Taiwan Food and Drug Administration

Assessment Report

Trade Name：比樂舒活錠 200 毫克 / Pirespa®Tablets 200mg

Active Ingredient：Pirfenidone

License Number：衛部藥輸字第 026734 號

Applicant：台灣塩野義製藥股份有限公司

Approval Date：2016/5/10

Indication：特發性肺纖維化

1. Background Information

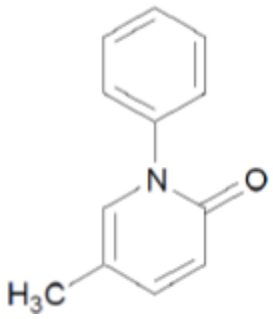
Trade Name	比樂舒活錠 200 毫克 / Pirespa-®Tablets 200mg
Active Ingredient(s)	Pirfenidone
Applicant	台灣塩野義製藥股份有限公司
Dosage Form & Strengths	膜衣錠 200 毫克
Indication	特發性肺纖維化
Posology	成人：Pirfenidone 通常初期投與量為 200mg，1 日投與 3 次(1 日 600mg)，飯後口服。一般觀察病患狀況並將每次投藥量再增加 200mg，依此方式逐步調整至每次投與量為 600mg(1 日 1800mg)。 劑量可適症狀做適當增減。
Pharmacological Category ATC Code	L04AX05

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, pirfenidone, is chemically designated as 5-methyl-1-phenyl-1H-pyridin-2-one and has the following structure:



It is white to slightly yellowish-white crystalline powder, with little odor, with a bitter taste. The molecular formula and the molecular weight are $C_{12}H_{11}NO$ and 185.22, respectively. The structure has no chiral center. It is not hygroscopic. It is sparingly soluble in water.

Adequate information of characterization of the drug substance has been provided. The structure of pirfenidone is confirmed by elemental analysis, UV spectrum, IR spectrum, mass spectrum, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR) and X-ray crystallography. The spectrum assignations were consistent with the declared chemical structure.

The specification includes tests for description, identification, heavy metals, related substances, water content, residue on ignition and assay.

2.1.2 Drug product

Pirfenidone drug product (Pirespa®) is a tablet contained 200 mg of drug substance packaged in blister. The excipients used in the drug product formulation comply with the compendial monographs. Quality by design is used in the process evaluation of manufacturing drug product. The operating parameters are set by two batches. The established operating parameters and test results are acceptable.

Adequate release and shelf-life specification have been presented for the Pirespa® tablets and the test items include description, identification, uniformity of dosage units, dissolution, microbial enumeration test, *Escherichia coli*, related substances and assay. Analytical methods are described well and validated.

Stability studies of bulk packaging under long term (30°C/65% RH) and accelerated condition (40°C/75% RH) have been carried out. The parameters evaluated during the stability study are description, identification, uniformity of dosage units, dissolution, related substances, assay, microbial enumeration tests, *Escherichia coli*. The results are met the specification. Stability studies of drug product under long term condition (25°C/60% RH and 30°C/65% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The precise mechanism of pirfenidone is not fully understood, but the submitted pharmacology data indicated the principal mechanism of action of pirfenidone is thought to be related to its antifibrotic and anti-inflammatory properties. The conventional safety pharmacology studies revealed pirfenidone has no clinically relevant effects on the respiratory system, but may affect the CNS, CVS or GI systems. Pirfenidone has effects on heart rate, blood pressure, ventricular contractions, and QT and QTc intervals in rats or dogs, thus it is necessary to pay attention to the cardiovascular effecst in the clinical use of pirfenidone.

2.2.2 Toxicological Studies

In pivotal repeated-dose toxicity studies in rats and dogs up to 9 months, the common toxic findings were neurological symptoms due to the CNS-depressive action of pirfenidone. Increased liver weights were observed with hepatic centrilobular hypertrophy and increased CYP content in all species. Transient vomiting was observed in dogs. These toxic signs were reversible after pirfenidone administration was stopped.

Preclinical studies on reproductive parameters in rats or rabbits did not indicate that pirfenidone caused impairment of fertility and reproductive performance, and induced teratogenicity. But maternal toxicity and acyclic/irregular cycle (e.g., prolonged estrous cycle) were noted in rats, and prolongation of the gestation period, decreased numbers of live newborn, and reduced pup body weights from the middle lactation period were also seen in rats. Aborted or delivered prematurely was noted in rabbits. Additionally, pirfenidone was shown to be transferred to fetuses via the placenta and also shown to be excreted in the milk in rats, pirfenidone should not be used during pregnancy or nursing women unless clearly necessary. Pirfenidone was unlikely to pose a genotoxic risk in humans, and pirfenidone lacked human-relevant carcinogenic potential. Pirfenidone may induce phototoxicity and photoirritation, and pirfenidone has photoclastogenic potential under UV exposure. These effects are likely to be avoidable/ minimized by protection (application of sunscreen [SPF 50+, PA+++]) from light exposure (sunlight or UV irradiation) in daily life.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Pirfenidone reaches its maximum concentration (T_{max}) 0.5 to 1 hr after a single dose in fasted state. Meal decreases C_{max} by 47 %, $AUC_{0\text{-}48hr}$ by 24 % and increases T_{max} to 1.83 hr. Pirespa® should be taken in fed state because the same posology conducted in pivotal study. The absolute bioavailability of pirfenidone has not been determined in humans. Protein binding rate of pirfenidone was 54~62% after single oral administration of 600 mg under fasted state in healthy subjects. The elimination half-life ($t_{1/2}$) was estimated about 2.17 to 2.55 hr after 200 mg to 600 mg TID administration in healthy subjects. The main metabolite of pirfenidone, 5-carboxy pirfenidone, is formed by CYP1A2 and shows no pharmacological activity. Approximately 80~85 % of a pirfenidone dose is eliminated in urine; with 90 % as the 5-carboxy pirfenidone.

No special population studies and drug-drug interaction studies was conducted. The sponsor only provided the assessment report of Esbriet®, drug containing same active substance (pirfenidone), but with different formula and dose regimen, from the US FDA with lack of PK bridging data between Pirespa® tablet and Esbriet® capsule. Thus, it is not satisfied as a NCE application from PK consideration. When considering the dosage regimen, the proposed dosage regimen in Taiwan is lower than that in the US. Thus, this drug has been approval due to clinical medical needs finally. Therefore, the dose adjustment for DDI and the dose recommendation for special population of Pirespa® should follow Esbriet® capsule US FDA labeling.

2.3.2 Interaction Studies

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1. The concomitant administration of pirfenidone and strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin), reduce Pirespa® to one tablet three times a day. Concomitant administration of pirfenidone and moderate CYP1A2 inhibitor (e.g., 750 mg ciprofloxacin BID), reduce Pirespa® to two tablets three times a day. The concomitant use of pirfenidone and a CYP1A2 inducer may decrease the exposure of pirfenidone (AUC decrease 50%).

2.3.3 Special Populations

For elderly, Pirespa® should be used carefully due to lower physically function in geriatrics.

Pirespa® should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Pirespa® if needed. The safety, efficacy, and pharmacokinetics of Pirespa® have not been studied in patients with severe hepatic impairment, so Pirespa® is not recommended to use in severe hepatic impairment patients.

Pirespa® should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Pirespa® if needed. The safety, efficacy, and pharmacokinetics of Pirespa® have not been studied in patients with end-stage renal disease requiring dialysis. Use of Pirespa® in patients with end-stage renal diseases requiring dialysis is not recommended.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy of pirfenidone for the treatment of idiopathic pulmonary fibrosis was mainly evaluated in a randomized, double-blind, placebo-controlled Japanese study (Study 0402P1032). A total of 275 patients were randomized in a 2:1:2 ratio to one of 3 groups: pirfenidone 1800 mg/day group (110 patients), pirfenidone 1200/day mg group (56 patients), and placebo group (109 patients). The primary endpoint of the study was change from baseline in vital capacity to Week 52 of treatment (or the last observation time point).

Results from Study 0402P1032 showed that the mean change from baseline in vital capacity at Week 52 was -0.09 L in the pirfenidone 1800 mg/day group, -0.08 L in the pirfenidone 1200 mg/day group, and -0.16 L in the placebo group. The

superiority to placebo in mean change of vital capacity was demonstrated in the pirfenidone 1800 mg/day group (difference= -0.07 L, p=0.0416 by ANCOVA) and the pirfenidone 1200 mg/day group (difference= -0.09 L, p=0.0394 by ANCOVA). The difference between the 1800 mg/day and 1200 mg/day groups was not significant (difference= -0.02 L, p=0.7077 by ANCOVA).

2.4.2 Safety Results

The most frequently reported adverse events in the pirfenidone 1800 mg, 1200 mg groups versus placebo group were photosensitivity (51.4%, 52.7%versus 22.4%), anorexia (16.5%, 10.9% versus 2.8%), decreased appetite (9.2%, 3.6% versus 2.8%),
rash (9.2%, 9.1% versus 8.4%) and γ-GTP increased (22.9%, 21.8% versus 9.3%). The severity of photosensitivity was mild in 71% of cases and moderate in 29% of cases.

2.5 Bridging Study Evaluation

Pirespa® 200-mg tablet, sponsored by Shionogi, had its own phase I to phase III trials conducted in Japanese patients and also has been approved by PMDA. Esbriet® 267-mg capsule, drug containing the same active substance, sponsored by InterMune had been approved by US FDA and EMA. Due to lack of PK bridging data between Pirespa® tablet and Esbriet® capsule, it cannot be determined the ethically sensitive issue of pirfenidone between Western and Asian subjects. However, the proposed dosage regimen in Taiwan is same as Japanese dosage regimen and drug metabolizing profiles in Taiwanese and Japanese are resemble each other. Thus, it is unlikely that there is great difference in PK between Taiwanese and Japanese. Hence, the bridge study evaluation is waived.

The primary and most of the key secondary endpoints were different in Asian (SP3) and Caucasian (PIPF-004) phase 3 studies. In addition, the baseline VC (FVC) and study duration were different. Therefore, it is difficult to compare the efficacy between races. In both Asian and Caucasian, skin and gastrointestinal disorders developed more in pirfenidone group. However, photosensitivity reaction occurred much more in Asian (51.4% in 1800 mg/day) than in Caucasian (12.2% in 2403 mg/day). In contrast, rash developed more in Caucasian (32.2% in 2403mg/day) than in Asian (9.2% in 1800 mg/day). The most common SAEs, AE leading to treatment discontinuation and cause of death are respiratory tract disorders, such as idiopathic pulmonary fibrosis with acute exacerbation, respiratory failure, pneumothorax, and pneumonia, no matter in Asian or in Caucasian.

2.6 Conclusion

Based on one phase 2 and one phase 3 study conducted in Japan, treatment with

pirfenidone 1800 mg/day statistically significantly reduced mean decline in vital capacity at Week 52 compared with placebo. Progression free survival was statistically significantly prolonged in the pirfenidone group compared with the placebo group. Therefore, Pirespa tablet is recommended for approval.

3. Post-Marketing Requirements

Routine post-marketing surveillance is adequate. No additional risk management plan is required.