Taiwan Food and Drug Administration

Assessment Report

Trade Name：喜繽果 50 毫克膜衣錠 / CIBINQO 50mg Film-coated Tablets
喜繽果 100 毫克膜衣錠 / CIBINQO 100mg Film-coated Tablets
喜繽果 200 毫克膜衣錠 / CIBINQO 200mg Film-coated Tablets

Active Ingredient：Abrocitinib

License Number：MOHW-PI 028233
MOHW-PI 028234
MOHW-PI 028235

Applicant：美商惠氏藥廠(亞洲)股份有限公司台灣分公司

Approval Date：2022/1/19

Indication：
適用於治療患有中度至重度異位性皮膚炎且適合接受全身性治療的成年人。

Indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy.

Background Information

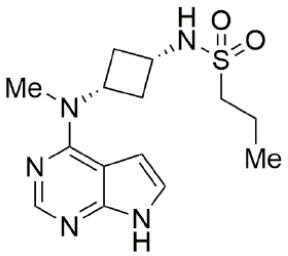
Trade Name	喜繽果 50 毫克膜衣錠 / CIBINQO 50mg Film-coated Tablets 喜繽果 100 毫克膜衣錠 / CIBINQO 100mg Film-coated Tablets 喜繽果 200 毫克膜衣錠 / CIBINQO 200mg Film-coated Tablets
Active Ingredient(s)	Abrocitinib
Applicant	美商惠氏藥廠(亞洲)股份有限公司台灣分公司
Dosage Form & Strengths	膜衣錠劑 50 mg ; 100 mg ; 200 mg
Indication	適用於治療患有中度至重度異位性皮膚炎且適合接受全身性治療的成年人。 Indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy.
Posology	建議劑量為 200 毫克或 100 毫克每日一次。
Pharmacological Category **ATC Code**	D11AH08

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Abrocitinib is used as the drug substance of CIBINQO film-coated tablets. Abrocitinib has the following chemical structure:



The molecular formula and the molecular weight of the drug substance are $C_{14}H_{21}N_5O_2S$ and 323.42 g/mol, respectively. It's a white to pale-colored powder.

The structure of abrocitinib is confirmed by NMR spectra, mass spectrum, IR spectrum, UV/VIS spectrum and X-ray crystallography.

The specification of the drug substance includes tests for appearance, identification, particle size, assay, impurities, residue on ignition and residual solvents.

2.1.2 Drug product

Drug product is supplied as film-coated tablets for oral administration containing 50 mg, 100 mg and 200 mg of abrocitinib. The excipients used in the drug product formulation comply with the compendial monographs and in-house specification.

Adequate specification has been presented for the drug product. The test items include appearance, identification, assay, impurities, dissolution, uniformity of dosage units and microbial limits. Analytical methods are described and well validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

Abrocitinib is a selective oral small molecule JAK1 inhibitor. Biochemically, abrocitinib showed its selectivity against JAK1 over the other 3 JAK isoforms and the other human kinases. Cell-based assays showed that abrocitinib preferentially inhibited signaling by receptors utilizing JAK1, and was less potent against JAK1 independent signaling pathways. In vitro, abrocitinib inhibited several JAK1-dependent cytokines implicated in atopic dermatitis (AD) pathogenesis. The 2 circulating human metabolites of abrocitinib, M1 and M2, are pharmacologically active and have a similar profile of JAKs and cytokine inhibition as abrocitinib.

In vivo, the anti-inflammatory effects of JAK1 inhibition by abrocitinib had been evaluated in the rat AIA model, which showed a significant improvement in disease progression and inhibition of cytokine-dependent STAT phosphorylation. Evidence from other JAK inhibitors, including oclacitinib and tofacitinib, which were tested respectively in a canine flea allergic dermatitis model and a chronic allergic dermatitis rat model, was employed by the applicant to further supported using a JAK inhibitor (e.g., abrocitinib) for the treatment for chronic dermatitis like AD.

Secondary pharmacology studies identified significant inhibition of binding or enzyme activity of MAO-A and VEGFR2 for abrocitinib, with IC50 values 4.8-and 1-fold the unbound human Cmax at MRHD, respectively. The follow-up studies and the monkey repeat-dose toxicity studies suggested a low safety concern associated with VEGFR2. In vitro hERG assay showed that the IC50 values of abrocitinib and the metabolites (M1, M2, M4) were 76-and >240-fold

the human unbound Cmax at MRHD, respectively.

In vivo safety pharmacology studies with abrocitinib identified no effects other than lower locomotor activity and lower body temperature in rats and increases in DBP and heart rate in monkeys.

GLP repeat-dose toxicity studies of abrocitinib in rats and monkeys up to the respective duration of 6 and 9 months showed findings generally consistent with the expected immunomodulatory pharmacology of abrocitinib. Target organs identified in the pivotal toxicology studies included the immune and hematolymphopoietic systems and bone. Most of the abrocitinib-related effects were reversible. The adverse abrocitinib-related opportunistic viral infection had been observed in rats and monkeys at high doses. The potential risk associated with pharmacological immunosuppression by abrocitinib is suggested to be monitored clinically. Adverse abrocitinib-related bone findings had been observed in the 1-month and the juvenile rat studies. The initial age of the animals in the 1-month study was corresponding to a human age of ≥12 years. The NOEL for the bone effects was around 6-fold unbound human AUC at the maximum recommended human dose (MRHD). On the other hand, abrocitinib was administered to juvenile rats during early postnatal bone development at an age comparable to approximately a 3-month-old human. The data indicated that juvenile rats were highly sensitive to JAK inhibition which led to adverse bone findings.

Abrocitinib is considered an in vitro aneugen. No other genotoxic effects were mentioned in a battery of in vitro and in vivo genotoxicity studies. As demonstrated in the carcinogenicity studies, non-adverse abrocitinib-related higher incidence of thymic epithelial cell hyperplasia had been noted in female mice. In rats, a higher incidence of abrocitinib-related thymus hyperplasia and benign thymomas had been reported in females. The exposure of the NOEL in female rats was corresponding to 0.6-fold the unbound AUC at MRHD.

Abrocitinib did not affect the rat male fertility; however, effects of abrocitinib on female rat fertility and increased post-implantation loss were observed. No abrocitinib-related maternal toxicity was noted in the embryo-fetal development studies in rats and rabbits. No malformation but increased abrocitinib-related fetal skeletal variations were observed in rats and rabbits. In the rat pre-and postnatal developmental study, effects on parturition and F1 postnatal development were observed. Lastly, abrocitinib had no phototoxicity potential as tested in vivo.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The oral absolutely bioavailability for CIBINQO was approximately 60%. Following

administered CIBINQO, abrocitinib T_{max} can be reached rapidly at 1 hour, $T_{1/2}$ was about 5 ~ 6 hour. The AD adult patients have higher exposure than healthy adult subjects. There was no clinically relevant difference in mean abrocitinib steady-state exposures in adolescent patients compared to adults at their typical body weights. These may be due to CYP enzyme activity and physiological factors difference. Over the clinical therapeutic range (50 mg ~ 200 mg), abrocitinib C_{max} and AUC_{tau} increased dose proportionally. High-fat meal elevated abrocitinib AUC and C_{max} by 26% and 29%; thus, regardless of food intake was acceptable. The human plasma protein binding ratio of abrocitinib was 0.64. The volume of distribution of abrocitinib was estimated to be 100.2 L. After taking a single dose of abrocitinib, parent drug was the most abounded compound in circulation. Abrocitinib was extensively metabolized by CYP enzyme [CYP2C19 (53%), CYP2C9 (30%), CYP3A4 (11%), and CYP2B6 (6%)], and then formed two active metabolites [M1 :11.3% of the dose; M2: 12.4% of the dose] and other inactive metabolites [M4; 13.8% of the dose]. At steady state, M2 and M4 are major metabolites and M1 is a minor metabolite. The total recovery was 94.5%, with 85.0% from urine (parent:<1% of the dose) and 9.5% from feces (parent: <1% of the dose).

2.3.2 Interaction Studies

Fluvoxamine or fluconazole increased the exposure of the active moiety of abrocitinib. Thus, the dose of abrocitinib is recommended to reduce by half when co-administered with drugs that are strong CYP2C19 inhibitors or strong CYP2C19/moderate CYP2C9 inhibitors. The exposure of the active moiety was reduced by approximately 56% when abrocitinib combined with rifampin. Therefore, co-adminstration with strong CYP2C19/CYP2C9 /CYP3A4 inducers drugs is not recommended. No dose adjustment for abrocitinib is required when co-administered with OAT3 inhibitors.

2.3.3 Special Populations

Gender and body weight have no significant impact on abrocitinib PK. Dedicated renal impairment study presented the exposure of active moiety in moderate (eGFR, 30-60 mL/min) or severe (eGFR, <30 mL/min) renal impairment subjects increased by approximately 110% or 191%, respectively; thus, the dose needed to reduce by 50% (i.e. 50 mg or 100 mg) in these two groups. The predicted elevated extent of the active moiety in mild (eGFR, 60 to 90 mL/min) renal impairment was not recognized as clinically relevant. So, no dose adjustment was required. Mild (Childs Pugh A) or moderate (Childs Pugh B) hepatic impairment patients did not need to adjust dose. Also, abrocitinib was not evaluated in patients with severe (Child Pugh C) hepatic impairment. Based on the CYP2C19 and CYP2C9 genetic polymorphism analysis, no dose adjustment was required according to the phenotype.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provided four pivotal studies ([B7451012], [B7451013], [B7451029] and [B7451036]) to support the efficacy of CIBINQO for the claimed indication.

Study [B7451012] met both co-primary endpoints demonstrating that both abrocitinib 100 mg and 200 mg treatment groups were superior to the placebo group:

- Statistically significantly ($p=0.0037$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved IGA responses for abrocitinib 100 mg (37/156; 23.7%) and 200 mg (67/153; 43.8%) treatment groups compared with the placebo group (6/76; 7.9%).
- Statistically significantly ($p<0.0001$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved EASI-75 responses for abrocitinib 100 mg (62/156; 39.7%) and 200 mg (96/153; 62.7%) treatment groups compared with the placebo group (9/76; 11.8%).

Study [B7451013] met both co-primary endpoints demonstrating that both abrocitinib 100 mg and 200 mg treatment groups were superior to the placebo group:

- Statistically significantly ($p=0.0008$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved IGA responses for abrocitinib 100 mg (44/155; 28.4%) and 200 mg (59/155; 38.1%) treatment groups compared with the placebo group (7/77; 9.1%).
- Statistically significantly ($p<0.0001$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved EASI-75 responses for abrocitinib 100 mg (69/155; 44.5%) and 200 mg (94/154; 61%) treatment groups compared with the placebo group (8/77; 10.4%).

Study [B7451029] met both co-primary endpoints demonstrating that both abrocitinib 100 mg and 200 mg treatment groups were superior to the placebo group:

- Statistically significantly ($p<0.0001$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved IGA responses for abrocitinib 100 mg (86/235; 36.6%) and 200 mg (106/219; 48.4%) treatment groups compared with the placebo group (18/129; 14%).
- Statistically significantly ($p<0.0001$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved EASI-75 responses for abrocitinib 100 mg (138/235; 58.7%) and 200 mg (154/219; 70.3%) treatment groups compared with the placebo group (35/129; 27.1%).

Study [B7451036] met both co-primary endpoints demonstrating that both abrocitinib 100 mg and 200 mg treatment groups were superior to the placebo group:

- Statistically significantly ($p=0.0147$ in 100mg; $p=0.0030$ in 200mg) higher proportion of participants achieved IGA responses for abrocitinib 100 mg (37/89; 41.6%) and 200 mg (43/93; 46.2%) treatment groups compared with the placebo group (23/94; 24.5%).
- Statistically significantly ($p=0.0002$ in 100mg; $p<0.0001$ in 200mg) higher proportion of participants achieved EASI-75 responses for abrocitinib 100 mg (61/89; 68.5%) and 200 mg (67/93; 72%) treatment groups compared with the placebo group (39/94; 41.5%).

2.4.2 Safety Results

The short-term safety of abrocitinib was evaluated from adolescent Study B7451036 and *Primary Safety Pool*, which included 12 to 16 weeks safety data of 1198 subjects enrolled from Phase 2 study B7451006, and Phase 3 studies B7451012, B7451013, and B7451029. The long-term safety was evaluated from *Full Cumulative Pool*, which included additional subjects from Phase 3 studies B7451014, B7451015, and B7451036. A total of 2105 subjects (1238.9 patient-years) have received abrocitinib 200 mg and 1023 subjects (849.9 patient-years) have received 100 mg.

The most common adverse drug reactions were nausea, headache, acne, herpes simplex, creatine phosphokinase increased, vomiting and dizziness. Infections, malignancy, major adverse cardiac events (MACE), and venous thromboembolism (VTE) were the potential or identified risks for the JAK inhibitors. Less than 1% of subjects had lymphopenia and thrombocytopenia. The nadir of platelet count was at Week 4.

2.5 Bridging Study Evaluation

According to observed PK parameters and population PK simulation results, Asian population (AD adult and adolescent patients) have higher exposure (30%~47%) than White population. This may be due to the lower body weight or higher incidence of poor metabolizers (PMs) in Asian population.

The bridging data for ethnic sensitivity of clinical efficacy and safety evaluation was from subgroup analysis of Study B7451013 [Asian subjects: 129 (33%)] and Study B7451029 [Asian subjects: 125 (14.9%)]. The efficacy results of Asian subjects were generally consistent with that of overall population. In general, the safety profile in Asian subjects was similar to that of overall population. The incidence rate of herpes zoster was slightly higher in Asian population.

Considering the therapeutic dose can be adjusted based on clinical evaluation and comparable efficacy/safety data in Asian subpopulation, abrocitinib was not deemed
ethnically sensitive from PK and clinical perspective.

2.6 Conclusion

In conclusion, CIBINQO as a treatment for moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy demonstrated a favorable risk-benefit profile with adequate evidence to recommend regular approval. The recommended starting dose will be different for younger and elderly (≥ 65 years of age) adults. During treatment, the dose should be decreased or increased based on tolerability and efficacy.

The overall benefit-risk profile of CIBINQO in the treatment for moderate-to-severe atopic dermatitis in adolescent 12 years and older is inconclusive. Larger safety pool with longer follow-up period is needed for further assessment on thromboembolic risk, fractures, and growth impairment.

3. Post-Marketing Requirements

The final study report of long-term extension study B7451015 should be submitted to TFDA for review once complete.