Taiwan Food and Drug Administration

Assessment Report

Trade Name：達再樂膜衣錠 200 毫克 /
KRAZATI Film-coated Tablets 200 mg

Active Ingredient：Adagrasib

License Number：MOHW-PI 028871

Applicant：台灣必治妥施貴寶股份有限公司

Approval Date：2025/02/08

Indication：

適用於治療曾接受過至少一次全身性療法，且帶有 *KRAS* G12C 突變之局部晚期或轉移性非小細胞肺癌 (NSCLC) 成年病人。
此適應症係依據腫瘤客觀反應率與反應持續時間加速核准，此適應症仍需執行確認性試驗以證明其臨床效益。

Treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy.
This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

Background Information

Trade Name	達再樂膜衣錠 200 毫克 / KRAZATI Film-coated Tablets 200 mg
Active Ingredient(s)	Adagrasib
Applicant	台灣必治妥施貴寶股份有限公司
Dosage Form & Strengths	膜衣錠 200mg
Indication	適用於治療曾接受過至少一次全身性療法，且帶有 KRAS G12C 突變之局部晚期或轉移性非小細胞肺癌 (NSCLC) 成年病人。 此適應症係依據腫瘤客觀反應率與反應持續時間加速核准，此適應症仍需執行確認性試驗以證明其臨床效益。 Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01XX77

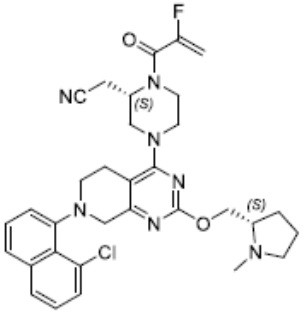
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Adagrasib

The drug substance, adagrasib, is chemically designated as {(2*S*)-4-[7-(8-chloronaphthalen-1-yl)-2-{[(2*S*)-1-methylpyrrolidin-2-yl]-methoxy}-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2-yl}acetonitrile and has the following structure:



It is a white to light brown solid. The molecular formula and the relative molecular mass for adagrasib are $C_{32}H_{35}ClFN_7O_2$ and 604.1, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of adagrasib has been confirmed by UV spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy and mass spectrum. Stereochemistry is determined by X-ray diffraction analysis. Adequate specification has been presented for the drug substance and the test items include appearance, identification, assay, related substances, stereoisomeric impurities, residual solvents, water content, polymorphic form, residue on ignition, particle size distribution and elemental impurities. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is supplied for oral use as white to off-white film-coated tablet containing 200 mg adagrasib. The specifications for excipients used in the tablet formulation are adequate.

Adequate specification has been presented for the film-coated tablet and the test items include appearance, identification, assay, degradation product content, uniformity of dosage, dissolution, water content and microbial limits. Batch analysis data from representative batches of the tablet are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of the tablet under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 12 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of the tablet can be presumed to have 24 months under the storage condition of 25°.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Adagrasib (MRTX849) is a covalent, mutant-selective inhibitor of the KRAS G12C protein, under development for the treatment of cancers harboring this specific genetic mutation.

In vitro pharmacology studies demonstrated that Adagrasib exhibits high affinity and irreversible covalent binding to the KRAS G12C variant protein. It selectively inhibited tumor cell growth in KRAS G12C mutation-positive cell lines, with minimal effects on wild-type (WT) KRAS cell lines. In vivo, adagrasib's anti-tumor efficacy was evaluated across multiple human KRAS G12C-mutant xenograft models, including lung, colon, and pancreatic cancers. These studies consistently revealed broad-spectrum anti-tumor activity in KRAS G12C-mutant tumors, with negligible activity in tumors expressing WT KRAS or other KRAS mutations.

Secondary pharmacology evaluations revealed off-target effects of Adagrasib on four receptors: alpha-1A adrenergic receptor, muscarinic M2 receptor, serotonin 5HT1A receptor, and serotonin 5HT1B receptor. Despite these interactions, Adagrasib did not produce significant clinical signs of central nervous system (CNS) or respiratory effects. Furthermore, the hERG assay indicated a low risk of QT interval prolongation at anticipated therapeutic exposures in humans.

2.2.2Toxicological Studies

In the 28-day rat study, adverse findings were observed in the lungs, trachea, heart, skeletal muscle, spleen, ovaries, uterus, and vagina. The NOAEL for rats was determined to be 150 mg/kg/day. In the 28-day study in dogs, target organs included the lungs, heart, bone marrow, and spleen, with a NOAEL of 10 mg/kg/day. Toxicity studies lasting up to 13 weeks in rats and dogs revealed macrophage infiltration and vacuolation in multiple tissues. Treatment with adagrasib was associated with foamy macrophages and vacuolated epithelium, consistent with phospholipidosis, a condition commonly linked to cationic amphiphilic drugs and characterized by "myeloid bodies."

Most toxicological findings, including these tissue changes, were reversible upon treatment cessation. The 13-week studies established NOAELs of 150 mg/kg/day in rats and 15 mg/kg/day in dogs, corresponding to safety margins of 2.4 and 0.3, respectively.

Adagrasib was not genotoxic in a standard battery of genotoxicity studies. The metabolites of adagrasib tested in genotoxicity assays were also negative. In alignment with ICH S9, carcinogenicity studies have not been conducted with adagrasib. Furthermore, adagrasib showed no phototoxicity potential in an in vitro phototoxicity assay.

Histopathological findings in male and female reproductive organs in rats and dogs suggest that adagrasib may impair fertility. In developmental and reproductive toxicology studies, administration of adagrasib to pregnant rats at doses of 270 mg/kg/day resulted in a higher incidence of skeletal malformations, including bent limb bones, as well as developmental variations such as bent scapulae, wavy ribs, and supernumerary short cervical ribs. These findings were associated with maternal toxicity, indicating secondary fetal effects. Similar maternal toxicity was observed in rabbits.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Adagrasib exposure increased more than proportionally with single doses ranged of 200 to 600 mg in healthy subjects. On the other hand, adagrasib exposure presents dose proportional following multiple doses ranged 400 to 600 mg BID in patients. Food intake does not exhibit a clinically meaningful effect on PK for administration of KRAZATI. KRAZATI can be administered with or without food. Following repeat dosing of 600 mg BID in patients, the steady state of adagrasib was reached within 8 days of dosing, and adagrasib accumulated approximately 6-fold relative to a single dose. The geometric mean V_z/F is 942 L, suggesting that adagrasib is extensively distributed into tissues.

M55a, M11, and M66 were the major metabolites of adagrasib after single-dose administration. However, M55a was not detected in human plasma at steady state after repeated dosing at 600 mg BID. It is due to the auto-inhibition effect on CYP3A4 of adagrasib. The CYP3A4-mediated intrinsic clearance is auto-inhibited by adagrasib after reaching the steady state, and then adagrasib will be metabolized by other enzymes (e.g. CYP2C8, 1A2, 2B6, 2C9, and 2D6). A mean 74.7% of the dose was recovered in

feces, and 4.5% was recovered in urine in the clinical mass balance study. It indicated that fecal elimination is the primary elimination route of adagrasib and its metabolites. The mean $t_{1/2}$ in patients was 23 hours. The geometric mean CL/F is 36.5 L/h. Adagrasib were metabolized via multiple recombinant CYP enzymes.

2.3.2 Interaction Studies

Co-administration of multiple-doses of itraconazole, a strong CYP3A4 inhibitor, 200 mg once daily with a single-dose of 200 mg adagrasib increased adagrasib C_{max} and AUC by approximately 2.4- and 4-fold. However, the C_{max} and AUC of adagrasib at steady-state in PBPK model were not affected by itraconazole following 200 mg QD regimen. The lack of itraconazole effect on adagrasib was due to the extent of auto-inhibition on CYP3A4-mediated intrinsic clearance by adagrasib at steady state. Therefore, strong CYP3A4 inhibitors need to be avoided until adagrasib reach the steady state.

In PBPK modeling, co-administration of multiple-doses of rifampin, a strong CYP3A4 inducer, following 600 mg QD, with multiple-doses of 600 mg adagrasib BID in patients is predicted to decrease adagrasib C_{max} by 61% and AUC by 66%. Co-administration of adagrasib with strong CYP3A4 inducers should be avoided.

Based on the drug exposure data from clinical studies and PBPK model, co-administration with sensitive CYP3A4, CYP2C9, CYP2D6, and P-gp substrates should be avoided unless otherwise recommended in the prescribing information for these substrates. No dosage adjustments for CYP2B6, BCRP, and MATE substrates are warranted during co-administration with adagrasib.

Adagrasib exhibits pH-dependent solubility and may be decrease absorption while co-ministered with acid-reducing agents. Co-administration of multiple doses of 40 mg pantoprazole, a PPI, once-daily with a single 600 mg dose of adagrasib decreased adagrasib C_{max} and AUC by approximately 38% and 32%, respectively. However, the adagrasib PK differences did not exhibit a clinically meaningful effect based on exposure-response analysis for efficacy. No dosage adjustments for acid-reducing agents are warranted during co-administration with adagrasib.

2.3.3 Special Populations

In Pop-PK analysis, the PK parameters of adagrasib was not influenced by health status, gender, age, ethnicity, weight, hepatic impairment based on National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria, renal impairment based on

creatinine clearance [CL_{CR}] or estimated glomerular filtration rate (eGFR), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and baseline tumor burden. Therefore, adagrasib can be administered without adjustment regard to these factors.

Following a single-dose of 600 mg adagrasib in subjects with normal renal function ($CL_{CR} \geq 90$ mL/min), mild ($CL_{CR} \geq 60$ and < 90 mL/min), moderate ($CL_{CR} \geq 30$ and < 60 mL/min), and severe ($CL_{CR} < 30$ mL/min) renal impairment, no clinically meaningful difference in adagrasib exposure was observed. Therefore, no dose adjustment for adagrasib is needed in subjects with mild, moderate, or severe renal impairment. Renal excretion of adagrasib was negligible in all renal function groups, with only 0.51% to 1.29% of the administered dose excreted in urine as unchanged adagrasib, supporting that the kidney does not play an important role in the elimination of adagrasib.

Following a single-dose of 600 mg adagrasib, the AUC_{∞} of adagrasib in subjects with mild (Child-Pugh [CP] Class A), moderate (CP Class B), and severe hepatic impairment (CP Class C) was generally similar to those in subjects with normal hepatic function. However, the unbound AUC_{∞} ($AUC_{\infty,u}$) of adagrasib in subjects with severe hepatic impairment was approximately 80% higher than those in subjects with normal hepatic function. It was due to the low albumin levels of subjects with severe hepatic impairment and higher protein-bound percentage of adagrasib in plasma (98-99%). $AUC_{\infty,u}$ tends to be sensitive to slight changes in fraction of unbound drug (f_u) and protein levels in plasma. However, adagrasib was eliminated predominately by liver (74.7% eliminated via feces in mass balance study), which indicated that the adagrasib clearance of liver was mainly affected by the blood flow to liver rather than f_u. The similar clearance value among all the hepatic impairment groups and normal hepatic function group was consistent to the PK properties. As the result, no dose adjustment for adagrasib is needed in subjects with mild to severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this NDA, the applicant is seeking registration of KRAZATI (Adagrasib) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received at least one prior systemic therapy. The applicant submitted Phase 2 Cohort A results from Study 849-001 to support the licensure of adagrasib. Results of Phase 2 Cohort A from Study 849-001 are summarized below.

- **Phase 2 Cohort A from Study 849-001**

Phase 2 Cohort A of Study 849-001 is a single arm study, which enrolled patients with advanced NSCLC with KRAS G12C mutation who had previously received treatment with at least a platinum-containing chemotherapy regimen and immune checkpoint inhibitor (CIT). All patients received adagrasib at a starting dose of 600 mg twice daily.

A total of 116 patients were enrolled, and all 116 received at least one dose of adagrasib. Of the FAS, 4 patients did not have measurable disease at baseline by BICR , and 112 patients (96.6%) were included in the FAS-BICR population.

As of the data cutoff date of 15 Jun 2021, the primary endpoint of ORR by BICR in the FAS-BICR population was 42.9% (48 patients; 95% CI: 33.5% to 52.6%). The lower bound of the 95% CI exceeded the prespecified threshold ORR of 23%. Based on disease assessments by BICR in the FAS-BICR population, median DOR was 7.3 months. The primary result is supported by disease assessments by Investigator in the FAS, in which ORR was 37.1% (43 patients; 95% CI: 28.3% to 46.5%) with median DOR of 8.3 months.

As of the data cutoff date of 15 October 2021, ORR by BICR in the FAS-BICR population was 42.9% (48 patients; 95% CI: 33.5% to 52.6%) with median DOR of 8.5 months. The result is supported by disease assessments by Investigator in the FAS, in which ORR was 37.9% (44 patients; 95% CI: 29.1% to 47.4%) with median DOR of 9.9 months.

2.4.2 Safety Results

The Applicant submitted 120-day Safety Update after query. A total of 196 subjects with NSCLC who were previously treated with platinum-based chemotherapy and/or CIT (192 subjects received both treatments) received adagrasib at the recommended dose of 600 mg BID.

The most commonly (≥ 20%) reported TEAEs were diarrhea, nausea, vomiting, fatigue, anemia, decreased appetite, dyspnea, blood creatinine increased, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, edema peripheral, constipation, hyponatremia, dizziness, and blood alkaline phosphatase increased. The most commonly (≥ 5%) reported Grade ≥ 3 TEAEs were anemia, dyspnea, pneumonia, fatigue, malignant neoplasm progression, hypoxia, hyponatremia, lipase increased, lymphocyte count decreased, lung infection, electrocardiogram QT prolonged, ALT increased, AST increased, and hypotension.

The majority (82.1%) of subjects had a treatment interruption or dose reduction because of TEAEs. The TEAEs most often (≥ 10%) leading to these dose modifications were nausea, vomiting, diarrhea, fatigue, ALT increased, and AST increased. Twenty-six (13.3%) subjects discontinued adagrasib treatment because of TEAEs. The most common (≥ 2 subjects) TEAEs that led to discontinuation were ejection fraction decreased, malignant neoplasm progression, pneumonia, pneumonitis, and respiratory failure.

Thirty-five (17.9%) subjects had TEAEs with outcome of death within 28 days of last dose. There were 4 treatment-related TEAEs leading to death: cardiac failure, pulmonary hemorrhage, acute respiratory failure, and pneumonitis.

One hundred and sixteen (59.2%) subjects experienced serious TEAEs. The most commonly (≥ 3%) reported serious TEAEs were pneumonia, dyspnea, malignant neoplasm progression, lung infection, sepsis, blood creatinine increased, respiratory failure, hypotension, pericardial effusion, pleural effusion, hypoxia, cardiac failure, hyponatremia, and dehydration.

QTcF interval was increased after adagrasib treatment. A positive relationship between adagrasib concentrations and QTc change was observed. Seventy-three (37.8%) subjects had QTcF ≥ 450 to ≤ 480 msec, 18 (9.3%) subjects had QTcF > 480 to ≤ 500 msec, and 13 (6.7%) subjecs had QTcF > 500 msec. The maximum change from baseline in QTcF was > 30 to ≤ 60 msec for 86 (44.6%) subjects and > 60 msec for 24 (12.4%) subjects.

2.5 Bridging Study Evaluation

At steady state, the Cmax, AUC, and accumulation ratio of AUC (Rac(AUC)) of adagrasib observed in Chinese patients were similar to those in global patients in pivotal study. Furthermore, covariate analysis in PopPK showed that no clinically meaningful differences in the PK of adagrasib were observed based on several covariates including race (White, Black, and Asian).Limited number of Asian subjects were enrolled in Study 849-001. However, there were 108 (23.8%) subjects enrolled from Asian regions, including China mainland, Hong Kong and Korea in the ongoing phase 3 Study 849-012. The interim efficacy and safety results of the Asian subgroup were generally consistent with the overall population.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team recommends approval of adagrasib.

1. Recommended indication:
   Treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy.
   This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s)
2. Recommended dose: 600 mg orally twice daily until disease progression or unacceptable toxicity

3. Post-Marketing Requirements

Submit the clinical study report (CSR) of the following trial(s) once available or after completion.

1. Confirmatory trial: Study 849-012, including East Asian subgroup analysis.