Taiwan Food and Drug Administration

Assessment Report

Trade Name：康恩賜膠囊 100 毫克 / Calquence Capsules 100mg

Active Ingredient：Acalabrutinib

License Number：MOHW-PI 028047

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date：2011/03/25

Indication：

1. **先前曾接受至少一種治療的被套細胞淋巴瘤 (Mantle Cell Lymphoma, MCL) 成年病人。**
   此適應症係依據整體反應率 (Overall response rate) 加速核准，仍須執行確認性試驗以證明其臨床效益。

   CALQUENCE is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
   This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2. **慢性淋巴球性白血病 (Chronic Lymphocytic Leukemia, CLL) 或小淋巴球性淋巴瘤 (Small Lymphocytic Lymphoma, SLL) 成年病人。**

CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

1. Background Information

Trade Name	康恩賜膠囊 100 毫克 / Calquence Capsules 100mg
Active Ingredient(s)	Acalabrutinib
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	Capsules 100mg
Indication	1. 先前曾接受至少一種治療的被套細胞淋巴瘤 (Mantle Cell Lymphoma, MCL) 成年病人。此適應症係依據整體反應率 (Overall response rate) 加速核准，仍須執行確認性試驗以證明其臨床效益。 CALQUENCE is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. 2. 慢性淋巴球性白血病 (Chronic Lymphocytic Leukemia, CLL)或小淋巴球性淋巴瘤 (Small Lymphocytic Lymphoma, SLL) 成年病人。 CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
Posology	1. CALQUENCE 單一療法：對於 MCL、CLL 或 SLL 病人，CALQUENCE 的建議劑量為 100 mg 每日口服兩次，間隔約 12 小時，直至疾病惡化或無法耐受之毒性。 CALQUENCE as Monotherapy: For patients with MCL, CLL, or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. 2. CALQUENCE 與 Obinutuzumab 併用：對於未曾接受治療的 CLL 或 SLL 病人，CALQUENCE 的建議劑量為 100 mg 每日口服兩次，間隔約 12 小時，直至疾病惡化或無法耐受之毒性。每 28 天為一治療週期，自第 1 週期開始 CALQUENCE 治療，obinutuzumab 則自第 2 週期開始共投予 6 個週期，建議劑量請參閱 obinutuzumab 仿單。同一天給藥時，先投予 CALQUENCE 再投予 obinutuzumab。

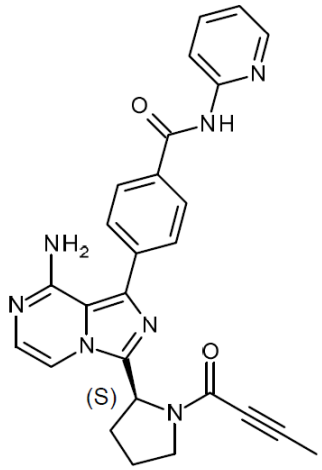
	CALQUENCE in Combination with Obinutuzumab: For patients with previously untreated CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE prior to obinutuzumab when given on the same day.
Pharmacological Category **ATC Code**	L01XE51

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of acalabrutinib is 4-{8-amino-3-[(2*S*)-1-(but-2-ynoyl)pyrrolidin- 2-yl]imidazo[1,5-a]pyrazin-1-yl}-*N*-(pyridin-2-yl)benzamide. Acalabrutinib is a white to yellow powder. The molecular formula for acalabrutinib is $C_{26}H_{23}N_7O_2$ and the molecular weight is 465.51 g/mol. It has the following structure:



The chemical structure of acalabrutinib is elucidated by elemental analysis, mass spectroscopy, IR-spectrum, UV-spectrum, ^{1}H-NMR, ^{13}C-NMR and single crystal X-ray diffraction.

The specification for acalabrutinib includes tests for description, identification, assay, impurities, enantiomeric purity, water content, particle size distribution and residue on ignition.

2.1.2 Drug product

Calquence capsules for oral administration is presented as a hard gelatin capsule, with a blue cap and yellow body, printed with “ACA 100 mg” in black ink and containing 100 mg of acalabrutinib. The specifications for the excipients are adequate.

The specification for the drug product includes tests for description, identification, assay, degradation products, dissolution and uniformity of dosage units. Analytical methods are described and well validated.

Stability studies of drug product under long term conditions (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Calquence (Acalabrutinib) is a drug for treating adult patients with Mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). Acalabrutinib is a covalent inhibitor of Bruton tyrosine kinase (BTK). It forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, permanently inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells.

The *in vitro* pharmacology studies indicated that both acalabrutinib and its M27 metabolite (ACP-5862) covalently inhibit BTK. Acalabrutinib exhibited better selectivity against the group of 3F-Cys kinases than other BTK inhibitors. Acalabrutinib has no inhibitory effects on T cell activation and EGFR phosphorylation and exhibits less inhibition on NK cells than other BTK inhibitors.

The *in vivo* pharmacology studies indicated that acalabrutinib inhibited tumor growth dose-dependently in the CLL and MCL xenograft models in mice. In a rat adjuvant-induced arthritis model, acalabrutinib exhibited a moderate effect on reducing ankle inflammation and ankle bone resorption. The *ex vivo* study showed that acalabrutinib did not exhibit significant effects on thrombus formation.

In a veterinary clinical study in dogs with spontaneous canine B cell lymphoma, acalabrutinib was generally well tolerated. High BTK occupancy was observed in tumor-bearing lymph nodes 3 hours after administration, but the pharmacokinetics were not dose-proportional due to the low animal numbers and large inter-animal variation. Safety pharmacology studies indicated that acalabrutinib did not significantly affect CNS, cardiovascular, and respiratory systems.

2.2.2 Toxicological Studies

The pivotal nonclinical toxicity studies indicated that the target organs were kidney, liver, heart, and pancreas in rats and the kidney in dogs. It seemed that the findings in the pancreas were rat-specific, and no other signs of pancreas dysfunction were observed. Since the kidney findings were observed in both rats and dogs, the renal functions have been monitored in clinical trials.

Reproductive toxicity studies in rats did not identify acalabrutinib-related effects on parental fertility or embryo-fetal development. Acalabrutinib exposure in-utero and via the milk of

offspring was well tolerated and did not exhibit systemic toxicity.

The genotoxicity studies presented negative results. Carcinogenicity and local tolerance were not evaluated. The genotoxicity of 5 impurities was evaluated, and the data was used to control the amount.

The *in vitro* phototoxicity study presented a positive result. Furthermore, acalabrutinib exhibited no genotoxicity under UV radiation. In addition, acalabrutinib did not lyse human erythrocytes at up to 1 mg/mL.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Acalabrutinib is rapidly absorbed after oral dosing with T_{max} occurring 0.5-1.5 hours in healthy subjects and subjects with B-cell malignancies. The absolute bioavailability of acalabrutinib is approximately 25%. Linear PK was observed from 75 mg to 250 mg following single and multiple dosing. No clinically relevant food effect was observed following co-administration of acalabrutinib with a standard high-fat, high-calorie meal.

There is no drug accumulation during repeated acalabrutinib dosing. The mean Vd at steady-state was 34 L, following a radiolabeled IV microtracer dose. Acalabrutinib and ACP-5862 are approximately 98% and 99% bound to human plasma proteins, respectively.

Acalabrutinib is primarily metabolized by CYP3A enzymes and to a lesser extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean AUC that is approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 has approximately 50% less potency for BTK inhibition than acalabrutinib.

Following a single oral dose of 100 mg acalabrutinib in humans, 84% of the dose was received in the feces and 12% of the dose was recovered in the urine (<1% as unchanged acalabrutinib). The median terminal elimination half-life of acalabrutinib and its active metabolite ACP-5862 were 1-2 h and 7 h, respectively.

2.3.2 Interaction Studies

In vitro studies indicated that CYP3A4/5 is the principal P450 isozyme responsible for the metabolism of acalabrutinib. Clinical studies to evaluate the impact of CYP3A modulation on acalabrutinib exposure indicated a 5-fold increase in acalabrutinib $AUC_{0\text{-last}}$ following co-administration with itraconazole (strong CYP3A inhibitor), and a decrease in acalabrutinib $AUC_{0\text{-last}}$ to 0.2-fold following co-administration with rifampin (strong CYP3A inducer) relative to acalabrutinib alone. The PBPK simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max} and AUC approximately 2- to 3-fold.

Based on *in vitro* studies, acalabrutinib has the potential to inhibit intestinal BCRP, while ACP-5862 may inhibit MATE1, following a 100-mg dose of acalabrutinib. A clinically meaningful DDI with acalabrutinib and/or ACP-5862 are not expected for various CYPs, UGTs, or transporters.

In healthy subjects, co-administration of acalabrutinib 100 mg with calcium carbonate reduced acalabrutinib geometric mean $AUC_{0\text{-last}}$ and C_{max} by 47% and 25%, respectively, whereas co-administration with omeprazole reduced the geometric mean $AUC_{0\text{-last}}$ and C_{max} by 43% and 21%, respectively, relative to when acalabrutinib was administered alone.

2.3.3 Special Populations

In dedicated hepatic impairment studies, compared to subjects with normal liver function, acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold, and 5.3-fold in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6) and severe hepatic impairment (Child-Pugh scale C, N=8), respectively. Population PK analysis showed that there was no impact of hepatic function as measured by NCI criteria on the systemic exposure to acalabrutinib.

No formal renal impairment study is planned for acalabrutinib, as renal excretion is a minor elimination pathway of acalabrutinib and its metabolites. Based on population PK analysis, no clinically relevant PK difference was observed in 433 subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m^2), 110 subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2) relative to 204 subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One Phase II single-arm study [ACE-LY-004] was evaluated for the efficacy of acalabrutinib for the treatment of adult patients with mantle cell lymphoma (MCL) who had received at least one prior therapy. Treatment of acalabrutinib 100 mg orally (PO) twice daily (BID) showed an 80.6% (95% CI: 72.6%, 87.2%) of the investigator-assessed objective response rate (ORR) according to the Lugano classification.

Two phase III clinical studies were evaluated and supported the efficacy of acalabrutinib for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

The Phase III study [ACE-CL-007] (ELEVATE-TN) in adult subjects with previously untreated CLL showed, in the interim analysis with overall median 28.3 months of time on study, that treatment arm of acalabrutinib 100 mg PO BID started on Cycle 1 (each cycle is 28 days) + obinutuzumab IV started on Cycle 2 for a maximum of 6 cycles demonstrated a statistically significant improvement in IRC-assessed progression-free survival (PFS)

compared with treatment arm of obinutuzumab IV + chlorambucil PO for a total of 6 cycles (median PFS: not yet reached vs. 22.6 months, respectively; HR (95% CI): 0.10 (0.06, 0.17); p-value <0.0001). As the key secondary analysis, the acalabrutinib monotherapy also demonstrated a statistically significant improvement in IRC-assessed PFS compared with the obinutuzumab + chlorambucil arm (median PFS: not yet reached vs. 22.6 months; HR (95% CI): 0.20 (0.13, 0.30); p-value <0.0001). The IRC-assessed objective response rate (ORR) difference between acalabrutinib + obinutuzumab and obinutuzumab + chlorambucil arms was 15.3% (95% CI: 8.3, 22.3), which was also statistically significant (p<0.0001).

The Phase III study [ACE-CL-309] (ASCEND) in adult patients with relapsed/refractory CLL showed, in the interim analysis with a median follow-up of approximately 16 months, that acalabrutinib monotherapy 100 mg PO BID demonstrated a statistically significant improvement in IRC-assessed PFS compared with the investigator's choice of either idelalisib + rituximab (IR) or bendamustine + rituximab (BR) (median PFS: not yet reached vs. 16.5 months; HR (95% CI): 0.31 (0.20, 0.49); p-value <0.0001).

2.4.2 Safety Results

Major adverse reactions include opportunistic infections, hemorrhage, pancytopenia, secondary primary malignancies, atrial fibrillation/flutter, headache, diarrhea and nausea. Dose modifications for adverse reactions are required, as shown in label.

2.5 Bridging Study Evaluation

The acalabrutinib exposure parameters (C_{max} and $AUC_{0\text{-}last}$) after acalabrutinib 100 mg BID oral dosing to the Japanese patients with advanced B-cell malignancies (Study D8220C00001, N=6) were compared to non-Japanese patients with CLL, RS or PLL (Study ACE-CL-001). Following multiple dose administration, the mean C_{max} and $AUC_{0\text{-}last}$ of acalabrutinib were 0.9 to 3.5 fold higher in the Japanese patients compared to the non-Japanese patients, however, the range (min to max) of individual data largely overlapped.

The mean C_{max} and AUC of active metabolite, ACP-5862, is approximately 10%~25% higher in the Japanese patients compared to the non-Japanese patients. As there was limited PK data from Japanese subjects for assessments of ethnic sensitivity, more PK data from East Asian (phase I Chinese study; D8220C00007) is required to be submitted in the future.

There were limited East Asian subjects in clinical trials (16 CLL/SCL and 13 MCL). Systemic exposure is higher (up to 2 folds) in Japanese as compared to Caucasians. The sponsor should provide more Asian clinical information to further clarify the influence of ethnic factors after initial licensing, using the following clinical trial database in which more East Asian subjects were enrolled: Study D8220C00007, D8220C00001, ACE-CL-312, ACE-CL-311, D822BC00001 and ACE-LY-308.

2.6 Conclusion

The efficacy for MCL was demonstrated by ORR and for CLL/SCL by PFS. The safety profile was acceptable. Accelerated approval of Calquence (acalabrutinib) for MCL and regular approval for CLL/SCL are recommended. Please refer to the approved label for detail description of indications.

3. Post-Marketing Requirements

(1) Final CSR of MCL confirmatory trials ACE-LY-308 for regular approval.
(2) Final CSR of Studies ACE-LY-004, ACE-CL-309 and ACE-CL-007 are also required for review of updated data.
(3) Final CSR of Studies D8220C00007, D8220C00001, ACE-CL-312, ACE-CL-311, D822BC00001 and ACE-LY-308 are required for evaluation of ethnic difference.