



## **Calquence<sup>®</sup>**

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

### **Summary of the Risk Management Plan (RMP) for Calquence<sup>®</sup> (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](http://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

- As monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are 65 years and older or have comorbidities (see “Properties/Effects”).
- As monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy (see “Properties/Effects”).

CALQUENCE contains acalabrutinib as the active substance and it is given orally by capsule or tablet.

## 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 Periodic Benefit-Risk Evaluation Report (PBRER) 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	Second primary malignancy
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**

<b>Important Identified Risk: Second Primary Malignancy</b>	
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 haemorrhage. There is a plausible mechanism of action linking CALQUENCE and SPMs. The reported rates of SPM for subjects in the CALQUENCE Mono HemMalig population were very common (per CIOMS-defined frequencies). Results from two pivotal Phase 3 studies for CLL (ACE-CL-007 and ACE-CL-309) demonstrated higher incidence rates of SPM (skin and non-skin) in the CALQUENCE arm as compared to rates in the comparators arms. It has been reported in 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	<p><b>Patient factors</b></p> <p>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).</p> <p><b>Additive or synergistic factors</b></p> <p>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, doxyrubicin [hydroxydaunomycin], vincristine [oncovin], and prednisolone), or CHOP-like or radiotherapy alone, was raised but not statistically significant. A combined modality of treatment was</p>

	<p>significantly associated with the risk for overall secondary malignant neoplasms but not for solid tumours (Pirani et al 2011).</p>
<p>Risk minimisation measures</p>	<p><b>Routine risk minimisation measures:</b> SmPC section(s): “Warnings and Precautions” and “Undesirable effects”</p> <p><b>Additional risk minimisation measures:</b> None</p>

**Table 3 Important Potential Risks**

<p><b>Important Potential Risk: Cerebrovascular events</b></p>	
<p>Evidence for linking the risk to the medicine</p>	<p>Cerebrovascular events have been observed with ibrutinib but are not considered causally associated (not listed in section 4.8 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.</p>
<p>Risk factors and risk groups</p>	<p>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</p>

	<p>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.</p> <p>Overall, atrial fibrillation (an important identified risk for CALQUENCE) may be associated with higher risk of cardiovascular events.</p>
<p>Risk minimisation measures</p>	<p>None</p>
<p><b>Important Potential Risk: Hepatotoxicity</b></p>	
<p>Evidence for linking the risk to the medicine</p>	<p>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.</p>
<p>Risk factors and risk groups</p>	<p>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</p>

	2020).
Risk minimisation measures	SmPC section(s): “Undesirable effects”

BTK=Bruton tyrosine kinase; SmPC=Summary of Product Characteristics; TIA=transient ischaemic attack.

**Table 4 Missing Information**

<b>Missing Information: Long-term Safety</b>	
Risk minimisation measures	None
Additional pharmacovigilance activities	<p><b>Additional pharmacovigilance activities:</b></p> <p><a href="#">ACE-CL-007</a></p> <p>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).</p>



<b>Missing Information: Use in Patients with Moderate to Severe Cardiac Impairment</b>	
Risk minimisation measures	SmPC section(s): “Warnings and precautions”
Additional pharmacovigilance activities	<p><b>Additional pharmacovigilance activities:</b></p> <p>D8223C00016</p> <p>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 (&gt; 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 &lt;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.</p>

### 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 randomized controlled Phase 3 study in previously untreated subjects with CLL is designed to determine whether treatment with acalabrutinib in combination with obinutuzumab (Arm B) results in a clinically significant improvement in PFS as compared with treatment with obinutuzumab in combination with chlorambucil (Arm A), and whether treatment with acalabrutinib 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 acalabrutinib in combination with obinutuzumab (Arm B), based on IRC assessment of PFS per IWCLL 2008 criteria, in subjects with previously untreated CLL.
- Secondary objectives:
  - To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus acalabrutinib 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
    - OS.
- 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 acalabrutinib.

## **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

Chronic lymphocytic leukemia (CLL), is the most prevalent adult leukemia 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 (Cancer Stat Facts). The median age at diagnosis for CLL is ~70 years (ASCO). 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 inhibitors (BTKi) are better tolerated than chemoimmunotherapy (CIT) in patients with CLL; however, serious and fatal cardiac arrhythmias beyond atrial fibrillation (AF) have occurred with ibrutinib and have limited its use in cardiac impaired patients (Imbruvica SmPC). The second generation, more selective BTKi acalabrutinib has shown a lower incidence of AF and cardiac adverse events (AEs) than ibrutinib (Byrd et al 2021). A review of the safety data for acalabrutinib suggests that it is well tolerated in patients with risk factors for developing cardiovascular diseases at screening, yet the safety profile of acalabrutinib 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 chronic lymphocytic leukemia and moderate to severe cardiac impairment.
- Secondary objective: To evaluate the extent and duration of tumor response and survival after acalabrutinib vs Investigators choice of treatment in patients with treatment naïve or relapsed/refractory chronic lymphocytic leukemia and moderate to severe cardiac impairment.

## 4. LIST OF REFERENCES

### **Andre et al 2004**

Andre M, Mounier N, Leleu X, Sonet A, Brice P, Henry-Amar M, et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. *Blood* 2004;103(4):1222-28. doi: 10.1182/blood-2003-04-1124.

### **Bond et al 2019**

Bond DA, Alinari L, Maddocks K. Bruton tyrosine kinase inhibitors for the treatment of mantle cell lymphoma: review of current evidence and future directions. *Clin Adv Hematol Oncol* 2019;17(4):223-33.

### **Byrd et al 2021**

Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol*. 2021;39(31):3441-52.

### **Chalasani and Bjornsson 2010**

Chalasani N, Bjornsson E. Risk factors for idiosyncratic drug-induced liver injury. *J Gastro* 2010;138(7):2246–59.

### **Moser et al 2006**

Moser EC, Noordijk EM, van Leeuwen FE, Baars JW, Thomas J, Carde P, et al. Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study. *Haematologica* 2006;91(11):1481-88.

### **Park et al 2019**

Park JY, Guo W, Al-Hijji M, El Sabbagh A, Begna KH, Habermann TM, et al. Acute coronary syndromes in patients with active hematologic malignancies – incidence, management, and outcomes. *Int J Cardiol* 2019;275:6-12. doi: 10.1016/j.ijcard.2018.10.008.

**Rodgers et al, 2019**

Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular Risks Associated with Gender and Aging. *J Cardiovasc Dev Dis.* 2019;6(2):19.

**Sandhu and Navarro 2020**

Sandhu N, Navarro V. Drug-induced liver injury in GI practice. *Hepatology communications.* 2020;4(5):631–45.

**Yao et al, 2022**

Yao Y, Lin X, Li F, Jin J, Wang H. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. *BioMed Eng Online.* 2022;21(4). <https://doi.org/10.1186/s12938-021-00973-6>.