Taiwan Food and Drug Administration

Assessment Report

Trade Name：Smyraf film-coated Tablets 50mg

Active Ingredient：Peficitinib Hydrobromide

License Number：MOHW-PI 027856

Applicant：Astellas Pharma Taiwan Inc. / 台灣安斯泰來製藥股份有限公司

Approval Date：2020/05/21

Indication：

合併 methotrexate 或其他傳統型疾病緩解型抗風濕藥物(DMARDs)，適用於治療患有中度至重度活動性類風溼性關節炎，且對至少一種傳統型疾病緩解型抗風濕藥物(DMARDs)無法產生適當治療反應或無法耐受之成人病人。
Smyraf 與 methotrexate 併用，經 X 光檢查顯示可減緩疾病造成的關節結構性受損。

Smyraf in combination with methotrexate or other conventional DMARDs, is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more conventional DMARDs.

Smyraf in combination with methotrexate has been shown to inhibit the progression of structure damage as measured by X-ray.

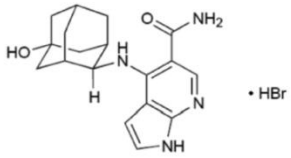
1. **Background Information**

Trade Name	Smyraf film-coated Tablets 50mg
Active Ingredient(s)	Peficitinib Hydrobromide
Applicant	Astellas Pharma Taiwan Inc.
Dosage Form & Strengths	Film-coated tablets、62.4 mg
Indication	Smyraf in combination with methotrexate or other conventional DMARDs, is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more conventional DMARDs. Smyraf in combination with methotrexate has been shown to inhibit the progression of structure damage as measured by X-ray. 合併 methotrexate 或其他傳統型疾病緩解型抗風濕藥物(DMARDs)，適用於治療患有中度至重度活動性類風溼性關節炎，且對至少一種傳統型疾病緩解型抗風濕藥物(DMARDs)無法產生適當治療反應或無法耐受之成人病人。 Smyraf 與 methotrexate 併用，經 X 光檢查顯示可減緩疾病造成的關節結構性受損。
Posology	For adults, the usual dosage is 150 mg as peficitinib orally administered once daily after a meal. The dose can be 100 mg depending on the patient's condition.
Pharmacological Category **ATC Code**	N/A

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Peficitinib hydrobromide is a white powder, non-hygroscopic solid.



The chemical structure of the drug substance is confirmed by elemental analysis, ultraviolet spectroscopy, IR, NMR (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, and single-crystal X-ray diffraction.

The proposed specifications for the drug substance include description, identification, impurities, residue on ignition, and assay. The analytical methods used have been adequately described and appropriately validated.

2.1.2 Drug product

Peficitinib hydrobromide tablets 50 mg and peficitinib hydrobromide tablets 100 mg are film-coated tablets. Each tablet contains 62.4 mg (equivalent to 50 mg of peficitinib) or 124.8 mg (equivalent to 100 mg of peficitinib) of the drug substance.

All excipients are well known ingredients and suitable for proposed formulation. The proposed specifications for the drug product include description, identification, related substances, uniformity of dosage units, dissolution, microbial limit, and assay.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The non-clinical pharmacology data demonstrated that peficitinib is an inhibitor of JAK family members (i.e., JAK1, JAK2, JAK3, and Tyk2) and suppressed IL-2-induced T cell proliferation and production of inflammatory cytokines such as IFN-γ and TNF-α. At a higher concentration, peficitinib inhibited EPO-induced proliferation of a human erythroleukemia cell line. Peficitinib hydrobromide also inhibited the progression of joint swelling and bone destruction in the arthritis model. Results from the safety pharmacology studies showed no apparent effect of peficitinib hydrobromide on the central nervous, cardiovascular, or respiratory systems.

2.2.2 Toxicological Studies

The results of the toxicology studies revealed effects on the immune system (a decrease in lymphocyte count, decreases in the number of T and NK cells, atrophic changes in the lymphoid organs), opportunistic infections and anemic changes .

Besides, effects on the GI tract and muscular tissue were noted, all of which were considered to be reversible changes. The results of the 26-week repeated-dose toxicity study in rats and 52-week repeated-dose toxicity study in cynomolgus monkeys showed that the exposure at the NOAEL (3 mg/kg per day for rats and 2 mg/kg per day for cynomolgus monkeys) was lower than the exposure at the maximum recommended clinical dose (150 mg per day). However, the changes observed were considered attributable to the pharmacological action of the drug or reversible changes that were seen with existing immunosuppressive agents.

Carcinogenicity studies showed the increased incidence of benign thymoma in rats; however, similar findings were seen with tofacitinib citrate, a JAK inhibitor, and other immunosuppressive agents, it was not considered a new safety concern.

Reproductive and developmental toxicity studies showed teratogenicity, embryo-fetal lethality, fetal growth retardation, abnormal parturition, and lethality in suckling pups. Clinically, peficitinib hydrobromide must not be administered to pregnant women and women of childbearing potential, and lactating women must be advised to avoid breast-feeding during treatment with this drug.

In the combination toxicity studies, effects on the immune system and anemic changes were observed; however, these changes were considered unlikely to cause great concern for humans. Peficitinib hydrobromide raised no concern for genotoxicity, the toxicity of metabolites or phototoxicity.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The exposure of peficitinib increases in a dose proportional manner across a dose range of 20-200 mg. The C_{max} appeared at 1 to 2 hours post dose. The elimination $T_{1/2}$ was 3.7~7.5 hr. After administrating 150 mg once daily under fed condition, peficitnib achieved steady state on the third day with minor accumulation. Compared to the absorption extent of healthy Japanese subjects following 150 mg single dose under fasted condition, meal has increase C_{max} 56.4% and AUC_{last} 36.8%. Due to the significant food effect, it was recommended to administer peficitinib with food in compliance with the administration guide in pivotal studies.

The protein binding rate of peficitinib was 72.83~75.20%, which mainly binds to albumin. According to animal distribution studies, peficitnib distributed rapidly into liver followed by kidney. Peficitinib-derived components would transfer into fetuses through placenta and secrete into breasting milk. SULT2A1 and NNMT were responsible for metabolizing peficitnib. In human mass balance study conducted with 100 mg single dose of ^{14}C-peficitnib, the urinary and fecal radioactivity were 36.8% and 56.6%, respectively.

2.3.2 Interaction Studies

Peficitnib was a substrate of P-gp, and would inhibit CYP3A, CYP2C8, BCRP, OATP1B1 and OCT1 transporters based on in vitro data. But no significant drug-drug interaction was observed in clinical drug-drug interaction studies.

2.3.3 Special Populations

No dose adjustment was recommended for mild, moderate and severe renal impaired population. For mild hepatic impaired subjects, minor increase of C_{max} and AUC by peficitinib was observed, suggesting no dose adjustment. However, peficitnib increases C_{max} and AUC significantly in moderate hepatic impaired subjects. It was recommended to reduce dose to 50 mg QD and use with caution. For severe hepatic impaired subjects, it was not recommended to use due to lack of sufficient investigation.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Three studies (CL-RAJ1, CL-RAJ3, and CL-RAJ4) were reviewed to evaluate the efficacy of peficitinib for the treatment of rheumatoid arthritis (including prevention of structural joint damage) in patients who had an inadequate response to conventional therapy. Study CL-RAJ1 was a Phase 2b trial conducted in rheumatoid arthritis (RA) patients with or without a history of RA treatment including untreated patients. Study CL-RAJ3 was a Phase 3 trial conducted in RA patients who had an inadequate response to at least 1 DMARD. Study CL-RAJ4 was a Phase 3 trial conducted in RA patients who had an inadequate response to MTX.

The primary efficacy variable of studies CL-RAJ1 and CL-RAJ3 was ACR20 response rate at week 12. The primary efficacy variables of study CL-RAJ4 were ACR20 response rate at week 12 and the change from baseline in Modified Total Sharp Score (mTSS) at week 28 (suppression of joint destruction).

In Study CL-RAJ1, the ACR20 response rates at week 12 (LOCF) were 10.7%, 23.6%, 31.6%, 54.5% and 65.5% in the placebo, peficitinib 25 mg, 50 mg, 100 mg and 150 mg groups, respectively. The differences from the placebo group were 12.9%, 20.9%, 43.8% and

54.8% in the peficitinib 25 mg, 50 mg, 100 mg and 150 mg groups, respectively, and were statistically significant in the peficitinib 50 mg ($p = 0.021$), 100 mg ($p < 0.001$) and 150 mg ($p < 0.001$) groups.

In Study CL-RAJ3, the ACR20 response rates at week 12 (LOCF) were 30.7%, 57.7% and 74.5% in the placebo, peficitinib 100 mg and peficitinib 150 mg groups, respectively. The differences from the placebo group were 27.0% and 43.8% in the peficitinib 100 mg and 150 mg groups, respectively, and were statistically significant in the peficitinib 100 mg ($p < 0.001$) and 150 mg ($p < 0.001$) groups.

In Study CL-RAJ4, the ACR20 response rates at week 12/ET (LOCF) were 21.8%, 58.6% and 64.4% in the placebo, peficitinib 100 mg and 150 mg groups, respectively. The differences from the placebo group were 36.9% and 42.6% in the peficitinib 100 mg and 150 mg groups, respectively, and were statistically significant in the peficitinib 100 mg ($p<0.001$) and 150 mg ($p<0.001$) groups. The mean changes from baseline in mTSS at week 28 (linear extrapolation) were 3.37, 1.62 and 1.03 in the placebo, peficitinib 100 mg and 150 mg groups, respectively. Based on the rank analysis of covariance model, the differences from the placebo group were statistically significant in the peficitinib 100 mg ($p < 0.001$) and 150 mg ($p < 0.001$) groups.

In summary, all of the three studies (CL-RAJ1, CL-RAJ3, and CL-RAJ4) showed significant improvement of ACR20 response rate for peficitinib 100 mg (all $p < 0.001$) and 150 mg (all $p < 0.001$) compared with placebo. Additionally, Study CL-RAJ4 showed significant improvement of mTSS at week 28 for peficitinib 100 mg ($p < 0.001$) and 150 mg ($p < 0.001$). It is notable that number of peficitinib monotherapy is very limited. The efficacy evidence from phase III clinical trial mainly came from peficitinib in combination with conventional DMARDs (including MTX).

2.4.2 Safety Results

Safety evaluation of peficitinib showed similar safety signals as other JAK inhibitors. The most common AEs were nasopharyngitis, creatine phosphokinase increased, upper respiratory tract infection, hepatic function impairment, and pharyngitis. There were 2 fatal AEs (diffuse large B-cell lymphoma, sarcoma uterus) judged as probably/possibly related to peficitinib treatment. Exposure-adjusted analysis of AE showed the incidence rate of serious infection, herpes zoster related disease, dyslipidemia, hypertension, neutropenia and lymphopenia, rhobdomyolysis/myopathy were higher for peficitinib treatment than placebo treatment. No tuberculosis cases noted in phase III clinical trials, and there were 2 HBV reactivation cases noted in phase III clinical trials and the extension study. Some AEs, such as hepatic impairment, serious infection, dyslipidemia, hypertension, had trend of dose-response

relationship. In summary, the safety profiles were generally acceptable for both peficitinib 100mg and 150mg dosages.

2.5 Bridging Study Evaluation

Peficitinib showed dose-proportional increase in exposure across dose range of 20-200 mg in Japanese healthy adults. The ratio was 1.57 to 1.77 and 1.35 to 1.66 for the C_{max} and AUC_{inf} in this dose range. In another study at 150 mg as multiple doses once daily (proposed posology), the exposure showed consistently higher (67% and 35% higher of C_{max} and AUC_{24h}, respectively) in Asian subjects than in non-Asian subjects. No genetic polymorphisms have been reported for sulfotransferases (SULT) 2A1 and nicotinamide N-methyltransferase (NNMT), the major metabolic enzymes of peficitinib. Factors caused higher exposure in Asian rather than non-Asians were still unknown. Peficitinib may be considered a drug with ethnically sensitive in PK.

In phase 3 studies [CL-RAJ3, CL-RAJ4], Asian patients have demonstrated efficacy/safety in proposed posology, and comparable peficitinib exposure was observed in Taiwanese, Japanese and Korean.

Two phase III pivotal studies (CL-RAJ3, CL-RAJ4) were conducted in East Asian, including 38 Taiwanese. The efficacy and safety of the East Asian were acceptable.

Since the majority of clinical data package was conducted in Japanese, the provided PK/PD information for East Asian was sufficient. There was no need to conduct additional bridging study from PK or clinical perspective.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The overall benefit-risk assessment of peficitinib in combination with DMARDs (including MTX) was favorable for patients with moderate to severe rheumatoid arthritis. The overall safety profile was acceptable and can be adequately managed by labeling, routine pharmacovigilance and risk management plan (RMP) in the post-market setting.

Peficitinib is approved for the following indication:

- Smyraf in combination with methotrexate or other conventional DMARDs, is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more conventional DMARDs.

- Smyraf in combination with methotrexate has been shown to inhibit the progression of structure damage as measured by X-ray.

3. Post-Marketing Requirements

Risk management plan is required. Safety signals including severe infection, TB reactivation, hepatitis B and hepatitis C reactivation, malignancy, lymphoproliferative disorders, venous thromboembolism, decrease of blood cell count, and dyslipidemia should be monitored in the post-market setting.