Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Pirfenidone capsules, oral

Month/Year of Review: July 2015
Generic Name: Pirfenidone
PDL Class: Pulmonary Fibrosis

End Date of Literature Search: January 2015
Brand Name (Manufacturer): Esbriet™ (Genentech)
Dossier Received: No

Research Questions:

- Is there evidence of efficacy for pirfenidone in the treatment of idiopathic pulmonary fibrosis (IPF) as demonstrated by clinical improvement in outcomes such mortality, functional status (e.g., exercise tolerance), quality of life or symptoms (e.g., acute exacerbations)? If so, is there direct comparative evidence with other treatments for IPF?
- Is there evidence of acceptable adverse effects for pirfenidone in comparison to other treatments for IPF?
- Are there subgroups of patients that may receive greater benefit or harm from pirfenidone therapy?

Conclusions:

- Studies used for approval of pirfenidone were the CAPACITY studies (004 and 006) and the ASCEND trial.[1-2] There is low to moderate strength of evidence that pirfenidone slows decline of percent-predicted forced vital capacity (FVC) relative to placebo. CAPACITY study 004 demonstrated a significant benefit in the primary efficacy endpoint of change in percent-predicted FVC from baseline to week 72 with pirfenidone 2,403 mg/day (-8.0%) compared to placebo (-12.4%) with an absolute difference of 4.4% (95% CI, 0.7% to 9.1%; p=0.001).[1] However, a subsequent study (CAPACITY study 006) did not demonstrate improvement with pirfenidone treatment, prompting the FDA to require the ASCEND trial.[1,2] In the ASCEND trial, the magnitude of treatment effect was estimated by comparing the distribution of patients in the pirfenidone group with those in the placebo group across two thresholds of change at week 52: a composite outcome of absolute ≥10% decline in percent-predicted FVC or death (pirfenidone 16.5% vs. placebo 31.8%; p<0.001; NNT of 7 for 1 year), or no decline in the percent-predicted FVC (pirfenidone 22.7% vs. placebo 9.7%; p<0.000001; NNT of 8 for 1 year).[2]
- There is low quality evidence that pirfenidone may reduce mortality in patients with IPF. There was a consistent but non-significant trend in decreased mortality in all Phase 3 trials that appeared to correlate with slower decline in FVC. Pooled 72-week trial data from two Phase 3 trials and 52-week data from another Phase 3 trial (n=1,247) demonstrated a non-significant decrease in all-cause mortality favoring pirfenidone relative to placebo (hazard ratio [HR] 0.69, 95% CI, 0.46 to 1.05, p=0.08).
- There is insufficient quality evidence that pirfenidone improves progression-free survival when it is defined as a composite endpoint of ≥10% decline in percent-predicted FVC, ≥15% decline in percent-predicted DLco, or death. The CAPACITY studies had conflicting results but the favorable trend in this composite outcome was primarily driven by decreased decline in FVC compared to placebo (HR 0.64, 95% CI, 0.44 to 0.95; p=0.023). In the ASCEND trial, 52% of patients in the pirfenidone group compared to 41% in the placebo group achieved progressive-free survival at week 52 (HR 0.57; 95% CI, 0.43 to 0.77;

p<0.001), which was alternatively defined as the time to first occurrence of any of the following: a decrease of 10% or more in predicted FVC, a decrease in 50 m or more in 6MWT or death. [1,2]

- There is low quality evidence that pirfenidone slows decline in the 6-minute walk test (6MWT) relative to placebo.[1,2] The absolute difference from placebo ranged from 16-32 meters (52.5 to 105 feet, or 17.5 to 35 yards), but it is unclear whether this is a clinically meaningful difference.[1,2]
- There is low quality evidence that pirfenidone does not improve dyspnea scores over 52 to 72 weeks compared to placebo.
- There are no head-to-head studies and therefore insufficient evidence to compare other treatments for IPF to pirfenidone. Patients in the clinical trials received pirfenidone as monotherapy and did not take concomitant treatment for IPF.
- There is moderate quality evidence pirfenidone commonly causes gastrointestinal-related adverse effects, as well as dermatologic photosensitivity reactions or rash.[3] Patients discontinued pirfenidone due to adverse reactions at a higher rate compared to placebo (14.6% vs. 9.6%, respectively). Discontinuations were primarily due to rash/photosensitivity and nausea.[3] Elevated liver enzymes (AST/ALT) were more common with pirfenidone compared to placebo and will require monitoring and may require dose reduction or interruption of pirfenidone therapy in affected patients.

Recommendations:

- Make pirfenidone non-preferred and restrict use to appropriate populations that meet prior authorization clinical criteria (see **Appendix 2**).

Background:

Idiopathic pulmonary fibrosis is a type of fibrosing interstitial pneumonia originally thought to be due to chronic inflammation. More recently abnormal wound healing has been implicated in the pathogenesis. In most IPF cases the etiology is unknown; however a link to cigarette smoking and environmental factors has been described. Familial pulmonary fibrosis accounts for less than 5% of IPF cases and genetic factors have been seen in sporadic cases of IPF.[4] IPF is chronic, progressive and unpredictable with a median survival rate of 2-3 years after diagnosis. Estimates of prevalence range from 2-29 cases per 100,000 in the population at large.[4] IPF is usually diagnosed between the ages of 40-70 years and is slightly more common in men than women. The diagnosis of IPF requires a detailed patient history to rule out other interstitial lung diseases. Most patients can be diagnosed based upon a specific interstitial pneumonia pattern seen on high-resolution computerized tomography (HRCT) of the chest. Patients may also be diagnosed by a specific combination of HRCT and surgical lung biopsy pattern.[4] Common symptoms of IPF are: chronic exertional dyspnea, cough, bibasilar inspiratory crackles and finger clubbing.[4] Staging of IPF is not currently used in practice to direct clinical decision making and there are no corresponding changes in percent-predicted FCV associated with different stages.[4] Indicators of disease progression are worsening respiratory symptoms, declining pulmonary function tests and acute respiratory decline.

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of IPF therapy.[5] Other clinically meaningful outcomes include acute exacerbation of IPF (usually measured by worsening dyspnea), all-cause non-elective hospitalizations and quality of life.[6] However, endpoints commonly studied in clinical trials include FVC and diffusion capacity for carbon monoxide (DLco) as a surrogate endpoint for lung function; 6-minute-walk test (6MWT) as a surrogate endpoint for functional status; HRCT imaging features; and biomarkers.[6,7] There is no consensus on the most appropriate surrogate outcomes to be used in IPF trials and there are no validated surrogate endpoints.[6] Further, it is uncertain what magnitude of difference for FVC or 6MWT constitutes a clinically meaningful change for patients with IPF.[5] Progression-free survival, usually assessed by combining decline in FVC and death, is a composite endpoint used in some IPF trials. The World Health Organization – Quality of Life Questionnaire (WHO-QoL) and St. George's Hospital Respiratory Questionnaire (SGRQ), which measure distress due to respiratory symptoms, are also used to measure the impact of IPF on patients' quality of life.

Multiple features have been identified with increased mortality in IPF patients (Table 1).[5] Predictors of disease progression and mortality have been demonstrated with FVC changes. Decreased survival rates have been associated with declining FVC rates of 5-10% or more, and a sign of disease progression is

indicated by a decrease in FVC of ≥10%.[4,6,9] Limited evidence suggests that small decreases in FVC (5-10%) is associated with poor outcomes. A decline in the 6MWT has also been correlated with increased mortality in patients with IPF.[9] Retrospective cohort studies have suggested a decline of 30 meters (m) in the 6MWT to be a clinically meaningful threshold.[6] Standards in conducting the 6MWT are lacking, making interpretation of this test result difficult, though it is thought to be a robust indicator of functional exercise capacity.[6,11]

The joint American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) evidence-based guideline on the diagnosis and management of IPF was updated in 2011.[4] Treatment recommendations and corresponding evidence designation, using the GRADE methodology, is presented in table 2. A wide range of medical therapies for IPF have been explored but none have clearly demonstrated a clinical benefit in IPF. A Cochrane review found no randomized controlled trials (RCTs) to assess the benefits of corticosteroid monotherapy in patients with IPF.[12] Observational cohort studies have failed to find a mortality benefit in patients treated with corticosteroids.[12] Treatment with azathioprine and prednisone has been studied in patients with IPF without demonstrating definitive benefits and is not currently recommended. Cyclophosphamide treatment in IPF has failed to show mortality benefits and is also not recommended. The use of everolimus failed to show improved efficacy in patients with IPF and may cause harm. A study of anticoagulant use in patients with IPF was discontinued early due to excess deaths in the warfarin group with a low probability of benefit from treatment.[14] Bosentan was studied in patients with IPF in the BUILD-1 and BUILD-3 trials but was not shown to improve outcomes and is therefore not recommended.[15,16] Ambrisentan, macitentan, sildenafil, interferon-gamma, etanercept and imatinib have been studied in IPF patients without benefit. The ATS/ERS/JRS/ALAT guideline weakly recommends against the use of pirfenidone but suggests it could be considered an option for patients who realize the expected benefits are small and there are risks of adverse reactions (ASCEND results not included in guideline).[4] The use of pirfenidone in IPF is weakly recommended by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[17] French practical guidelines and National Institute for Health and Care Excellence (NICE) recommend pirfenidone in patients with mild to moderate IPF (FVC ≥50%).[18,19] The only treatment shown to improve survival in IPF patients is lung transplantation.[4] Pirfenidone and nintedanib are currently the only drugs approved by the FDA for IPF, with the evidence for their use presented below.

Table 1. ATS/ERS/JRS/ALAT Statement on Selected Features Associated with Increased Risk of Mortality in IPF.[8]

Baseline Factors	**Longitudinal Factors**
Level of dyspnea	Decrease in FVC ≥10% absolute value
DLco <40% predicted	Decrease in DLco by ≥15% absolute value
Desaturation ≤88% during 6MWT	Worsening of fibrosis on HRCT
Extent of honeycombing on HRCT	
Pulmonary hypertension	

Definitions of abbreviations: 6MWT= 6-minute walk-test; DLco = diffusion capacity for carbon monoxide; HRCT = high-resolution computer tomography.

Raghu G, Collard H, Egan J, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guideline for Diagnosis and Management. Am J Respir Crit Care Med 2011;183:788-824.

Table 2. ATS/ERS/JRS/ALAT Treatment Recommendations.[4]

	Treatment	Evidence Grade
Recommendation AGAINST the use of treatment in IPF is STRONG	Corticosteroid Monotherapy	Very low
	Colchicine	Very low
	Cyclosporine A	Very low
	Combined corticosteroid and immune-modulator therapy	Low
	Interferon γ 1b	High
	Bosentan	Moderate
	Etanercept	Moderate
Recommendation AGAINST the use of treatment in IPF is weak	Combined acetylcysteine and azathioprine and prednisone	Low
	Acetylcysteine monotherapy	Low
	Anticoagulation	Very low
	Pirfenidone	Low
Recommendation for therapy in IPF patients is STRONG	Long-term oxygen therapy	Very low
Recommendation for procedure in IPF patients is STRONG	Lung transplantation	Very low
Recommendation AGAINST procedure in patients with respiratory failure due to IPF is WEAK	Mechanical ventilation	Low
Recommendation for procedure in IPF patients is WEAK	Pulmonary rehabilitation	Low
Recommendation for therapy in IPF patients with acute exacerbations is WEAK	Corticosteroids	Very low
Recommendation AGAINST the treatment of associated IPF conditions is WEAK	Pulmonary hypertension	Very low
Recommendation for therapy in IPF patients is WEAK	Asymptomatic gastroesophageal reflux	Very low

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Pirfenidone was initially studied in a Phase 3, double-blind, randomized, controlled trial of 275 Japanese patients with mild IPF assessing pirfenidone 600 mg three times daily, pirfenidone 400 mg three times daily or placebo.[20] Study enrollment was dependent upon desaturation results using the 6MWT, which is a measure that has not been validated in IPF. There were also less current smokers in the high dose pirfenidone group (4.6%) compared to placebo (12.5%). Both doses of pirfenidone were superior to placebo for the primary endpoint of change in VC from baseline to week 52 (-90 mL, -80 mL and -160 mL, respectively). Progression of disease, as indicated by VC, was low in all groups with decline ranging from 3-6% from baseline assessment. Progression-free survival, defined as death or ≥10% decline in VC from baseline, was only statistically significant between the high dose pirfenidone group compared to placebo (p=0.0280).[19]

In the U.S., the FDA approved pirfenidone based on two of three randomized clinical trials demonstrating efficacy of improved FVC with consistent numerical trends in improved all-cause mortality compared to placebo in mild to moderate IPF patients.

The first two trials were CAPACITY 004 and CAPACITY 006, which were identical double-blind, placebo-controlled, randomized trials of 72 weeks' duration.[1] In study 004, 435 IPF patients 40-80 years of age were randomized in a 2:1:2 ratio to pirfenidone 801 mg three times daily, pirfenidone 399 mg three times daily (used as a reference only) or placebo.[1] Study 006 included 344 patients randomized in a 1:1 ratio to pirfenidone 801 mg three times daily or placebo.[1] In both trials, pirfenidone was given in three divided doses with food and titrated over 2 weeks. Patient populations were similar with the majority of patients being

white males with mild to moderate IPF and few comorbidities or concomitant lung disorders. Patients in study 006 had a shorter baseline walk distance and higher utilization of supplemental oxygen compared to study 004; however, baseline percent predicted FVCs were similar. Other IPF treatments were prohibited, though immunosuppressant drugs were briefly allowed for acute exacerbations of IPF, acute respiratory decompensation or progression of IPF. In both trials, the primary endpoint was absolute change in percent-predicted FVC from baseline to week 72. Key secondary endpoints included: time to worsening of IPF (defined as time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever came first), change in progressive-free survival (defined as time to first occurrence of either: ≥10% absolute decline in percent-predicted FVC, or ≥15% absolute decline in percent-predicted DLco, or death), change in dyspnea, and change in 6MWT, all analyzed from baseline to week 72. All-cause mortality and IPF-associated mortality were exploratory endpoints.

In study 004, pirfenidone reduced decline in percent-predicted FVC compared to placebo by -8.0% and -12.4%, respectively, which was a statistically significant difference.[1] The clinical significance of this difference is unknown, though a decline in FVC greater than 10% has been associated with disease progression and increased mortality.[4,5,8] There were significantly less patients who experienced a percent-predicted decline in FVC ≥10% compared to placebo (NNT of 7 for 72 weeks). Pirfenidone was associated with an increase in progression-free survival, a composite endpoint of ≥10% decline in percent-predicted FVC, ≥15% decline in percent-predicted DLco, or death, which was primarily driven by decline in FVC, compared to placebo (HR 0.64, 95% CI, 0.44 to 0.95; p=0.023). However, changes in dyspnea scores and the 6MWT were not statistically different between pirfenidone and placebo.

Study 006 did not yield results consistent with study 004 despite enrolling similar patients and using the same methodology. There was no statistically significant difference in the primary endpoint of mean change of percent-predicted FVC at week 72 between pirfenidone (-9.0%) and placebo (-9.6%).[1] The number of patients with a categorical change in ≥10% percent-predicted FVC and difference in progression-free survival were also not significantly different between the pirfenidone and placebo groups. The only key secondary endpoint that favored pirfenidone was an improved 6MWT of 32 m (105 feet, or 35 yards) at week 72 compared to placebo (p=0.0009).

If the primary efficacy analyses from both study 004 and study 006 each showed efficacy, then the secondary outcome variables were to be analyzed using pooled data from both studies.[5]However, because that was not achieved, the pooled data will not be presented. Still, it is important to note exploratory analyses of pooled overall all-cause mortality data and mortality due to IPF showed a beneficial trend with pirfenidone, though pooling the data still did not have enough statistical power to demonstrate a significant difference from placebo.[5]

The FDA required a third clinical trial demonstrating efficacy with pirfenidone before drug approval could be granted, and so the ASCEND trial was conducted.[1,5] The study design of the ASCEND trial was similar to the CAPACITY trials with an important difference in study duration: the ASCEND trial was 52 weeks instead of 72 weeks. Other differences included inclusion of patients with lower percent-predicted DLco, higher FEV1/FVC ratio and longer time since IPF diagnosis.[2] The primary endpoint was similar to the CAPACITY trials, an absolute change in percent predicted FVC from baseline at week 52, but this outcome was rather reported as two distinct measures: 1) a composite of the proportion of patients with an absolute decline of 10% or more in the percent-predicted FVC or death, or 2) the proportion of patients with no decline in the percentage of the predicted FVC. Key secondary endpoints were also similar to the CAPACITY trials.

Pirfenidone was associated with decreased decline in percent-predicted in FVC versus placebo (p<0.001).[3] Decline in percent predicted FVC of ≥10% or death at week 52 was 16.5% for pirfenidone and 31.8% for placebo (p<0.001). However, the difference was largely due to ≥10% decline in FVC. Patients with no decline in percent-predicted FVC was higher in patients treated with pirfenidone compared to placebo with a NNT of 8 over 1 year. The absolute difference of 27 m (88 feet, or 30 yards) in the 6MWT favored pirfenidone, but the clinically meaningful benefit of the result is unclear. Fifty-two percent of patients in the pirfenidone

group compared to 41% in the placebo group achieved progressive-free survival at week 52 (HR 0.57; 95% CI, 0.43 to 0.77; p<0.001), which was defined as the time to first occurrence of any of the following: a decrease of 10% or more in predicted FVC, a decrease in 50 m or more in 6MWT or death.[3]

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of an IPF therapy.[5] Mortality data in the CAPACITY and ASCEND trials were analyzed in various ways by the drug sponsor and by the FDA.[5] Mortality was evaluated differently between the CAPACITY trials and the ASCEND trial. In the CAPACITY trials, mortality was assessed for about 120 weeks, from the time the first patient was enrolled until the last patient enrolled finished 72 weeks of treatment.[5] All-cause mortality in the CAPACITY trials numerically favored pirfenidone but the difference was not statistically significant (HR 0.85; 95% CI, 0.53 to 1.37; p=0.51). However, when mortality data were pooled and assessed only during the treatment period (i.e., 72 weeks), there was a statistically significant difference in IPF-related mortality that favored pirfenidone (HR 0.45; 95% CI, 0.24 to 0.95).[5] However, the results should be interpreted with caution as it was limited to by assessment while on treatment (typical method to assess mortality as an adverse event), the nature of the post-hoc analysis, and lack of adjudication of cause of death, which resulted in inconsistent analysis of the data.[5] In the ASCEND trial, mortality was only assessed for 52 weeks and cause of death was adjudicated.[5] All-cause mortality benefit also numerically favored pirfenidone but was not statistically demonstrated. When all-cause mortality data were pooled between all Phase 3 trials (72 weeks for the CAPACITY trials and 52 weeks for the ASCEND trial), the trend continued to favor pirfenidone versus placebo, but the sample size was still not large enough to demonstrate a statistically significant difference (HR 0.69; 95% CI, 0.46 to 1.05; p=0.08).[5] However, if pre-specified censoring rules by the drug manufacturer were applied to the data (pooled mortality data of all 3 trials was truncated at 52 weeks), mortality was statistically benefitted pirfenidone versus placebo (3.5% vs. 6.7%, respectively; HR 0.52; 95% CI, 0.31 to 0.87; p=0.01; NNT of 31 for 1 year).[2,5]

Clinical Safety:

The adverse events identified as events of interest in the Phase 3 trials are liver-related adverse events, gastrointestinal adverse events, rash and photosensitivity, dizziness and falls, and carcinogenicity.[5] However, none of these adverse events resulted in death and resolved upon permanent discontinuation of pirfenidone. In the overall safety database, ALT and AST elevations were infrequent, but occurred in a larger proportion of patients on pirfenidone than on placebo. The most common adverse reactions occurring in at least 10% of patients receiving pirfenidone were primarily gastrointestinal or dermatologic in nature. Prominent gastrointestinal adverse events were nausea, gastrointestinal reflux, vomiting and anorexia. Common dermatologic adverse events included rash (30%) and photosensitivity (9%) but there were no cases of Stevens-Johnson syndrome, erythema multiforme or toxic epidermal necrolysis, and no cases were life-threatening or led to hospitalization.[5] Dizziness was also often reported in patients receiving pirfenidone, with 5.4% of cases of dizziness associated with falls.[5] Adverse effects were deemed to be dose-related. Severe adverse reactions were similar in the pooled pirfenidone and placebo groups, 33% and 31%, respectively.[1] Discontinuations due to adverse events was higher in the pirfenidone treated groups compared to placebo, with rates ranging from 14%-20%.[1,2,19] The number of cancers in the studies were balanced across treatment groups, but the studies were too small to exclude a definitive cancer risk and the animal carcinogenicity study was positive for pirfenidone.[5] Common adverse events that occurred at a rate of at least 10% and occurred more commonly than placebo are listed in Table 3.

Table 3. Common Adverse Events Occurring in ≥10% of Pirfenidone-treated Patients and Occurring More Commonly than Placebo in Phase 3 Clinical Trials.[3]

Adverse Event	% of Patients (0 to 118 Weeks)	
	Pirfenidone 2403 mg/day (n=623)	Placebo (n=624)
Nausea	36%	16%
Rash/Photosensitivity	30%	10%
Abdominal Pain	24%	15%
Diarrhea	26%	20%
Fatigue	26%	20%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%

Pharmacology and Pharmacokinetic Properties:[3]

Parameter	
Mechanism of Action	In vitro studies show regulation of the activity of transforming growth factor (TGF) β and tumor necrosis factor (TNF) α. Mechanism in IPF is unknown.
Oral Bioavailability	Has not been determined in humans.
Distribution and Protein Binding	Pirfenidone binds to human plasma proteins, primarily to serum albumin. The mean binding at concentrations seen in clinical trials is 58%.
Elimination	80% in the urine
Half-Life	3 hours
Metabolism	Liver by CYP1A2 and multiple other CYP enzymes

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Hospitalizations
3) Disease Progression (FVC, VC)
4) Functional Status (e.g., exercise tolerance (6MWT)
5) Quality of life
6) Symptom improvement (e.g., acute exacerbations)

Primary Study Endpoint:
1) Change in percent predicted FVC or VC

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity /Applicability
1. Noble, et al. (CAPACITY - 004)[1,5] DB, PG, PC, RCT Phase 3	1. Pirfenidone 801 mg TID (PIR) 2. Pirfenidone 399 mg TID (PIR2) 3. Placebo (P) Randomized 2:1:2 72 weeks	Demographics: Age: 67 years Men: 72% White: 96% Predicted FVC: 76% 6MWT: 413 m Current Smokers: 4% Key Inclusion Criteria: Age 40-80 years; Dx of IPF in previous 48 months; No improvement in disease severity over past year; Predicted FVC ≥50%; Predicted DLco ≥35%; Either predicted FVC or predicted DLco of ≤90%; 6MWT ≥150 m. Key Exclusion Criteria: Concomitant tx for IPF; Obstructive airway disease; Connective tissue disease; Wait list for lung transplant	ITT: 1. 174 2. 87 3. 174 Attrition*: 1. 51 (29%) 2. 22 (25%) 3. 39 (22%) *Excludes death or lung trans-plantation	**Primary Endpoint**: (week 72) Change in %-predicted FVC from baseline: PIR: -8.0% vs. PIR2: -10.2% vs. P: -12.4% PIR vs. P: ARR 4.4% (95% CI, 0.7 to 9.1%; P=0.001) **Key Secondary Endpoints**: (week 72) ≥10% decline %-predicted FVC: PIR 20% vs. P 35% ARR 14.4% (95% CI, 7.4 to 21.3; P=0.001) Progression-free Survival (≥10% decline %-predicted FVC, ≥15% decline %-predicted DLco or death): PIR 138 (79.3%) vs. P 116 (66.7%) HR 0.64 (95% CI, 0.44 to 0.95; p=0.023) Worsening IPF (time to acute exacerbation, death, lung transplant or hospitalization for respiratory problem): PIR (NR) vs. P (NR) HR 0.84 (95% CI, 0.50 to 1.42; p=0.515) Mean change in Dyspnea (UCSD SoBQ, scale 0-120): PIR +12.1 vs. P +15.2 ARR -3.1 (95% CI, -8.5 to 2.3; p=0.509) Mean change in 6MWT: PIR -60.4 m vs. P -76.8 m ARR 16.4 m (95% CI, -10.9 to 43.7 m; p=0.171)	NA 14.4%/7 NA NS NS NS	Serious Adverse Events: PIR: 28% PIR2: 41% P: 28% p-value NR Discontinuations due to adverse effects: PIR: 15% P: 9% Pooled analysis w/ CAPACITY 006; p-value NR Nausea: PIR: 35% PIR2: 25% P: 18% p-value NR Rash: PIR: 31% PIR2: 17% P: 10% p-value NR Photosensitivity: PIR: 14% PIR2: 7% P: 1% AST/ALT 3x ULN: PIR 4.1% P: 0.6% Pooled analysis w/ CAPACITY 006; p-value NR	NA NA NA NA NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Randomized by independent statistician via computer-generated permuted block code and stratified by region; groups allocated via interactive voice response system. Groups well matched. Performance: All personnel involved in the study were masked to group assignment until after final database lock. Detection: States ITT analysis performed; power/sample size calculations not reported; appropriate statistical tests applied; unclear if data assessor blinded. Attrition: Overall attrition high, with higher attrition in PIR group. Imputed missing data as average value, or worst rank outcome for death. **Applicability**: Patients: Patients with mild to moderate IPF; nearly all patients white; 48% diagnosed w/ IPF within last year; 65% were former smokers; 16% required supplemental oxygen; 65% enrolled from U.S. Intervention: The 2403 mg/day regimen based on 1800 mg/day dose used in Japanese studies to the predicted body weight of US citizens. A second regimen of 1197 mg/day only summarized descriptively. PIR dose titrated over 2 weeks. No data on final mean dose of PIR considering dose-adjustments were permitted for intolerance during study. Adherence was high (>80%). Comparator: Placebo control appropriate. Outcomes: Change in FVC is an accepted surrogate endpoint but it is unknown what magnitude of change affects mortality. Significant difference in progression-free survival primarily driven by the criterion of decline in FVC. Post-hoc analysis of pooled data from CAPACITY 006 demonstrated a favorable overall all-cause mortality trend with PIR vs. P (8% vs. 10%; HR 0.77; 95% CI, 0.47 to 1.28; p=0.315) and favorable IPF-related mortality trend with PIR vs. P (5% vs. 8%; HR 0.62; 95% CI, 0.35 to 1.13; p=0.117); no adjudication was performed. Setting: 110 centers in 13 countries (USA n=64). Drug sponsor participated in the study design, data collection, data analysis and writing the report.

Author: Kathy Sentena Date: July 2015

2. Noble, et al. (CAPACITY - 006)[1,5] DB, PG, PC, RCT Phase 3	1. Pirfenidone 801 mg TID (PIR) 2. Placebo (P) Randomized 1:1 72 weeks	Demographics: Age: 67 years Men: 72% White: 99% % Predicted FVC: 74% 6MWT: 389 m Current Smokers: PIR 0% vs P 5% Key Inclusion Criteria: See CAPACITY 004 Key Exclusion Criteria: See CAPACITY 004	ITT: 1. 171 2. 173 Attrition*: 1. 47 (27%) 2. 40 (23%) * Excludes death or lung trans-plantation	**Primary Endpoint**: (week 72) Change in %-predicted FVC from baseline: PIR: -9.0% vs. P: -9.6% ARR 0.6% (95% CI, -3.5 to 4.7%; p=0.50) **Key Secondary Endpoints**: (week 72) FCV decline ≥10%: PIR 23% vs. P 27% ARR 3.8% (95% CI, -2.7 to 10.2) P=0.440 Progression-free Survival (time to ≥10% decline in %-predicted FVC, ≥15% decline in %predicted DLco or death): PIR 126 (73.7) vs. P 123 (71.9%) HR 0.84 (95% CI, 0.58 to 1.22; p=0.355) Worsening IPF (time to acute exacerbation, death, lung transplant or hospitalization for respiratory problem): PIR (NR) vs. P (NR) HR 0.73 (95% CI, 0.43 to 1.24; p=0.248) Mean change in Dyspnea (UCSD SoBQ, scale 0-120): PIR +11.9 vs. P +13.9 ARR -2.0 (95% CI, -7.6 to 3.6; p=0.604) Mean change in 6MWT: PIR -45.1 m vs. P -76.9 m ARR +31.8 m (95% CI, 3.2 to 60.4; p=0.0009)	 NS NS NS NS NS NA	Serious Adverse Events: PIR: 32% P: 28% p-value not reported Discontinuations due to adverse effects: PIR: 15% P: 9% Pooled analysis w/ CAPACITY 004; p-value NR Nausea: PIR: 65 (38%) P: 28 (16%) p-value not reported Rash: PIR1: 58 (34%) P: 22 (13%) p-value not reported Photosensitivity: PIR: 10% P: 2% p-value not reported AST/ALT 3x ULN: PIR 4.1% P: 0.6% Pooled analysis w/ CAPACITY 004; p-value NR	 NA NA NA NA NA	**Quality Rating**: **Internal Validity (Risk of Bias)**: Selection: No current smokers in the pirfenidone group yet 8 in the placebo group; otherwise, see CAPACITY 004. Performance: See CAPACITY 004. Detection: See CAPACITY 004. Attrition: See CAPACITY 004. **Applicability**: Patients: Patients with mild to moderate IPF; nearly all patients white; 62% were former smokers; ; 28% required supplemental oxygen. Intervention: See CAPACITY 004 Comparator: See CAPACITY 004 Outcomes: No statistically significant difference between PIR and P in primary endpoint of change in FVC. No statistically significant difference in key secondary endpoints progression-free survival, worsening IPF, or change in dyspnea scores; unaware of individual outcomes of composite secondary endpoints. It is uncertain what constitutes a clinically meaningful change in 6MWT. Post-hoc analysis of pooled data from CAPACITY 004 demonstrated a favorable overall all-cause mortality trend with PIR vs. P (8% vs. 10%; HR 0.77; 95% CI, 0.47 to 1.28; p=0.315) and favorable IPF-related mortality trend with PIR vs. P (5% vs. 8%; HR 0.62; 95% CI, 0.35 to 1.13; p=0.117); no adjudication was performed. Setting: See CAPACITY 004

3. King, et al. (ASCEND)[2,5] DB, PG, PC, RCT Phase 3	1. Pirfenidone 801 mg TID w/ meals (PIR) 2. Placebo (P) 52 weeks	Demographics: Age: 68 years Men: 79% % Predicted FVC: 68% 6MWT: 418 m Current smokers: Not reported Key Inclusion Criteria: Age 40-80 years; Dx of IPF; Predicted FVC 50-90%; DLco 30-90%; FEV_1 /FVC ≥0.80 6MWT ≥150 m Key Exclusion Criteria: FEV1/FVC ratio <0.8 after administration of bronchodilator; Absolute increase of ≥12% and an increase of 200 mL in predicted FEV1 and /or FVC after bronchodilator use compared to bronchodilator use at screening; Connective tissue disease; Asthma or COPD; Expected lung transplant ≤1 year; Severe hepatic or renal disease; Unstable cardiac or pulmonary disease; Concomitant tx for IPF unless needed for another indication	ITT: 1. 278 2. 277 Attrition*: 1. 72 (26%) 2. 55 (20%) * Does not include death or lung trans-plantation	**Primary Endpoint**: (week 52) ≥10% decline %-predicted FCV or death: PIR 46 (16.5%) vs. P 88 (31.8%) ARR 15.3% (95% CI, 8.1 to 22.1%; p<0.001) No decline %-predicted FVC: PIR 63 (22.7%) vs. P 27 (9.7%) ARR 13% (95% CI, 7.0 to 19.0%; p<0.000001) **Key Secondary Endpoints**: (week 52) Mean change in 6MWT: PIR -33.6 m vs. P -60.2 m ARR 26.7 m (p=0.04) Post-hoc analysis: Decrease of ≥50 m in 6MWT or death: PIR 72 (25.9%) vs. P 99 (35.7%) (p=0.04) ARR 9.8% (CI not provided) Progression-free Survival (≥10% decline %-predicted FVC, ≥50 m decrease 6MWT, or death): PIR 144 (51.8%) vs. P 113 (40.8%) HR 0.57 (95% CI, 0.43 to 0.77; p<0.001) Mean change in Dyspnea (UCSD SoBQ, scale 0-120): Data NR but p=NS Post-hoc analysis: Increase ≥20 points in UCSD SoBQ: PIR 81 (29.1%) vs. P 100 (36.1%) (p=0.16) All-cause mortality: PIR 11 (4%) vs. P 20 (7.2%) HR 0.55 (95% CI 0.26 to 1.15, p=0.10) Mortality from IPF: PIR 3 (1.15) vs. P 7 (2.5%) HR 0.44 (95% CI, 0.11 to 1.72; p=0.23)	 15.3%/7 13%/8 NA 9.8%/10 11%/9 NS NS NS	Serious Adverse Events*: PIR: 52 (18.7%) P: 56 (20.2%) p-value NR *Excludes worsening IPF Discontinuations due to adverse effects: PIR 40 (14.4%) P 30 (10.8%) p-value NR AST/ALT 3x ULN: PIR 8 (2.9%) P 2 (0.7%) p-value NR Nausea: PIR 100 (36%) P 37 (13.4%) p-value NR Gastrointestinal Reflux: PIR 36 (11.9%) P 18 (6.5%) p-value NR Anorexia: PIR 44 (15.8%) P 18 (6.5%) P-value NR Rash: PIR 78 (28.1) P 24 (8.7%) p-value NR	 NA NA NA NA NA NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Patients were randomized by permuted-block design via a computer generated randomization code and the study drug was assigned by means of an interactive voice-response system. Both groups well matched. Performance: Described as double-blind and both treatments were "visually equivalent". Detection: True ITT analysis performed; power/sample size calculations not described; appropriate statistical tests applied; data assessor blinded to allocation when FVC, DLco and mortality data analyzed. Attrition: Overall attrition high, with higher attrition in PIR group. Imputed missing data as average value, or worst rank outcome for death. **Applicability**: Patients: Patients had mild to moderate IPF; majority of patients were white males; 63% were former smokers. Intervention: PIR dose titrated over 2 weeks. No data on final mean dose of PIR since dose adjustments were permitted for intolerance during study. Adherence was high (>80%). Comparator: Placebo control appropriate. Outcomes: Change in FVC is an accepted surrogate endpoint but it is unknown what magnitude of change affects mortality. It is uncertain what constitutes a clinically meaningful change in 6MWT. Significant difference in progression-free survival primarily driven by the criterion of 6MWT and decline in FVC. Pooled all-cause mortality data from ASCEND and CAPACITY trials when analyzed by the FDA do not demonstrate a significant difference between PIR (7.1%) vs. P (9.3%) (HR 0.75; 95% CI, 0.50 to 1.11; p=0.14). Pooled mortality data provided by the drug sponsor, which utilized more strict censoring rules, showed a more favorable but still non-significant trend (PIR (6.1%) vs. P (8.7%); HR 0.69; 95% CI, 0.46 to 1.05; p=0.08). Setting: 127 sites and 9 countries (USA n=87). Drug sponsor participated in the study design and writing the final manuscript.

4. Taniguchi, et al. 2010[19] DB, PG, PC, RCT Phase 3	1. Pirfenidone 600 mg TID (PIR1) 2. Pirfenidone 400 mg TID (PIR2) 3. Placebo (P) Randomized 2:1:2 52 weeks	Demographics: Age: 65 years Men: 81% VC: 2.437 L 6MWD: NR Current Smokers: 12% Key Inclusion Criteria: Age 20-75 years; Diagnosis of IPF; SpO2 desaturation of ≥5% difference between resting SpO_2 and the lowest SpO_2 during a 6MET; and Lowest SpO_2 during the 6MET of ≥85% while breathing air. Key Exclusion Criteria: Improved symptoms in the previous 6 months; Use of immuno-suppressants or oral corticosteroids at a dose >10 mg/day during the preceding 3 months; Chronic or acute respiratory illness	mITT: 1. 108 2. 55 3. 104 Attrition: 1. 40 (37%) 2. 15 (27%) 3. 31 (30%)	**Primary Endpoint**: (52 weeks) Change in VC from baseline: PIR1: -0.09 (0.02) L PIR2: -0.08 (0.03) L P: -0.16 (0.02) L PIR1 vs P: Adjusted mean 0.07 L (0.03), p=0.0416 PIR2 vs P: Adjusted mean 0.09 L (0.04), p=0.0394 PIR1 vs. PIR2: p=NS **Key Secondary Endpoints**: (52 weeks) Progression-free survival (death or ≥10% decline in VC): PIR1: 45 (42.5%) PIR2: 26 (47.3%) P: 40 (38.5%) PIR1 vs. P: ARR 3.2%% (no CI); p=0.028 PIR2 vs. P: ARR 8.8%% (no CI); p=0.066 PIR1 vs. PIR2: ARR 5.6% (no CI); p=0.91	NA NA NA 19.7%/6 NA NA	Photosensitivity: PIR1: 56 (51.4%) PIR2: 29 (52.7%) P: 24 (22.4%) PIR1 vs P: (p<0.01) PIR2 vs P: (p<0.01) Anorexia: PIR1: 18 (16.5%) PIR2: 6 (10.9%) P: 3 (2.8%) PIR1 vs. P: (p<0.01) PIR2 vs. P: (p=0.06) Discontinuations due to adverse effects: PIR1: 20 (18.3%) PIR2: 11 (20%) P: 14 (13.1%) p-value NR	29.0%/3 30.3%/3 13.7%/7 NA NA	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Patients randomized with a modified minimization method, including some random allocation based on biased coin design to balance baseline SpO_2. Imbalance in allocation of current smokers, with less allocated to the PIR1 group. Performance: Described as double-blind with matching placebo. Detection: Statistical assumptions to power study provided; appropriate statistical tests used. No details on blinding of outcome data assessors. Modified ITT performed as 8 patients excluded after randomization. Confidence intervals not provided for outcomes. Attrition: Overall attrition high. Used LOCF imputation for missing data, which can bias results when studying progressive diseases. **Applicability**: Patients: All Japanese patients; 92% of patients were treatment naïve with relatively mild functional impairment based on PFTs. Intervention: Doses titrated over 2 weeks to pirfenidone 600 mg TID and pirfenidone 400 mg TID. Comparator: Placebo control appropriate. Outcomes: VC and progression-free survival are appropriate endpoints. Only high dose pirfenidone was associated with a significant improvement in progression free survival and decreased disease progression. Serious adverse events other than those resulting in treatment discontinuation not reported. Small changes in outcomes and lack of reported confidence intervals makes assessment of clinical applicability of results difficult. Setting: 73 centers in Japan.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DLco = carbon monoxide diffusing capacity; dx = diagnosis; FEV_1 = forced expiratory volume in one second, HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; ITT = intention to treat; m = meters; LOCF = last observation carried forward; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PFT = pulmonary function test; PG = parallel group; PIR = pirfenidone; PP = per protocol; SoB = shortness of breath; SpO_2 = oxygen saturation measured by pulse oximetry; SSD = sum of squared differences; TID = three times daily; tx = treatment; UCSD SoBQ = University of California, San Diego Shortness of Breath Questionnaire; scores range from 0 to 120, with larger scores indicating greater shortness of breath (minimally clinically important difference, 5 – 11 points); ULN = upper limit of normal; 6MET = 6-min steady-state exercise test ; 6MWT = 6-min walk test

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ESBRIET safely and effectively. See full prescribing information for ESBRIET.

ESBRIET® (pirfenidone) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

ESBRIET is a pyridone indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 801 mg (three capsules) three times daily taken with food. (2)
- Upon initiation of treatment, the daily dosage should be titrated to the full dosage of nine capsules per day over a 14-day period as follows:

Treatment days	Dosage
Days 1 through 7	1 capsule three times a day with meals
Days 8 through 14	2 capsules three times a day with meals
Days 15 onward	3 capsules three times a day with meals

- Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 5.3)
- Prior to treatment, conduct liver function tests. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 267 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with ESBRIET. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
- Photosensitivity and rash: Photosensitivity and rash have been noted with ESBRIET. Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily. Temporary dosage reductions or discontinuations may be required. (5.2)
- Gastrointestinal disorders: Nausea, vomiting, diarrhea, dyspepsia, gastro-esophageal reflux disease, and abdominal pain have occurred with ESBRIET. Temporary dosage reductions or discontinuations may be required. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact InterMune at 1-888-486-6411 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g., fluvoxamine) increase systemic exposure of ESBRIET and may alter the adverse reaction profile of ESBRIET. Discontinue fluvoxamine prior to administration of ESBRIET or reduce to one capsule three times a day. Consider dosage reduction with use of ciprofloxacin. (7.1)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with severe hepatic impairment. (8.6, 12.3)
- Renal Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with end stage renal disease on dialysis. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of ESBRIET. (8.8)

Appendix 2: Suggested Prior Authorization Criteria

Idiopathic Pulmonary Fibrosis (IPF) Agents

Goal: Restrict use of IPF agent to populations in which the drug has demonstrated efficacy.

Length of Authorization: Up to 1 year

Requires PA:

- Non-preferred drugs

Preferred Alternatives:

- None at this time

Approval Criteria		
1. Is this request for continuation of therapy (patient has already been on IPF drug)	Yes: Go to Renewal Criteria	No: Go to #2
2. Does the patient have a diagnosis of idiopathic pulmonary fibrosis (ICD-9 516.31)?	Yes: Go to #3	No: Pass to RPH; Deny for medical appropriateness.
3. Is the treatment prescribed by a pulmonologist?	Yes: Go to #4	No: Pass to RPH; Deny for medical appropriateness.
4. Does the patient have a forced vital capacity (FVC) >50%?	Yes: Go to #5	No: Pass to RPH; Deny for medical appropriateness.
5. Is the patient a current smoker?	Yes: Pass to RPH; Deny for medical appropriateness. Efficacy of approved drugs for IPF may be altered in smokers due to decreased exposure (see prescribing information).	No: Go to #6
6. Are pirfenidone and nintedanib concurrently prescribed in this patient?	Yes: Pass to RPH; Deny for medical appropriateness. Safety and efficacy of concomitant therapy has not been established.	No: Approve for up to 12 months.
Renewal Criteria		
Is there evidence of disease progression (defined as ≥10% decline in percent-predicted FVC) within the previous 12 months?	Yes: Pass to RPH; Deny for medical appropriateness.	No: Approve for up to 12 months.

P&T/DUR Review: *7/15 (KS)*
Implementation: ***TBD***