigator's Choice of Treatment in Patients with Chronic Lymphocytic Leukemia and Moderate to Severe Cardiac Impairment

Rationale

CLL is the most prevalent adult leukaemia in Europe and the Western societies (Yao et al 2022). As of 2019, the global incidence of CLL was over 100,000 cases, with an estimated 200,000 people with CLL living in the US alone (SEER 2024). The median age at diagnosis for CLL is ~70 years (American Society of Clinical Oncology 2024). While the prevalence of people with both CLL and cardiovascular disease is unreported, patients with CLL are likely to have at least the same risk of cardiovascular disease as the general population (Park et al 2019), estimated as 75% in people between 60 and 79 years of age and 86% in those > 80 years (Rodgers et al 2019).

Bruton tyrosine kinase (BTK) inhibitors are better tolerated than chemoimmunotherapy in patients with CLL; however, serious and fatal cardiac arrhythmias beyond atrial fibrillation have occurred with ibrutinib and have limited its use in cardiac-impaired patients (Imbruvica SmPC). The second generation, more selective BTK inhibitor CALQUENCE has shown a lower incidence of atrial fibrillation and cardiac AEs than ibrutinib (Byrd et al 2021). A review of the safety data for CALQUENCE suggests that it is well tolerated in patients with risk factors for developing cardiovascular diseases at screening, yet the safety profile of CALQUENCE in CLL patients with significant cardiovascular diseases or with moderate to severe cardiac impairment has not been established.

Study objectives

- Primary objective: To evaluate the safety and tolerability of acalabrutinib monotherapy vs Investigator's choice of treatment in patients with treatment naïve or relapsed/refractory (R/R) CLL and moderate to severe cardiac impairment.
- Secondary objective: To evaluate the extent and duration of tumour response and survival after acalabrutinib vs Investigators choice of treatment in patients with treatment naïve or (R/R) CLL and moderate to severe cardiac impairment.

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