OPEN ACCESS Freely available online

ISSN: 0975-0851
Journal of Bioequivalence & Bioavailability

Research Article

Assessment of Bioequivalence between the Higher Strengths of Pirfenidone 400 mg and 600 mg with Equivalent Doses of Pirfenidone 200 mg

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ABSTRACT

Background: The standard of care for idiopathic pulmonary fibrosis is pirfenidone 200 mg tablets thrice daily (t.i.d, 600 mg/day) which is titrated to achieve the desired maintenance dose i.e 1800-2400 mg/day (600 mg-800 mg, t.i.d). However, this is associated with a high pill burden and can impact patient compliance. Therefore, two higher strengths (400 mg and 600 mg) of pirfenidone tablets have been developed which offer greater flexibility to facilitate tailored dosing and likely to improve patient compliance.

Methods: Two studies were conducted using an open-label, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover design in fed conditions with a washout period of 5-6 days between administration. In the first study, a single dose of 400 mg pirfenidone tablet was compared with 2 × 200 mg pirfenidone tablets and in the second study a single dose of 600 mg pirfenidone tablet was compared with 3 × 200 pirfenidone tablets. The assessment of bioequivalence between treatments in study 1: pirfenidone 1 × 400 mg vs. 2 × 200 mg tablets and study 2: pirfenidone 1 × 600 mg vs. 3 × 200 mg tablets was done by comparing the pharmacokinetic parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Results: 17 subjects were evaluated in the study with the lower strength (400 mg) and 43 subjects were evaluated in the study with the higher strength (600 mg). The ratios and 90% CI for the geometric mean in study 1 were 102.90% (89.33%-115.97%) for C_{max}, 104.61% (92.74%-116.58%) for AUC_{0-t} and 107.94% (95.75%-120.75%) for $AUC_{0-\infty}$. The ratios and 90% CI for the geometric mean in study 2 were 97.96% (91.41%-104.99%) for C_{max}, 97.79% (93.96%-101.78%) for AUC_{0-t} and 97.88% (94.10%-101.81%) for $AUC_{0-\infty}$. One adverse event was reported in study 1 and 4 adverse events in study 2. None of the adverse events were deemed to be serious AEs. All the treatments were well tolerated.

Conclusion: Single doses of pirfenidone 400 mg tablets when compared with pirfenidone 2 × 200 mg tablets and pirfenidone 600 mg tablets when compared with the 3 × 200 mg tablets met the bioequivalence criteria in terms of rate and extent of absorption under fed condition.

Keywords: Pill burden; Adherence; Bioequivalence; Pharmacokinetics; Idiopathic pulmonary fibrosis; Pirfenidone

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Received: 05-Apr-2022, Manuscript No. JBB-22-16010; **Editor assigned:** 08-Apr-2022, PreQC No. JBB-22-16010 (PQ); **Reviewed:** 27-Apr-2022, QC No. JBB-22-16010; **Revised:** 09-May-2022, Manuscript No. JBB-22-16010 (R); **Published:** 18-May-2022, DOI:10.35248/0975-0851.22.14.473

Citation: Joshi H, Kumar M, Gogtay J, Lopez M, Gole M, Sharma R (2022) Assessment of Bioequivalence between the Higher Strengths of Pirfenidone 400 mg and 600 mg with Equivalent Doses of Pirfenidone 200 mg. J Bioequiv Availab. 14:473

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is an irreversible and chronic lung disorder of unknown aetiology characterised by a progressive destruction of lung parenchyma leading ultimately to respiratory insufficiency and death. Age, gender, smoking status, and gastroesophageal reflux are some of the risk factors [1-3]. Although the pathophysiology is unclear, fibroblast dysfunction due to chronic injury of alveolar epithelial type II cells is considered the primary reason [4].

The global prevalence of IPF is about 13-20 per 100,000 individuals, and the median survival duration of the affected patients is about 3 years if left untreated [5]. Though its prevalence in India remains unclear, it is estimated that there could be potentially 130,000 IPF patients in India, when extrapolated from the UK data and considering a conservative prevalence of 10 cases per 100,000. Brazil, Russia, India, and China seem to be the most highly affected countries worldwide [6,7].

Pirfenidone (5-methyl-1-phenyl-2-1H-pyridone) is an antifibrotic agent approved for IPF treatment [8,9]. Treatment with pirfenidone in patients with mild to moderate IPF slows down the disease progression and improves survival [10]. Furthermore, pirfenidone significantly reduced the decline in 6-minute-walk distance, a measure of functional disease status. Evidence also shows that treatment with pirfenidone should be continued lifelong to maximise outcomes [11]. Pirfenidone is recommended to be taken along with food, as concomitant intake of food reduces the rate and extent (about 20%) of absorption, which is associated with better tolerability [12].

In the initial stages, a gradual dose titration of pirfenidone is required to manage and adequately monitor the adverse effects and to prevent treatment discontinuation [13,14]. A single 200 mg tablet of pirfenidone is administered with food 3 times a day (600 mg/day; weeks 0-2) and gradually increased to 1200 mg/day (weeks 2-4), 1800 mg/day (weeks 5-7) and subsequently to a maximum dose of 2400 mg/day from week 8 onwards. Therefore, 800 mg 3 times a day, will amount to a total of twelve 200 mg tablets in a day (4 × 200 mg, 3 times a day) which may impact patient compliance.

As for all chronically ill patients, adherence to a complex regimen might be challenging and nonadherence might reduce the full potential of pirfenidone treatment in patients with IPF. The concerns of pill burden and the reduced patient adherence with pirfenidone are further complicated due to the intake of additional concomitant medications owing to the high degree of comorbidity in IPF patients [15,16].

Higher-strength pirfenidone tablets 400 mg and 600 mg have been introduced by Cipla Ltd (India) for improved dosing flexibility and reduction in pill burden. The aim of this research was to assess the bioequivalence of pirfenidone after a single-dose oral administration of 400 mg and 600 mg tablet compared with an equivalent dose taken using the 200 tablets under fed conditions in healthy volunteers. Two studies were conducted, one evaluated bioequivalence for 400 mg pirfenidone and the other study evaluated for 600 mg pirfenidone.

MATERIALS AND METHODS

Ethics

Both the studies were conducted in accordance with the declaration of Helsinki, current ICH GCP guidelines, relevant national laws and regulations, and the study protocols were approved by Central Drugs Standard Control Organization (CDSCO), India, and required ethical committee approvals were taken before start of the studies. Voluntary written informed consent was obtained from all study subjects.

Study design

The two studies were conducted using an open-label, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover design in fed conditions with a washout period of 5-6 days between administration. In one study (study 1), a single dose of 400 mg pirfenidone tablet was compared with 2 × 200 mg pirfenidone tablets and in the other study (study 2), a single dose of 600 mg pirfenidone tablet was compared with 3 × 200 pirfenidone tablets.

In both studies, according to the randomization schedule, the drug was administered orally with 240 ml ± 2 ml drinking water with the subject in the sitting position. Subjects were dosed in a staggered sequence, with a 2 min interval between each participant. All study drugs were supplied by Cipla Ltd, India. A mouth check was performed using a torch and a disposable spatula to confirm that the study drug was swallowed completely. Participants were not allowed to drink water from 1 h before dosing up to 1 hour after dosing. The participants were asked to remain in the sitting or semi-reclining or ambulatory position for the first 2 hours after the drug administration. Thereafter, the subjects were allowed to engage in normal activities except severe physical exertion.

In both the studies, after overnight fasting, the subjects received the dose 30 minutes after food. The studies were conducted at Therapeutic Drug Monitoring Laboratory, Mumbai, India and at VerGo Pharma Research Pvt. Ltd, Goa, India. Both studies compared the rate and extent of absorption of pirfenidone after the administration of single-dose administration and also evaluated the safety and tolerability of pirfenidone.

Study subjects

Healthy adult subjects were included in both the studies if they met the following criteria: healthy males aged 18-45 years; Body Mass Index (BMI), 18.5 kg/m^2-30.00 kg/m^2; normal laboratory investigations, no history of contraindication or allergy to the drug or any of the related compounds, negative results for drug urinalysis, alcohol saliva test, and had not participated in any pharmacokinetic studies at least 3 months prior to entry into the studies. Moreover, the subjects had to avoid tobacco products, xanthine-containing products, and grapefruit products.

Subjects were excluded if they had hypersensitivity to pirfenidone or any of its active ingredients; a history or presence

of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, or neurological disorder; had received treatment that could affect the hepatic microsomal enzyme system within 1 month of entering into the studies; a history or presence of significant alcoholism or drug abuse in the past 1 year prior to entry into the studies; significant smoking; significant asthma, urticaria, or other allergic reactions; significant gastric or duodenal ulceration; significant thyroid disease or pituitary tumor; cancer; difficulty in providing blood samples or swallowing tablets or capsules. Subject also had to have a systolic blood pressure, <60 mm Hg or >90 mm Hg; pulse rate, <60 bpm or >100 bpm; oral temperature, <35˚C or >37.5˚C; respiratory rate, <12 or >20 breaths per minute; no major illness in the 3 months before screening; no blood donation in the past 3 months before entry into the studies; and negative results for HIV I or II, hepatitis A, B, and C, or syphilis. Further, those using any prescribed or over-the-counter medications in the past 2 weeks prior to entering into the studies and those consuming an unusual diet 2 weeks before admission for dosing and were not willing to avoid the diet until study completion were excluded.

Sample collection and bioanalysis

In both the studies, the pre-dose blood sample was obtained within an hour of dosing, and post-dose blood samples were obtained at 0.50, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00 h after dosing. In addition, the study with the higher strength 600 mg had two additional post-dose blood samples at 18.00 h and 24.00 h.

Pirfenidone in human plasma was quantified using the validated LC-MS/MS method. Within 45 min of blood sample collection, the samples were centrifuged at 4000 rpm under sodium vapor light for 10 min at 10˚C to separate the plasma. Plasma samples were then stored at -70˚C ± 15˚C in a deep freezer, and the amount of the drug was analyzed after extracting from the plasma. In brief, drug plasma samples were vortexed for 30 s with 0.1 mL of perchloric acid, and 5 mL of extracting solvent dichloromethane was added. The whole mixture was shaken for 10 min at 10 rpm in a shaker and centrifuged for 10 min at 3000 rpm. From this, 4 mL of the organic layer was collected and evaporated at 50˚C until dryness under a nitrogen stream for 15 min in a low volume evaporator. The residue was then reconstituted in the mobile phase and injected onto the LC-MS/MS system. The details are further provided in Table 1.

Table 1: HPLC, LC-MS.MS specifications for studies 1 and 2.

Variables	Study 1	Study 2
HPLC	Perkin Elmer, Series 200, GmbH, UK	Shimadzu, Japan
LC/MS/MS	Applied Biosystem, 2000 Q trap, Thermo Fisher Scientific Services, UK	API 3200 SIL-HTC AB, Sciex, USA
Software used	Analyst 1.3	Analyst 1.6.2
Column type	Cosmosil C18 (150 mm × 4.6 mm, i.d.) 5 µm, (Nacalai Tesque, Kyoto, Japan)	Zorbax SB-C18, 4.6 × 75 mm, 3.5 µm (Agilent.Technologies)
Mobile Phase	10 mM Ammonium Acetate : acetonitrile:formic acid (5:95:0.1 %, v/v/v)	Acetonitrile: 0.10% formic acid in water (80:20 v/v)
Flow Rate	1.0 mL/minute (75% Spliting)	1.000 mL/min
Sample Extraction	Protein precipitation	Liquid-Liquid extraction with ethyl acetate as extraction solvent
Sample Processing Volume	50 µL	100 µL
Internal Standard	Nevirapine	Pirfenidone D5
Linearity Range	300.0 ng/mL to 20000.0 ng/mL	60.138 ng/mL to 16026.369 ng/mL

Note: Study 1: Pirfenidone 1 × 400 mg vs. 2 × 200 mg tablets, Study 2: Pirfenidone 1 × 600 mg vs. 3 × 200 mg tablets

The validation method used allowed for the selective determination of pirfenidone in a linear range within 60.138 ng/mL to 20000 ng/mL, with a Lower Limit of Quantification (LLOQ) of 60.138 ng/mL. The validation parameters assessed were selectivity, linearity, intra- and inter-run precision, intra- and inter-run accuracy, matrix effect, residual effect, and stability of pirfenidone under different conditions.

Safety evaluation

Participants were monitored for Adverse Events (AEs) throughout the study. Sitting blood pressure, radial pulse rate, respiratory rate, and oral temperature were measured before dosing and at frequent intervals after dosing in each treatment period. Clinical examination was performed at check-in and before check-out in each treatment period. Participants were questioned for well-being at the time of clinical evaluation and during the recording of the vital signs. An additional 6 mL of blood was collected from each subject after blood sampling was completed for the post-study safety assessment (hematology and biochemistry investigations). Incidence of AE was recorded, including the intensity and causal relationship to the investigational products.

Pharmacokinetic and statistical analysis

Both the studies were powered to assess bioequivalence of the higher strengths 400 mg/600 mg vs. 200 mg pirfenidone tablets with a power of at least 80% and 5% significance level.

A non-compartmental model was utilized to assess the PK parameters using WinNonlin enterprise software Version 3.1 (Pharsight Corporation, USA). Primary PK parameters in the studies included the observed maximum plasma concentration (C_{max}), area under the plasma concentration versus time curve

from time zero to the time of the last quantifiable concentration (AUC_{0-t}) and AUC from zero extrapolated to infinity ($AUC_{0-\infty}$). Secondary PK parameters included observed time to reach peak concentration (T_{max}), elimination half-life ($t_{1/2}$) and K_{el}.

A separate ANOVA model using a generalized linear model was used to analyze each of the parameters. The log-transformed (ln-transformed) values for the PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) were analyzed for the statistical difference between the treatments.

RESULTS

Demographic characteristics of study subjects

17 subjects completed Study 1 and 43 subjects completed Study 2. The number of subjects withdrawn after randomisation was 1 each in both the studies. The reasons of withdrawal were simple abandonment for personal reasons and occurrence of an adverse event post dose. The subjects in both the studies had similar demographic characteristics with a mean age of 32 years, ranging from 21 to 44 years. Subject demographic details for both the studies are presented in Table 2.

Table 2: Demographics of subjects enrolled.

Parameter	Pirfenidone 400 mg N=18	Pirfenidone 600 mg N=44
Age (± SD), years; range	32.47 ± 5.27; 24-43	32.8 ± 5.91; 21-44
Weight (± SD), Kg; range	67.07 ± 6.83; 52-80.6	70.197 ± 9.8584; 52.85-90.78
Height (± SD), cm; range	168.69 ± 6.27; 159.5-185	169.33 ± 5.099; 160.1-182.7
BMI (± SD), kg/m^2; range	23.40 ± 1.65; 18.5-24.9	24.46 ± 3.07; 18.88-29.87

Note: Study 1: Pirfenidone 1 × 400 mg vs. 2 × 200 mg tablets; Study 2: pirfenidone 1 × 600 mg vs. 3 × 200 mg tablets; BMI: Body Mass Index; SD: Standard Deviation

Pharmacokinetic and statistical analysis

The mean plasma concentration-time curves for both the strengths are shown in Figures 1 and 2.

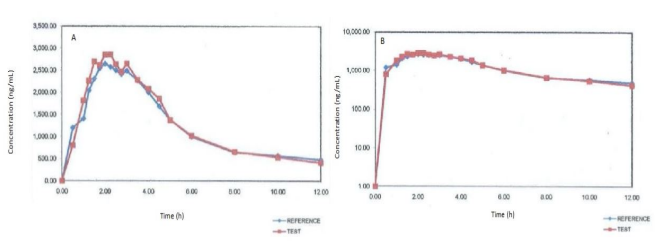

Figure 1: Linear (A) and semi-logarithmic (B) plots of mean plasma concentrations vs. time curve of pirfenidone, after administration of reference (R, two 200 mg tablets of pirfeniodone) and test (T, single tablet of 400 mg pirfenidone) products, under fed conditions (study 1).

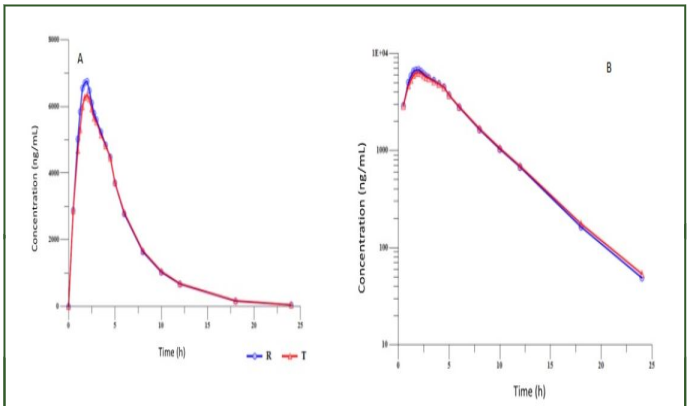

Figure 2: Linear (A) and semi-logarithmic (B) plots of mean plasma concentrations vs. time curve of pirfenidone, after administration of reference (R, three 200 mg tablets of pirfeniodone) and test (T, single tablet of 600 mg pirfenidone) products, under fed conditions (study 2).

The effect of food on pirfenidone PK was consistent for all the strengths and resulted in similar concentration time profiles. The measures of central location and dispersion for all pharmacokinetic parameters with both the strengths are summarised in Table 3.

Table 3: Mean pharmacokinetic parameters of pirfenidone with doses 400 mg and 600 mg.

Parameter	Pirfenidone 400 mg N=17		Pirfenidone 600 mg N=43	
	2 × 200 mg	1 × 400 mg	3 × 200 mg	1 × 600 mg
C_{max} (ng/mL)	3419.38 ± 1212.76	3561.73 ± 1507.37	7819.03 ± 2062.08	7818.06 ± 2657.22
AUC_{0-t} (ng/mL.h)	11825.06 ± 5384.41	12327.81± 5464.68	39598.04 ± 13406.75	39098.07 ± 15271.86
$AUC_{0-\infty}$ (ng/mL.h)	13403.53 ± 5626.36	14405.04 ± 5716.72	40193.58 ± 13666.26	39747.97 ± 15709.49
T_{max} (h)a	2.25 ± 0.80	2.32 ± 0.72	1.95 ± 0.81	2.19 ± 1.11
Kel (1/h)	0.38 ± 0.17	0.33 ± 0.14	0.26 ± 0.06	0.26 ± 0.07
t½ (h)	2.12 ± 0.82	2.49 ± 0.97	2.82 ± 0.73	2.80 ± 0.82

Note: The data are presented as mean ± SD, aT_{max} : median (min-max); AUC_{0-t}: The area under plasma drug concentration-time curve up to time "t", C_{max}: Concentration maximum a drug achieves after dosing; $AUC_{0-\infty}$: The area under plasma drug concentration-time curve to infinite time; T_{max}: The time of the first occurrence of C_{max}; K_{el}: Elimination rate constant; t : Elimination half-life.

After oral administration of the single-dose, all strengths of pirfenidone were absorbed rapidly with comparable T_{max} values. No significant differences were observed in the parameters C_{max} and AUC_{0-t} and $AUC_{0-\infty}$ between the higher strengths (400 mg and 600 mg) and equivalent dose of the lower strength (200 mg). Table 4 shows the geometric mean ratios for pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and the respective 90% CIs for the bioequivalence analysis (Table 4).

Table 4: Bioequivalence of pirfenidone when administered under fed conditions.

Parameter	The ratio of geometric least-square means	Intrasubject % CV	90% confidence limit (%) Test vs. reference		Power
			Lower limit	Upper limit	
400 mg tablet/ 2 × 200 mg tablets					
C_{max} (ng/mL)	102.9	21.92	89.33	115.97	83.18
AUC_{0-t} (ng/mL.h)	104.61	19.17	92.74	116.58	92.81
$AUC_{0-\infty}$ (ng/mL.h)	107.94	19.44	95.75	120.75	91.89
600 mg tablet/ 3 × 200 mg tablets					
C_{max} (ng/mL)	97.96	19.25	91.41	104.99	99.97
AUC_{0-t} (ng/mL.h)	97.79	11.06	93.96	101.78	100
AUC_{0-inf} (ng/mL.h)	97.88	10.88	94.1	101.81	100

C_{max} : Concentration maximum a drug achieves after dosing; AUC_{0-t}: The area under plasma drug concentration-time curve up to time "t"; $AUC_{0-\infty}$: The area under plasma drug concentration-time curve to infinite time.

The ratios and 90% CI for the geometric mean for 400 mg pirfenidone/ 200 × 2 mg pirfenidone were 102.90% (89.33%-115.97%) for C_{max} , 104.61% (92.74%-116.58%) for AUC_{0-t} and 107.94% (95.75%-120.75%) for $AUC_{0-\infty}$. The ratios and 90% CI for the geometric mean for 600 mg pirfenidone/200 × 3 mg pirfenidone were 97.96% (91.41%-104.99%) for Cmax, 97.79% (93.96%-101.78%) for AUC_{0-t} and 97.88% (94.10%-101.81%) for $AUC_{0-\infty}$.

All 90% CIs were within the range of 80% to 125%. Thus, the treatments were considered bioequivalent under study conditions.

Tolerability

No serious or life-threatening Adverse Events (AEs) were seen or reported. A total of 5 AEs (1 adverse event in Study 1 and 4 adverse events in Study 2) were reported in both the studies. All the AEs were reported as mild to moderate. The most common adverse event was high eosinophil count, reported by 3.2% of the subjects which was considered mild and unlikely to be related to the treatments. The other adverse events included clinically significant hematological values (1.6%), emesis (1.6%) and ST elevation in V1-V2 of ECG (1.6%). ST elevation in V1-V2 of ECG was mild and considered possibly related to the treatment. Emesis was moderate and considered related to the treatment and resulted in withdrawal of the subject from the study. The clinically significant hematological values were considered mild and possibly related to the treatment.

DISCUSSION

The results of this research confirmed that the higher strengths of pirfenidone 400 mg and 600 mg have a similar rate and extent of absorption as compared to equivalent doses of the lower strength 200 mg pirfenidone. The higher strengths also had an acceptable safety and tolerability profile. All the adverse events reported in the two studies were mild or moderate in intensity. Both the studies were conducted under the fed state as administration after food slows the rate of absorption and reduces peak plasma concentrations of pirfenidone. Further, gastrointestinal adverse events can be reduced by taking pirfenidone with food [17,18].

IPF typically occurs in people over the age of 50 and tends to affect more men than women [19]. Comorbidities such as lung cancer, pulmonary hypertension and cardiovascular diseases are commonly found in elderly patients with IPF which can influence survival. These patients therefore have increased use of concomitant medications which also impacts patient compliance in IPF [20].

Pirfenidone is used to slow the progression of IPF [21]. Once titrated to the maximum dose (2400 mg/day), it must be taken 800 mg 3 times a day, amounting to a total of twelve 200 mg tablets in a day (4 × 200 mg, 3 times a day). This high pill burden and complex treatment regimen furthers ads complexity to the poor compliance in IPF patients who are already burdened with other concomitant medications due to co-morbid conditions. Ultimately, this leads to suboptimal therapeutic effectiveness and reduced Quality of Life (QoL) in patients [22,23]. Hence, the simplified dosing regimen offered by the higher strengths such as 400 mg and 600 mg pirfenidone can offer the benefit of reduced pill burden and improve patient compliance.

The pharmacokinetic profile of pirfenidone has previously been described in healthy volunteers and these published studies have reported T_{max} of 2.05 h and $t_{1/2}$ of 2.74 h [24,25]. In our research, the T_{max} values ranged from 1.95 h to 2.32 h. Similarly, $t_{1/2}$ values ranged from 2.12 h to 2.82 h across the treatments evaluated.

Both the higher strengths 400 mg and 600 mg pirfenidone tablets in the fed state met the bioequivalence criteria {90% Confidence Intervals (CI) 80.00%-125.00%} for the GLSM ratios of natural log-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ vs. equivalent doses of 200 mg tablets.

CONCLUSION

The higher strengths 400 mg and 600 mg pirfenidone tablets are bioequivalent to the corresponding doses of 200 mg pirfenidone

tablets and would aid in reducing the pill burden, improve patient adherence and offer improved flexibility in dose titration. There is no significant differences were observed in the parameters of C_{max} and AUC_{0-t} and $AUC_{0-\infty}$ between the higher strengths (400 mg and 600 mg) and equivalent dose of the lower strength (200 mg). Single doses of pirfenidone 400 mg tablets when compared with pirfenidone 2 × 200 mg tablets and pirfenidone 600 mg tablets when compared with the 3 × 200 mg tablets met the bioequivalence criteria in terms of rate and extent of absorption under fed condition. There are no serious or life-threatening adverse events with the use of pirfenidone tablets.

ACKNOWLEDGMENTS

The authors thank the investigators and participants of both the studies. The authors also thank the Contract Research Organizations (CROs; Therapeutic Drug Monitoring Laboratory, Mumbai, India and Vergo Pharma Research Ltd, Goa, India) and the staff from the CROs involved in the study. The authors also thank Ms. Monali Mehta for reviewing the manuscript and Ms Juliet Rebello for revising the manuscript.

SOURCES OF FUNDING

Both studies were funded by Cipla India Ltd.

CONFLICT OF INTEREST

All authors are employees of Cipla Ltd, Mumbai.

CONTRIBUTIONS FROM THE AUTHORS

JG and ML conceived the idea of novel strength development and provided critical inputs on the manuscript, MG contributed to conducting both the studies and was additionally responsible for the clinical strategy the studies, MK provided critical inputs and guided Study 2, RS contributed to the conduct of Study 2 and aided in finalizing the study report and HJ was involved in the strategy for study 2. All authors contributed to critically evaluating the initial draft and revising it; all authors accept the submitted version of the manuscript.

ETHICS AND PERMISSIONS

Study 1 was approved by the Institutional Ethics committee C/o Shikhshana Prasaraka Mandali's Institute of Advanced Training and Research in Interdisciplinary Sciences (Registration No. ECR/179/Inst/MH/2013 and study 2 was approved by the Aavishkar Ethics committee (Registration No. ECR/138/Indt/GA/2013)).

PREVIOUS PRESENTATIONS

None

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