Taiwan Food and Drug Administration

Assessment Report

Trade Name：達伯坦錠 4.5 毫克 / PEMAZYRE Tablets 4.5 mg

Active Ingredient：Pemigatinib

License Number：MOHW-PI 028063

Applicant：台灣東洋藥品工業股份有限公司

Approval Date：2021.04.08

Indication：適用於成人接受過全身性藥物治療、腫瘤具有 FGFR2 融合或重排、不可手術切除的局部晚期或轉移性膽管癌

Indicated for the treatment of adults with previously systemic therapy treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

Background Information

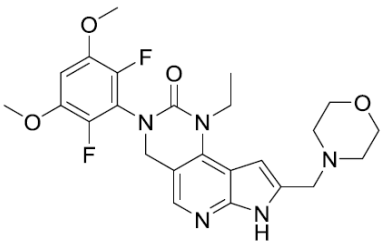
Trade Name	達伯坦錠 4.5 毫克 / PEMAZYRE Tablets 4.5 mg
Active Ingredient(s)	Pemigatinib
Applicant	台灣東洋藥品工業股份有限公司
Dosage Form & Strengths	錠劑 /4.50 mg
Indication	適用於成人接受過全身性藥物治療、腫瘤具有 FGFR2 融合或重排、不可手術切除的局部晚期或轉移性膽管癌。 Indicated for the treatment of adults with previously systemic therapy treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01EX20

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Pemigatinib is used as the drug substance of PEMAZYRE™ tablet. Pemigatinib has the following chemical structure:



The molecular formula and the molecular weight of the drug substance are $C_{24}H_{27}F_2N_5O_4$ and 487.5 g/mol, respectively. It's a white to off-white solid.

The structure of pemigatinib is confirmed by NMR spectra, mass spectrum, IR spectrum, UV spectrum, and elemental analysis.

The specification of the drug substance includes tests for appearance, identification, assay, related substances, water content, residual solvents, elemental impurities, residue on ignition, crystallinity and particle size.

2.1.2 Drug product

Drug product is supplied as immediate release uncoated tablets for oral administration in strengths of 4.5 mg, 9 mg and 13.5 mg. The excipients used in the drug product formulation comply with the compendial monographs.

Adequate specification has been presented for the drug product. The test items include appearance, identification, assay, degradation products, dissolution, content uniformity and water content. Analytical methods are described and well validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

Pemigatinib is an oral kinase inhibitor of fibroblast growth factor receptors (FGFR) 1, 2, and 3. It is indicated for the treatment of adults with cholangiocarcinoma (CCA) with a FGFR2 fusion or other rearrangement. The FGFR genetic alterations activate FGFR signaling, which regulates cell proliferation, survival, migration, and angiogenesis and may drive tumorigenesis. Pemigatinib inhibits FGFR phosphorylation and the downstream signaling and selectively decreases cell viability in cancer cells with FGFR genetic alterations.

In vitro, pemigatinib was a potent and selective inhibitor of FGFR1, FGFR2, and FGFR3 via demonstrating its activity in a series of enzyme-based and cell-based assays. Compared with cancer cell lines or normal cells without FGFR dependence, pemigatinib was approximately 30-500 folds more potent in cell growth inhibition of cancer cell lines with genetic alterations in FGFR1/2/3. *In vivo*, pemigatinib potently inhibited tumor growth in several xenograft cancer models with dependence on FGFR1, FGFR2, or FGFR3 activity, including a patient-derived xenograft model of cholangiocarcinoma that expressed an oncogenic FGFR2-TRA2B fusion protein. *In vivo* IC_{50} value gathered in a PK-PD analysis of pFGFR2 inhibition in KATO-III gastric cancer was consistent with the *in vitro* IC_{50} value obtained in a whole blood assay. A single dose of pemigatinib in mice resulted in a dose-dependent increase of serum phosphate, the endogenous PD marker for FGFR inhibition.

Secondary pharmacodynamics studies revealed no significant cross-reactivity against receptors, channels, enzymes, or kinases other than FGFR1, FGFR2, and FGFR3. The risk of unintended pharmacological activity is low. *In vitro* GLP hERG assay showed that the IC_{50} value of pemigatinib was approximately 360-fold higher than the unbound mean clinical C_{max}

at the therapeutic dose in humans. Safety pharmacology studies of pemigatinib revealed no adverse findings regarding central nervous system and respiratory parameters in rats and cardiovascular functions in monkeys.

The repeated-dose toxicology studies of pemigatinib in rats and monkeys identified notable findings including hyperphosphatemia, cartilage (monkey only) and physeal dysplasia, and mineralization in various tissues including kidneys, stomach, mesenteric, gastric pulmonary arteries, aorta, heart, lung, eye (cornea; rat only), and ovaries (monkey only). Changes in the bone marrow were also observed in rats. These findings were mostly attributed to the intended pharmacologic effects of pemigatinib. The possible pemigatinib-related findings also included lens opacities of moderate severity and slight attenuation of retinal vessels noted in the 28-day monkey study. In addition, the repeated-dose rat studies had shown an increase in corneal crystals in all pemigatinib-treated groups, which was considered an exacerbation of a spontaneously occurring condition. In the monkey studies, the fully reversible mild-to-moderate elevation of ALT and/or AST was noted in animals at higher doses, but no other parameters or microscopic changes in liver were observed.

Pemigatinib was negative in a battery of genotoxicity studies and thus not expected to exhibit a genotoxic risk to humans. Pemigatinib was teratogenic in a non-GLP embryo/fetal development study in pregnant rats. The result was consistent with the substantial role of FGF/FGFR signaling in embryo-fetal development. No additional developmental and reproductive toxicity studies were performed with pemigatinib. Lastly, pemigatinib did not demonstrate phototoxic potential in an *in vitro* assay.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following multiple-dose administration in participants with advanced malignancies, pemigatinib exhibited rapid absorption achieving C_{max} at approximately 1 to 2 hours post-dose with linear PK over a dose range of 1 to 20 mg. Steady-state was achieved within 4 days following repeated once daily dosing. With repeated once daily dosing, pemigatinib accumulated with a median accumulation ratio of 1.63 Administration of pemigatinib with a high-fat and high-calorie meal had no clinically meaningful effect on pemigatinib PK. The apparent steady-state volume of distribution was moderate (235 L).

*In vitr*o, pemigatinib was 90.6% bound to human plasma proteins at concentrations ranging from 1 to 10 μM. Pemigatinib is predominantly metabolized by CYP3A4 *in vitro*. Unchanged pemigatinib is the primary circulating component in plasma with mean elimination half-life of approximately 15 hours. Following a single oral 13 mg dose of radiolabeled pemigatinib, 82.4% of the dose was recovered in feces (1.4% as unchanged) and 12.6% in urine (1% as

unchanged). The exposures of pemigatinib in participants with cancer were approximately 50% higher than those in healthy participants.

2.3.2 Interaction Studies

An *in vitro* study demonstrated that pemigatinib was not a potent inhibitor or inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Pemigatinib is an inhibitor of P-gp, OCT2, and MATE1.

A CYP3A4-mediated DDI study (INCB 54828-104) showed that co-administration of a strong CYP3A4 inhibitor (itraconazole) increased pemigatinib C_{max} 17% and $AUC_{0\text{-}inf}$ 88%, respectively compared to administration of pemigatinib alone; a strong CYP3A4 inducer (rifampin) decreased pemigatinib C_{max} 62% and $AUC_{0\text{-}inf}$ 85%, respectively compared to administration of pemigatinib alone. The PBPK model-predicted geometric mean AUC of pemigatinib was increased by approximately 50%~80% when pemigatinib was co-administered with a moderate CYP3A inhibitor. The predicted geometric mean AUC of pemigatinib was decreased by more than 50% when it was co-administered with moderate CYP3A inducer. In gastric pH–modifying agents mediated DDI study (INCB 54828-106), co-administration of esomeprazole with pemigatinib; showed an approximately 35% and 8% decrease in C_{max} and $AUC_{0\text{-}inf}$, respectively however, the marginal decrease in exposure is not anticipated to be clinically meaningful.

2.3.3 Special Populations

In a population PK analysis, the impact of age, body weight, race/ethnicity, gender, tumor type (cholangiocarcinoma), and FGFR2 alteration on pemigatinib clearance was not statistically significant. In the population PK model, there were no significant differences in apparent clearance of pemigatinib in participants with mild (N=134, 42.1%) or moderate (N=38, 11.9%) renal impairment compared to participants with normal renal function (146, 45.9%).

In the population PK model, there were no significant differences in apparent clearance of pemigatinib in participants with mild (N=94, 29.4%) or moderate (N=11, 3.5%) hepatic impairment compared to participants with normal hepatic function (N=213, 67%). In addition, 2 clinical pharmacology studies in organ dysfunction participants are ongoing: a hepatic impairment study (INCB 54828-107) and a renal impairment study (INCB 54828-108).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Sponsor provided one Phase II study (54828-202) to support the efficacy of PEMAZYRE™ Tablets 4.5 mg, 9 mg, 13.5 mg (Pemigatinib) for the claimed indication. The major design features and results of study 54828-202 were summarized as follows:

Study 54828-202:

This is a prospective, open-label, multi-national study of pemigatinib in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma who have progressed on at least 1 line of prior systemic therapy.

Participants were assigned to one of the following cohorts based on tumor FGF/FGFR status

- Cohort A: FGFR2 rearrangements or fusions
- Cohort B: FGF/FGFR alterations other than FGFR2 rearrangements or fusions
- Cohort C (United States only): negative for FGF/FGFR alterations

The primary endpoint is Objective response rate (ORR) in participants with tumors with FGFR2 rearrangements or fusions (Cohort A) based on the central genomics laboratory results.

In Cohort A, ORR based on IRC-assessed, confirmed tumor responses was 35.5% (95% CI: 26.50%, 45.35%), including 3 complete responses (2.8%) and 35 partial responses (32.7%). The study achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR > 15%).

The median DOR was 7.49 months (95% CI: 5.65, 14.49). The median PFS and OS were 6.93 months (95% CI:6.18, 9.59) and 21.06 months(95%CI: 14.82, NE), respectively. Compared to the experience of 2nd-line FOLFOX for biliary tract cancer, Study 54828-202 showed much longer OS.

2.4.2 Safety Results

Dose reduction and interruption rate were comparable between different analysis populations. In the overall population, sixty-two participants (42.5%) had TEAEs leading to pemigatinib interruption. The most frequent events leading to pemigatinib interruption were stomatitis (7.5%), palmar-plantar erythrodysesthesia syndrome (5.5%), arthralgia (4.8%), and fatigue (4.1%). The tolerability of proposed dosing was acceptable.

All participants in Study INCB 54828-202 had at least 1 TEAE. The majority of these events was Grade 1 or 2 in severity and considered related to pemigatinib by the investigator. Treatment-emergent events of ≥ Grade 3 severity occurred in 63.7% of participants. The most frequently reported TEAE by preferred term was hyperphosphatemia (58.2%), alopecia (49.3%), diarrhea (46.6%), fatigue (42.5%), dysgeusia(40.4%), nausea (39.7%), constipation and stomatitis (34.9% each), dry mouth (33.6%), and decreased appetite (32.9%).The most frequent TEAE ≥ Grade 3 included hypophosphatemia(12.3%), arthralgia(6.2%), stomatitis(5.5%), fatigue(4.8%), abdominal pain(4.8%) and palmar-plantar erythrodysaesthesia syndrome(4.1%)。

In the overall population, sixty-five participants (44.5%) had serious TEAEs. The most frequently reported serious TEAEs were abdominal pain and pyrexia (4.8% each) and cholangitis and pleural effusion (3.4% each).

AESI (incidence) included:

- Nail toxicity (42.5%): Most nail toxicity events were Grade 1 or 2 in severity; only 2.1% of these events were ≥ Grade 3. None of the events of nail toxicity were considered serious, and none led to discontinuation.

-Hyperphosphatemia (60.3%): hyperphosphatemia is consistent with the on-target pharmacologic effect of FGFR inhibition None of these events were ≥ Grade 3 in severity, serious, or led to discontinuation.

- Hypophosphatemia (22.6%): The mechanism is unclear. TEAEs of hypophosphatemia ≥ Grade 3 were observed in12.3% of participants. Among them, two patients (both Cohort A) had clinical s/s: one had sinus bradycardia, the other one had Grade 3 hyponatremia (serious), Grade 2 seizure, and Grade 3 dehydration. All other events of ≥ Grade 3 hypophosphatemia were mainly laboratory findings and not associated with clinically significant signs or symptoms.

-Serous retinal detachment (4.1%) and eye disorders (5%): With the exception of 1 event, events were Grade 1 or 2 in severity and not serious. The only serious event was retinal detachment (Grade 3) considered unrelated to pemigatinib by the investigator. The most frequently reported eye disorders were dry eye (25.3%), trichiasis (8.2%), punctate keratitis (6.2%), and growth of eyelashes (5.5%). Most of these eye TEAEs were Grade 1 or 2 in severity.The eye events ≥ Grade 3 were dry eye, retinal artery occlusion, keratitis, and vision blurred in a single participant each.

No clinically meaningful trends were noted in hematology, coagulation, urinalysis, vital signs, or ECG results.

2.5 Bridging Study Evaluation

The mean $C_{max,ss}$ at 13.5 mg in Japanese (N=19, Study INCB 54828-102) and Caucasian (N=49, Study INCB 54828-101) participants with advanced malignancies were 203 and 277 nmol/L, respectively. The mean $AUC_{,ss\ 0\text{-}24}$ in Japanese and Caucasian participants with advanced malignancies were 2640 and 3045 hr•nmol/L, respectively. The geometric mean values of both $C_{max,ss}$ and $AUC_{,ss\ 0\text{-}24}$ were slightly lower in Japanese compared to Caucasian, but the difference observed in exposure parameters were not considered clinically relevant. The effect of race on pemigatinib PK was also evaluated via the population PK analysis. The estimated CL/F showed that Japanese participants (N=28, 8.8% of analysis population) had similar oral clearance compared with Western participants. Overall, race is not a sensitive factor on pemigatinib PK.

The sponsor submitted Asian subgroup analysis in Study INCB 54828-202 for bridging study evaluation. Among a total of 22 Japanese participants, eleven were in Cohort A. Based on the limited information, ORR and safety profile were generally comparable between the Asian population and the Non-Asian population.

In summary, bridging study was waived for pemigatinib.

2.6 Conclusion

PEMAZYRE (pemigatinib) as a treatment for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement demonstrates a favorable risk-benefit profile with enough evidence to recommend accelerated approval.

3. Post-Marketing Requirements

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial of Study INCB 54828-302. The sponsor has to submit the CSR of Study INCB 54828-302 after completion.