Taiwan Food and Drug Administration

Assessment Report

Trade Name：
杰百康膜衣錠 50 毫克/
JAYPIRCA FILM-COATED TABLETS 50mg
杰百康膜衣錠 100 毫克/
JAYPIRCA FILM-COATED TABLETS 100mg

Active Ingredient：Pirtobrutinib

License Number：MOHW-PI

Applicant：台灣禮來股份有限公司

Approval Date：

Indication：單一療法適用於先前曾接受至少兩線全身性療法(包括一種 Bruton's tyrosine kinase (BTK)抑制劑)的復發性或難治型被套細胞淋巴瘤(MCL)成人病人。此適應症係依據腫瘤反應率加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

JAYPIRCA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Background Information

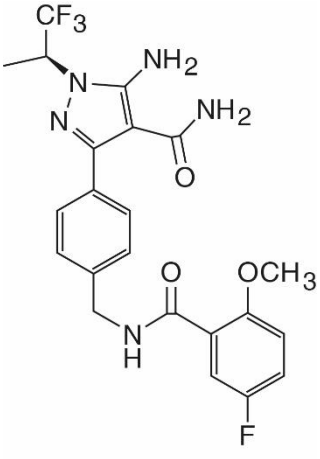
Trade Name	杰百康膜衣錠 50 毫克 / JAYPIRCA FILM-COATED TABLETS 50mg 杰百康膜衣錠 100 毫克 / JAYPIRCA FILM-COATED TABLETS 100mg
Active Ingredient(s)	Pirtobrutinib
Applicant	台灣禮來股份有限公司
Dosage Form & Strengths	膜衣錠 50 毫克/100 毫克
Indication	單一療法適用於先前曾接受至少兩線全身性療法(包括一種 Bruton's tyrosine kinase (BTK)抑制劑)的復發性或難治型被套細胞淋巴瘤(MCL)成人病人。此適應症係依據腫瘤反應率加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 JAYPIRCA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Posology	200 mg once daily orally.
Pharmacological Category **ATC Code**	not yet assigned

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

Drug Substance

The drug substance, pirtobrutinib, is chemically designated as 5-amino-3-{4-[(5-fluoro-2-methoxybenzamido)methyl]phenyl}-1-[(2*S*)-1,1,1-trifluoropropan-2-yl]-1*H*-pyrazole-4-carboxamide and has the following structure:



It is a white to practically white to yellow to brown solid. The molecular formula and the molecular weight are $C_{22}H_{21}F_4N_5O_3$ and 479.44 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of pirtobrutinib has been confirmed by MS, FTIR, NMR, single crystal X-Ray analysis and elemental analysis.

The drug substance specification includes tests for appearance, identification, impurities, enantiomeric impurity, methanesulfonic acid, ethyl methanesulfonate, residual solvents, assay, residue on ignition and water.

Drug Product

The drug product is an immediate release tablet for oral use. Each tablet contains 50 mg or 100 mg of pirtobrutinib. The specifications for excipients used in the drug product formulation are adequate.

The drug product specification includes appearance, identity, uniformity of dosage units, dissolution, degradation products and assay. Analytical methods are described well and validated.

Stability studies of the drug product under long term conditions (30°C/65% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Pirtobrutinib is a non-covalent, reversible small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Biochemical analysis demonstrated that pirtobrutinib is an ATP-competitive inhibitor of BTK and BTK C481S.

In vitro, pirtobrutinib demonstrated equilibrium binding and inhibitory activity against

human BTK and BTK C481 resistance mutant(s) in purified enzyme assays with low nanomolar KD (≤ 1 nM) and single-digit nanomolar IC50 values, respectively. In cellular assays, pirtobrutinib inhibited autophosphorylation of BTK and BTK C481 mutants expressed in HEK cells with IC50 values of nanomolar range (3.9-13.9 nM). Pirtobrutinib inhibited BTK signaling and cell proliferation in multiple human B-cell lymphoma cell lines with single-digit nanomolar IC50 values, but not a non-BTK expressing cell line. Pirtobrutinib also showed inhibitory activity on the activation of human B-cells in PBMCs or whole blood with IC50 values of nanomolar range. In vitro reversibility of pirtobrutinib's binding to BTK was also demonstrated. In human PBMCs, pirtobrutinib occupied BTK in a dose-dependent manner with > 95% mean BTK occupancy at concentrations equivalent to 1- and 1.5-fold the unbound plasma Cmax at the 200 mg clinical dose.

In vivo, orally dosing of pirtobrutinib BID in mouse xenograft tumor models of human ABC-DLBCL and human MCL cell lines significantly inhibited the growth of tumors in a dose-dependent manner and was well tolerated. Also, pirtobrutinib significantly inhibited tumor growth and induced tumor regressions in a DLBCL model expressing BTK C481S.

In vitro, pirtobrutinib showed > 300-fold selectivity for BTK against most of the human non-BTK kinases tested. Nevertheless, pirtobrutinib showed IC50 values of nanomolar to single-digit micromolar range for eight of 371 non-BTK kinases including ERBB4, MEK2, BRK, MEK1, TXK, CSK, YES1, FYN, and TEC. In cell-based assays, pirtobrutinib showed > 100-fold selectivity for BTK with IC50 values of nanomolar range for TEC and BRK, and > 5 micromolar for the rest of the potential off-targets. No significant effects of pirtobrutinib on the other receptors or enzymes were found.

Safety pharmacology endpoints were evaluated in repeated-dose toxicity studies and no effects of pirtobrutinib were noted, except minor effects on QTc in dogs receiving doses that were not tolerated. Based on the findings that no QTc prolongation was observed at doses up to 6-fold human unbound Cmax at 200 mg in a GLP dog cardiovascular safety pharmacology study, and a hERG IC50 measured in vitro is approximately 51-fold human unbound Cmax value at 200 mg QD, low risk of QTc prolongation in humans at clinically relevant doses could be justified.

GLP oral repeated-dose studies in rats and dogs were conducted. No acute toxicity or treatment-related adverse effects were identified in animals receiving a single dose of pirtobrutinib in these repeated-dose studies. Generally, dogs were more sensitive to pirtobrutinib than the rats. The target organs of toxicity included lymphoid

tissues/organs, bone marrow (dog), gastrointestinal tract (large intestines; dog), lung (dog), eye (cornea; dog), and pancreas (rat). Recoverable decreases in red cell mass were noted in both species, which might be relevant to the anemia reported in the clinical trials. Suppression of immune response [e.g., T-cell dependent antibody response (TDAR)] and a shift in the balance of T and B lymphocytes in the blood and or spleen, mainly due to decreases in B lymphocytes, an expected pharmacologic effect of pirtobrutinib, were noted in both species. The exposures of pirtobrutinib at NOAEL in 3-month rat and dog studies provided safety margins of < 1-fold (except 4-fold exposure in female rats) for the recommended clinical dose.

Pirtobrutinib was not mutagenic in an Ames assay but was aneugenic in in vitro micronucleus assays at concentrations > 40-fold unbound Cmax in humans at 200 mg QD. Anyhow, pirtobrutinib was not genotoxic in vivo.

In a GLP pilot EFD study of pirtobrutinib in rats, embryofetal developmental toxicities including increased post-implantation loss, decreased fetal weights, and skeletal and visceral malformation/variations in the absence of maternal toxicity were observed. The NOAEL for maternal and embryofetal developmental toxicities corresponded to < 4-fold and approximately 1-fold the human exposure at 200 mg QD, respectively.

In line with ICH S9, it's acceptable that carcinogenicity studies and an EFD study in a second species were not conducted. Lastly, pirtobrutinib was not phototoxic in vitro.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The active ingredient of JAYPIRC film-coated tablets is pirtobrutinib, which is a kinase inhibitor and used to treat adult patients with relapsed or refractory mantle cell lymphoma (MCL). Food delayed the time to reach the peak plasma concentration by 0.5 to 1 hour, decreased C_{max} by 23%, but did not have impact on the AUC of pirtobrutinib. Thus, JAYPIRCA can administered with or without food.

The absolute bioavailability of pirtobrutinib was 85.5%. Based on the investigation in patients with haematological malignancies following 200 mg once daily (QD), C_{max} was achieved after approximately 2 hours. Pirtobrutinib exposure (AUC) and C_{max} increases proportionally following single oral doses ranging from 300 mg to 800 mg and once daily doses ranging from 25 to 300 mg. Steady state was achieved after approximately 5 days of QD dosing. The mean (CV%) accumulation ratio was 1.48, based on AUC after administration of 200 mg dosages.

The mean apparent oral volume of distribution was 52.3 L (Vc/F:32.8 L; Vp/F:19.5 L). The plasma protein binding was high (96%) and independent of concentration (0.5-50 μM). The blood-to-plasma ratio is approximately 0.79. Pirtobrutinib is metabolized by CYP3A4, UGT1A8, and UGT1A9. Pirtobrutinib was the primary drug-related component in plasma (86.7% of the total circulating radioactivity), and the amount of each of three metabolites (M1, M2 and M4) in plasma was <10%. There were 57.0% (parent drug: 10%) and 37.3% (parent drug: 18.2%) of the radioactive dose recovered in urine and feces, respectively. The mean CL/F of pirtobrutinib was 1.14 L/h with a mean elimination half-life estimated to be 18.8 hours, based on pop-PK analysis.

2.3.2 Interaction Studies

The AUC of pirtobrutinib increased by 11% when combined use with omeprazole (a PPI), but C_{max} and T_{max} did not change. Thus, pirtobrutinib can be administered without regard to acid reducing agents. When pirtobrutinib was combined use with CYP 3A4 modulator, itraconazole (a strong CYP3A4 and P-gp inhibitor) increased AUC_{inf} of pirtobrutinib by 49%, and the AUC_{inf} and C_{max} of pirtobrutinib were decreased by approximately 71% and by 42% following multiple doses of rifampin (a strong CYP3A4 inducer). The dose adjustment of coadministration with CYP3A4 modulator adopted the recommendation in EMA SPC.

2.3.3 Special Populations

Age (range 27-95 years), gender, and body weight (range 35.7-152.5 kg) had no clinically meaningful effect on the exposure of pirtobrutinib. Dose of pirtobrutinib did not have to adjust according to the degree of hepatic dysfunction. Based on population PK analysis, minimal change apparent clearance was observed in patients with mild (60 mL/min/1.73 m^2 ≤ eGFR <90 mL/min/1.73 m^2), moderate (30 mL/min/1.73 m^2 ≤ eGFR <60 mL/min/1.73 m^2) renal impairment; thus, it is not necessary to adjust dose in these two population. Severe (eGFR: <30 mL/min/1.73 m^2; based on CKD-EPI equation) renal impairment increased the AUC and unbound AUC_{inf} of pirtobrutinib by 36% and 34%, respectively. However, the increasing extent of AUC was elevated to 62% and 68% when recalculating PK data using BSA-adjusted eGFR (please refer to the US FDA assessment report and label). Considering the metabolism and excretion pathway of pirtobrutinib and exposure-response relationship for safety, it is acceptable not to adjust pirtobrutinib dose in severe renal impairment, but advise to take care of the happening of adverse events.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study LOXO-BTK-18001 was a phase 1/2, multicenter, open-label and ongoing study

in order to evaluate the efficacy and safety of pirtobrutinib is subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and B cell non-Hodgkin lymphoma, including MCL who had failed or were intolerant to standard of care.

The Primary Analysis Set (PAS) included the first 90 subjects with MCL enrolled from either phase 1 or phase 2, irrespective of pirtobrutinib starting dose, that had received a prior BTK inhibitor containing regimen and was the primary population to support the proposed indication.

The median age of PAS was 70 (range: 46 to 87) years. The majority of subjects were male (80.0%) and White (84.4%). Most subjects had classic/leukemic histology (77.8%), Ann Arbor Stage IV disease (75.6%), and baseline simplified MCL International Prognostic Index (s-MIPI) as intermediate risk (55.6%) or high risk (22.2%). The median number of lines of prior systemic therapy was 3 (range: 1 to 8) with 31 (34.4%) subjects received ≥ 4 lines of prior systemic therapy. All subjects received prior BTK inhibitor, 95.6% received prior anti-CD20 antibody, 87.8% received prior chemotherapy, 21.1% received prior hematopoietic stem cell transplantation (HSCT), and 4 (4.4%) subjects received prior CAR-T therapy.

The overall response rate (ORR) by independent review committee (IRC) assessment was 57.8% (95% confidence interval [CI]: 46.9%, 68.1%). The Kaplan-Meier estimates for the probability of remaining response by IRC assessment at 9 months and 12 months were the same at 57.1% (95% CI: 39.3%, 71.5%).

2.4.2 Safety Results

The safety data were from 725 subjects with MCL, CLL/SLL and other B cell non-Hodgkin lymphoma, including 164 subjects with MCL. The median time on treatment was 8.05 (range: 0 to 34.0) months. Most (88.3%) subjects received pirtobrutinib 200 mg once daily as starting dose.

Nearly all (93.9%) subjects experienced at least one adverse event (AE). The most common (> 10%) AEs included fatigue (26.3%), diarrhea (22.1%), contusion (19.0%), nausea (14.9%), cough (14.8%), anemia (13.9%), dyspnea (13.7%), arthralgia (13.0%), constipation (12.8%), back pain (12.6%), neutrophil count decreased (12.3%), headache (12.1%), pyrexia (12.0%), edema peripheral (11.4%), abdominal pain (11.0%), platelet count decreased (10.2%), and neutropenia (10.1%).

Approximate half (46.9%) subjects had Grade 3 or 4 AEs. The most common (> 5%)

Grade 3 or 4 AEs were neutrophil count decreased (10.6%), neutropenia (8.6%), and anemia (7.7%).

Two hundred and fifty-five (35.2%) subjects had serious AEs (SAEs). The most common (> 1%) SAEs included pneumonia (4.7%), COVID-19 pneumonia (3.9%), COVID-19 (2.3%), febrile neutropenia (1.8%), anemia (1.7%), pyrexia (1.5%), sepsis (1.5%), and acute kidney injury (1.4%).

Forty-five (6.2%) subjects had fatal AEs. Fatal AEs that occurred in more than 1 subject included COVID-19 pneumonia (9 [1.2%] subjects), COVID-19 (6 [0.8%] subjects), and dyspnea, multiple organ dysfunction syndrome, pneumonia, respiratory failure, sepsis and septic shock (2 [0.3%] subjects each).

AEs leading to dose interruption occurred in 252 (34.8%) subjects. Few subjects reported AEs leading to a dose reduction (5.1%) or treatment discontinuation (6.2%).

2.5 Bridging Study Evaluation

Based on population PK analysis, there was 30 patients (5.9%) belonged to East Asian population. Mean apparent clearance and volume of distribution were 18% and 14% lower in East Asian patients. As a result, PK exposure following 200 mg QD were 23% and 17% higher for AUC_{ss} and $C_{max,ss}$, respectively, in East Asian patients, compared to non-East Asian patients. Overall, it is not necessary to adjust dose for East Asian population after considering the PK characteristic of pirtobrutinib and exposure-response relationship.

There were 32 Asian (Japan and South Korea) patients enrolled in the study LOXO-BTK-18001, half (n=16) of whom were MCL patients. The preliminary results showed similar efficacy results and safety profile as non-Asian population. Only that the incidence of cytopenia was slightly higher in Asian population but the severity of cytopenia in Asian population was not higher than Non-Asian population. Besides, the events could be monitored and was manageable.

The confirmatory, phase 3, multinational, multicenter, open-label, randomized, active-controlled Study LOXO-BTK-20019 is ongoing. This study will enroll subjects from China, Japan, and Korea and is expected to provide more Asian clinical data.

Overall, no significant ethnic differences were observed in the limited Asian PK and clinical data. The bridging study of pirtobrutinib was waived.

2.6 Conclusion

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

1. Recommended indication: JAYPIRCA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor.

   This indication is approved under accelerated approval based on response rate. Continued approval of this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
2. Recommended dose: 200 mg once daily orally.

3. Post-Marketing Requirements

Submit the clinical study report (CSR) of the following trials once available or after completion:

1. Confirmatory trial: Study LOXO-BTK-20019, including East Asian subgroup analysis.
2. Other trials:
   (1) Study LOXO-BTL-18001 and US FDA Approval Letter PMR 4389-2 (long-term safety).
   (2) US FDA Approval Letter PMR 4389-3 (risk of secondary primary malignancies).