Pirfenidone (ESBRIET®)
National Drug Monograph
February 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]	
Description/ Mechanism of Action	Pirfenidone is a pyridone analogue (specifically, 5-methyl-1-phenyl-2-[1H]-pyridone). The mechanism of pirfenidone has not been definitively established.
Indication(s) under Review in this document	Pirfenidone is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).
Dosage Form(s) Under Review	Capsule containing 267mg of pirfenidone
REMS	No REMS
Pregnancy Rating	Pregnancy Category C

Executive Summary	
Efficacy	• US approval of pirfenidone was based upon three Phase 3 multicenter, randomized, double-blind, placebo-controlled trials conducted in patients with mild-to-moderate IPF: CAPACITY and ASCEND. • In two concurrent trials reported together as CAPACITY (004 and 006), patients were randomized to receive pirfenidone 1197mg/day (study 004) or 2403mg/day (studies 004 and 006) for 72 weeks and the change in percentage of predicted forced vital capacity (FVC) was assessed as the primary efficacy endpoint. Study 004 demonstrated a relative 35.5% reduction in mean decline of % predicted FVC following pirfenidone 2403mg daily and a 14.4% absolute difference in the proportion of patients with FVC decline ≥ 10%. • Patients enrolled in ASCEND were randomized to receive pirfenidone 2403mg daily; drug effect on change in percentage predicted FVC or death was assessed as the primary endpoint at week 52. Pirfenidone, compared with placebo, resulted in a relative reduction of 47.9% in the proportion of patients who had an absolute decline ≥ 10% in predicted FVC or who died; in addition, there was a relative increase of 132.5% in the proportion of patients with no decline in FVC. • A fourth RCT, the Pirfenidone Clinical Study Group in Japan trial, randomized patients to receive pirfenidone 1,200 or 1,800mg daily. The primary efficacy endpoint was amount of decline in vital capacity (VC). Pirfenidone 1,200 or 1,800mg daily for 52 weeks significantly reduced VC decline by 80 and 90ml, respectively. • Progression-free survival (PFS) was assessed as a secondary endpoint in CAPACITY, ASCEND, and the Pirfenidone Clinical Study Group in Japan trials. PFS was improved in every study with the exception of CAPACITY 006. • In an prespecified analysis of a pooled population of 1247 patients from ASCEND and CAPACITY (performed by the ASCEND investigators), pirfenidone 2403mg daily for one year reduced all-cause mortality 48% and IPF-related deaths by 68%.
Safety	• Pooled safety data for pirfenidone is available from the CAPACITY and ASCEND trials. At the recommended dosage of 2403 mg/day, 14% of patients discontinued pirfenidone because of an adverse event (compared to 9.6% on placebo). The most common adverse reactions were nausea (36%) and rash (30%); photosensitivity occurred in 9% of patients taking pirfenidone.
Potential Impact	• Pirfenidone is an FDA approved treatment for IPF, available as an oral capsule for

	three-time daily administration. Compared with placebo, pirfenidone reduces disease progression in patients with IPF, has an acceptable side effect profile and was associated with fewer deaths. There were no effective pharmacological therapies for IPF prior to the simultaneous FDA approval (October, 2014) of pirfenidone and another agent, nintedanib.

Background

Purpose for review

The purpose of the review is to evaluate the efficacy and safety of pirfenidone in the treatment of IPF.

Other therapeutic options

Non-formulary Alternative	Other Considerations
Nintedanib	Supplemental oxygen, pulmonary rehabilitation, and other supportive measures; lung transplant

Efficacy (FDA Approved Indications)[1, 2, 3]

Literature Search Summary

A literature search was performed on PubMed/Medline (1995 to December 2014) using the search terms pirfenidone and idiopathic pulmonary fibrosis. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical trials published in peer-reviewed journals are included.

Review of Efficacy

The FDA approval of pirfenidone was based on data from a large, placebo-controlled Phase 3 study (ASCEND) which was supported by two other large Phase 3 trials collectively known as CAPACITY (Table 1).

The CAPACITY studies (004 and 006) were two concurrent, multinational, multicenter, randomized, double-blind, Phase III studies that together enrolled 779 patients with mild to moderate IPF. The primary endpoint was the change in the percentage predicted forced vital capacity from baseline to the end of the study, at 72 weeks. Forced vital capacity, or FVC, is a measure of how well the lungs work based on the volume of air one can exhale with force after inhaling as deeply as possible. Percentage predicted FVC is calculated by dividing the actual FVC measurement by a predicted FVC based upon sex, age, and height.

ASCEND was a multinational, multicenter, randomized, double-blind, Phase III study that enrolled 555 patients with mild to moderate IPF. The primary endpoint was the change in percentage predicted FVC from baseline to the end of the study, measured at 52 weeks.

Data from the CAPACITY trials and from ASCEND are included in the prescribing information for pirfenidone.

Table 1. Summary of Phase 3 Randomized Controlled Clinical Trials supporting the FDA indication for pirfenidone (PIR) [1, 2, 3]

			Primary Efficacy Analysis	
			Proportion of pts	Proportion of pts

Study	Population (Inclusionary Criteria)	Regimen	w/ decline of ≥10% predicted FVC or death vs placebo (relative %Δ)	with no decline in % predicted FVC
CAPACITY (004)	Patients 40 to 80 years old with diagnosis IPF[a]; 50 to 90% of predicted FVC; 35 to 90% predicted DL_{CO}[b]; 6MWT[c] ≥ 150m	PIR 2403mg daily x 72 weeks[d]	20% vs 35% (↓41.7%) p < 0.001	Not assessed
CAPACITY (006)	See CAPACITY 004	PIR 2403mg daily x 72 weeks	23% vs 27% (↓15.2%) NS	Not assessed
CAPACITY (004 + 006)	Pooled population	PIR 2403mg daily x 72 weeks	21% vs 31% (↓30.2%) p < 0.003	Not assessed
ASCEND	Patients 40 to 80 years old inclusive with confirmed IPF ≥ 6 months[a]; 50-90% of predicted FVC; 30-90% of predicted DL_{CO}; FEV_1[e]/FVC ≥ 0.80; 6MWT ≥ 150m	PIR 2403mg daily x 52 weeks	16.5% vs 31.8% (↓47.9%) p < 0.001	22.7% vs 9.7% (↑132.5%) p < 0.001

[a] Diagnosis of IPF was confirmed per ATS/ERS (2000) [CAPACITY] or ATS/ERS/JRS/ALAT (2011) [ASCEND] Consensus Guidelines[4,5]
[b] Carbon monoxide diffusing capacity (DL_{CO}); DL_{CO} measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries
[c] Six minute walk test (6MWT)
[d] Eighty-seven patients were randomized to 1197mg daily; their results are excluded
[e] Forced expiratory volume in 1 second (FEV_1)

Overall Quality of Evidence: High (Refer to Appendix A; note ASCEND and CAPACITY were sponsored by InterMune, the developer of pirfenidone).

FVC, 6 minute walk distance, and DL_{CO} are considered reliable, valid, and responsive measures of disease status as well as independent predictors of survival in patients with IPF.[6, 7]

CAPACITY (004): Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes[2]

- A total of 435 patients were enrolled and randomly assigned to receive pirfenidone 1197mg (n = 87), pirfenidone 2403mg daily (n = 174), or placebo (n = 174) for 72 weeks. *This monograph will focus on results obtained with the FDA recommended dose of 2403mg daily.*
- Inclusionary criteria are detailed in Table 1; exclusionary criteria included obstructive airway or connective tissue disease, alternative etiology for interstitial lung disease, or candidacy for lung transplant.
- There were almost identical numbers in each treatment group for the following baseline characteristics: definite diagnosis of IPF by high-resolution computed tomography (HRCT), history of surgical lung biopsy, and % of patients with diagnosis of IPF ≤ 1 year previous to enrollment. Additional demographics and baseline characteristics revealed no outlying baseline imbalances (Table 2).
- Study drug was administered with food in 3 equally divided doses and gradually increased to 2403mg over a 2 week period. Adherence to the study treatment was high; 88% of patients in all pirfenidone groups (004 and 006) and 93% in all placebo groups (004 and 006).
- The primary efficacy outcome is expressed in Table 1 as proportion of patients with decline of ≥10% predicted FVC or death vs placebo; in addition, pirfenidone 2403mg/day reduced mean decline in percentage predicted FVC compared to placebo (-8.0%[SD 16.5] vs -12.4% [18.5], respectively. Treatment effect was significant by week 24 and was persistent until week 72.
- Progression-free survival time (*footnote*) was the only secondary efficacy outcome measure positively affected by pirfenidone: a 36% reduction in risk of death or disease progression was observed (p = 0.0235).

- The mean values of the following secondary measures were unchanged by treatment: 6MWT distance, DL_{co} % predicted, dyspnea score, worst peripheral oxygen saturation (SpO_2) during 6MWT, time to worsening IPF, and categorical change in HRCT-diagnosed fibrosis.

Progression-free survival time in CAPACITY 004 and 006 was defined as the time to the first occurrence of any one of the following: a confirmed decrease of ≥ 10% in the percentage of predicted FVC, 15% decline in predicted DL_{CO}, or death.

Table 2: CAPACITY 004- demographics and baseline characteristics administered pirfenidone 2403mg/day or placebo; data expressed as number (%) or mean value ± SD[2]

Characteristics	Pirfenidone (n = 174)	Placebo (n = 174)
Age	65.7 (8.2)	66.3 (7.5)
Male sex – no. (%)	118 (68%)	128 (74%)
Smoking status		
Never – no. (%)	56 (32%)	51 (29%)
Former – no. (%)	110 (63%)	114 (66%)
Current – no. (%)	8 (5%)	9 (5%)
Lung physiological features		
FVC (% predicted)	74.5 (14.5)	76.2 (15.5)
DL_{CO} (% predicted)	46.4 (9.5)	46.1 (10.2)
A-a gradient (mm Hg)	17.7 (10.6)	18.9 (14.7)
6MWT distance (m)	411.1 (91.8)	410.0 (90.9)
Use of supplemental oxygen - no. (%)	29 (17%)	25 (14%)

CAPACITY (006): Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes[2]

- A total of 344 patients were enrolled and randomly assigned to receive pirfenidone 2403mg daily (n = 171) or placebo (n = 173) for 72 weeks.
- Inclusionary criteria are detailed in Table 1; exclusionary criteria mirrored those of CAPACITY 004.
- There were no outlying imbalances between the two treatment groups for the following baseline characteristics: definite diagnosis of IPF by HRCT, history of surgical lung biopsy, and % of patients with diagnosis of IPF ≤ 1 year previous to enrollment. Additional demographics and baseline characteristics were equally similar (Table 3).
- Early study drug dose up-titration and adherence to study treatment was as described for CAPACITY 004.
- In CAPACITY 006, at week 72, there was no significant difference between the pirfenidone and placebo groups for the primary outcome measure relating to proportion of patients with a ≥ 10% decline in predicted FVC. However, a significant treatment effect was noted at every time point from week 12 to week 48 ($p \leq 0.021$) as well as in a repeated-measures analysis of % predicted FVC change over all assessment time points ($p = 0.007$).
- Mean change in 6MWT distance was the only secondary efficacy outcome measure positively affected by pirfenidone where an absolute difference of +31.8m was found versus placebo ($p = 0.0009$). The mean values of the remaining secondary measures were unchanged by pirfenidone administration: progression-free survival time, DL_{co} % predicted, dyspnea score, worst SpO_2 during 6MWT, time to worsening IPF, and categorical change in HRCT-diagnosed fibrosis.
- The authors speculated that the difference in FVC outcomes between 004 and 006 may have been related to a lower than expected rate of FVC decline in the placebo group in 006. In addition, 006 had a greater proportion of patients with a recent diagnosis of IPF, and the placebo group in 006 had a greater proportion of patients with obstructive airway disease (which had been an exclusionary criterion).

CAPACITY 004 and 006 were not sufficiently powered to assess effects on secondary outcome measures of all cause or IPF-related mortality; however, hazard ratios favored pirfenidone (see page 6 for mortality analysis of a pooled population of CAPACITY and ASCEND patients).

In March, 2010, on the strength of CAPACITY, a FDA Advisory Committee recommended for approval of pirfenidone; however, the NDA was eventually declined in view of the findings in CAPACITY 006. The FDA complete response letter cited the need for an additional clinical trial to support the efficacy of pirfenidone in IPF. The European Medicines Agency approved pirfenidone for treatment of IPF in early 2011.[8]

Table 3: CAPACITY 006 - demographics and baseline characteristics administered pirfenidone 2403mg/day or placebo; data expressed as number (%) or mean value ± SD[2]

Characteristics	Pirfenidone (n = 171)	Placebo (n = 173)
Age	66.8 (7.9)	67.0 (7.8)
Male sex – no. (%)	123 (72%)	124 (72%)
Smoking status		
Never – no. (%)	59 (35%)	64 (37%)
Former – no. (%)	112 (65%)	101 (58%)
Current – no. (%)	0	8 (5%)
Lung physiological features		
FVC (% predicted)	74.9 (13.2)	73.1 (14.2)
DL_{CO} (% predicted)	47.8 (9.8)	47.4 (9.2)
A-a gradient (mm Hg)	18.3 (11.1)	17.0 (10.4)
6MWT distance (m)	378.0 (82.2)	399.1 (89.7)
Use of supplemental oxygen - no. (%)	48 (28%)	49 (28%)

Costabel et al. (2014) reported selected findings from an open-label extension study (RECAP) in patients who completed the CAPACITY trials; 178 patients who had been given placebo in CAPACITY were given pirfenidone 2403mg/day for 60 weeks.[9] Efficacy outcomes for these 178 patients were similar to those reported for pirfenidone-treated patients in CAPACITY (16.3% of RECAP patients given pirfenidone 2403mg/day had a FVC ≥ 10% decline compared with 16.8% and 24.8% in CAPACITY pirfenidone and placebo groups, respectively. In addition, overall survival in patients newly treated with pirfenidone was similar to that seen in pirfenidone-treated patients in CAPACITY).

ASCEND: Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis[3]

- ASCEND commenced in July, 2011 in response to the FDA request for additional efficacy data. The results were published in May, 2014 and the drug received FDA approval the following October.[7]
- Inclusionary criteria are detailed in Table 1. A total of 555 patients were enrolled and were randomly assigned to receive pirfenidone 2403mg daily (n = 278) or placebo (n = 277) for 52 weeks. A detailed list of exclusionary criteria is contained in a supplement to the published study.
- Patients in both groups had a diagnosis of IPF made 1.7 ± 1.1 years previously and confirmed centrally. There were no significant imbalances in diagnostic methods or findings between the two groups regarding assessments by HRCT or frequency of surgical lung biopsy. Demographics and baseline characteristics of both groups are detailed in Table 4.
- The study drug was administered with food in 3 equally divided doses and was gradually increased to the full dose over a 2 week period. Adherence to the study treatment was high; 85.3% and 92.4% of the pirfenidone and placebo groups received at least 80% of the prescribed doses of the assigned study drug, respectively.
- Primary efficacy outcomes are detailed in Table 1; significant between-group differences were also found in key secondary efficacy outcome endpoints. At week 52:
    - The absolute difference in 6MWT distance was +26.7m for pirfenidone patients when compared to those receiving placebo; a decrease of ≥ 50m in 6MWT distance or death occurred in 25.9% of the pirfenidone group compared to 35.7% administered placebo (both p = 0.04).
    - Pirfenidone, compared to placebo, improved PFS time (*footnote*; p < 0.001) and reduced the relative risk of death or disease progression by 43%
- Analysis of all-cause mortality and deaths from IPF in ASCEND revealed fewer deaths in the pirfenidone group than in the placebo group but the differences were not statistically significant. However, in a prespecified analysis of a pooled population of 1247 patients from ASCEND and CAPACITY, at 1 year, pirfenidone reduced all-cause mortality 48% and deaths from IPF 68% (hazard ratio, 0.52; 95% CI, 0.31 to 0.87; p = 0.01 and hazard ratio, 0.32; 95% CI, 0.14 to 0.76; p = 0.006; respectively).

Table 4: Demographics and baseline characteristics for patients enrolled in ASCEND[3]

Characteristics	Pirfenidone (n = 278)	Placebo (n = 277)
Age (years)	68.4 ± 6.7	67.8 ± 7.3
Male sex – no. (%)	222 (79.9)	213 (76.9)
Former smoker – no. (%)	184 (66.2)	169 (61.0)

Lung physiological features		
FVC (% predicted)	67.8 ± 11.2	68.6 ± 10.9
FEV_1:FVC	0.84 ± 0.03	0.84 ± 0.04
DL_{CO} (% predicted)	43.7 ±10.5	44.2 ± 12.5
6MWT distance (m)	415.0 ± 98.5	420.7 ± 98.1
Use of supplemental oxygen – no. (%)	78 (28.1)	76 (27.4)

Progression-free survival in ASCEND was defined as the time to the first occurrence of any one of the following: a confirmed decrease of ≥ 10% in the percentage of predicted FVC, a confirmed decrease of ≥ 50m in 6MWT distance, or death

The Pirfenidone Study Group in Japan Trial[10]

- The Pirfenidone Study Group in Japan (PSGJ) Trial was a 1-year, multicenter, double-blind, randomized, placebo-controlled, phase III efficacy and safety study.
- Eligible patients were randomized in a 2:1:2 ratio; pirfenidone 1800mg/day (n = 108), pirfenidone 1200mg/day (n = 55), or placebo (n = 104). Study drug was administered in 3 equally divided doses; initial doses were increased at week 2 and week 4, but thereafter remained constant for the final 48 weeks of the study.
- Inclusionary criteria required patients to be 20-75 years of age, with the diagnosis of IPF confirmed based upon ATS/ERS (2000) and Japanese Respiratory Society Consensus (2004) criteria. Patients were also required to meet the following pulse oximetry arterial oxygen saturation criteria for enrollment: 1) have a ≥ 5% difference between resting SpO_2 and the lowest SpO_2 during a 6 minute exercise test (6MET) and 2) have a SpO_2 ≥ 85% during the 6MET on room air.
- Patients were excluded who had a decrease in symptoms of IPF during the preceding 6 months, were on immunosuppressant therapy and/or oral corticosteroid equivalent of > 10mg prednisone/day during the preceding 3 months, had clinical features of idiopathic interstitial pneumonia other than IPF, or had evidence of known co-existing pulmonary hypertension, asthma, tuberculosis, bronchiectasis, aspergillosis, or severe respiratory infection.
- The revised primary efficacy endpoint was the amount of change (L) in vital capacity (VC) from baseline to week 52; secondary efficacy endpoints were PFS time (*footnote*) and the change in the lowest SpO_2 during the 6MET (the original primary endpoint). The study authors stated that the primary endpoint was revised prior to un-blinding due to an evolved knowledge of objective measurements used to assess IPF.
- Demographics and patient characteristics are summarized in Table 5. Approximately 1/3 of patients in each treatment group had been recently diagnosed with IPF (within 1 year). At week 52, for the primary efficacy measure, the decrease in VC was less with pirfenidone 1800 and 1200mg/day than with placebo (0.09L, p = 0.042 and 0.08L, p < 0.04 *versus* 0.16L for placebo, respectively). For the secondary measures, compared with placebo, high dose pirfenidone (1800mg/day) significantly increased PFS time (p = 0.0280) while only a marginal difference was detected between low dose pirfenidone (1200mg/day) and placebo (p = 0.0655). No statistically significant differences were detected in the mean changes of the lowest SpO_2 between the 3 groups. Drop-out rates were relatively high for all treatment groups: pirfenidone 1800mg, 1200mg, and placebo groups were 37%, 27.3%, and 29.8%, respectively.
- Compared to CAPACITY and ASCEND, the PSGJ trial enrolled fewer patients with a recent diagnosis of IPF, excluded patients who had received alternate IPF therapies in the preceding 3 months, and generally utilized lower doses of pirfenidone. The PSGJ trial has been criticized for its high drop-out rates and mid-stream alteration of the primary outcome measure. Despite these issues, the magnitude of treatment effect in the PSGJ trial appears consistent with that found in the latter two trials.

Data from PSGJ and a previous phase II trial was central to the regulatory approval of pirfenidone in Japan in October, 2008.[2]

Progression-free survival time in the PSGJ trial was defined as the time to death and/or ≥ 10% decline in VC from baseline.

Table 5: The Pirfenidone Study Group in Japan Trial - demographics and baseline characteristics for patients administered pirfenidone 1800 or 1200mg/day or placebo; data expressed as number (%) or mean value ± SD.[10]

Characteristics	Pirfenidone 1800mg/day (n = 108)	Pirfenidone 1200mg/day (n = 105)	Placebo (n = 55)
Age	65.4 (6.2)	63.9 (7.5)	64.7 (7.3)
Male sex – no. (%)	85 (78.7%)	47 (85.5%)	81 (77.9%)
Smoking status			

Never – no. (%)	5 (4.6%)	10 (18.2%)	13 (12.5%)
Former – no. (%)	81 (75%)	33 (60%)	70 (67.3%)
Current – no. (%)	22 (20.4%)	12 (21.8%)	21 (20.2%)
Lung physiological features			
VC (% predicted)	73.3 (16.8)	76.2 (18.7)	79.1 (17.4)
DL_{CO} (% predicted)	52.1 (16.8)	53.6 (19.1)	55.2 (18.2)
A-a gradient (mm Hg)	18.4 (11.3)	16.9 (9.6)	17.4 (9.7)
6MWT distance (m)	Not reported		
Use of supplemental oxygen - no. (%)	Not reported		

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

Pirfenidone is being investigated for the potential treatment of numerous off-label conditions; the following trials are listed in www.clinicaltrials.gov with varying statuses (not yet recruiting, recruiting, completed with/without results):

- European Trial of Pirfenidone in Bronchiolitis Obliterans (post lung transplantation), A European Multi-center Study
- Pirfenidone: A New Drug to Treat Kidney Disease in Patients With Diabetes
- Oral Pirfenidone for the Pulmonary Fibrosis of Hermansky-Pudlak Syndrome
- Pirfenidone in Children and Young Adults With Neurofibromatosis Type I and Progressive Plexiform Neurofibromas
- Clinical Trial of Pirfenidone in Adult Patients With Neurofibromatosis 1
- Pirfenidone in Treating Young Patients With Neurofibromatosis Type 1 and Plexiform Neurofibromas
- Safety and Tolerability of Pirfenidone in Patients With Systemic Sclerosis−Related Interstitial Lung Disease (SSc-ILD) (LOTUSS)
- Pirfenidone, an Antifibrotic and Antiinflammatory Drug (Hepatitis C)
- Effect of Topical Pirfenidone in Diabetic Ulcers
- Pirfenidone to Treat Hypertrophic Cardiomyopathy
- Pirfenidone to Treat Kidney Disease (Focal Segmental Glomerulosclerosis)
- Permeability Factor in Focal Segmental Glomerulosclerosis
- Pirfenidone in Treating Patients With Fibrosis Caused by Radiation Therapy for Cancer
- Safety and Efficacy Study of Pirfenidone to Treat Grade 2 or Above Radiation-induced Lung Injury
- Development of a Non-Invasive Treatment for Uterine Leiomyoma (Fibroids)

Safety (for more detailed information refer to the product package insert)[1,2,3,11]

	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• Elevated liver enzymes (ALT, AST, and bilirubin) have occurred with pirfenidone; monitoring is recommended during treatment. • Photosensitivity and rash have been noted with pirfenidone; avoid exposure to UV light and/or use sunscreen or protective clothing.

- Gastrointestinal disorders (Nausea, vomiting, diarrhea, dyspepsia, GERD, and abdominal pain may occur with pirfenidone

Safety Considerations

The safety assessment of pirfenidone is primarily based on pooled data from three phase III clinical trials reported as CAPACITY and ASCEND in which a total of 623 patients received 2403mg/day of pirfenidone and 624 patients received placebo. The mean age of subjects was 67 years (range 40 to 80) and most were male (74%) and Caucasian (95%). The mean exposure to pirfenidone was 62 weeks (range 2 to 118 weeks).

- Patients treated with pirfenidone 2403mg/day in CAPACITY and ASCEND had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Most of these reactions occurred within the initial 6 months. Patients should avoid or minimize exposure to sunlight, use sunblock (SPF 50, or higher), and wear protective clothing. Also, patients should avoid concomitant medications known to cause photosensitivity. Pirfenidone dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash.
- In CAPACITY and ASCEND, nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients taking pirfenidone than in those taking placebo (Table 6). The incidence of gastrointestinal events was highest early in the course of treatment (≤ 3 months) and decreased over time; pirfenidone dosage modifications may be necessary for some gastrointestinal adverse reactions
- Valeyre et al. (2014) reported a safety analysis performed in 789 patients enrolled in RECAP (an open label extension study of patients previously in CAPACITY 004 and 006) and Study 002 (an open-label, compassionate-use study of patients with IPF or secondary pulmonary fibrosis given pirfenidone 40mg/kg/day).[11] The safety outcomes in this integrated patient population given pirfenidone 2015 ± 527mg daily for a median treatment period of 2.6 years were similar to those reported in the CAPACITY and ASCEND RCTs.

Table 6: Incidence of selected gastrointestinal adverse reactions occurring with pirfenidone or placebo in CAPACITY and ASCEND

Gastrointestinal Adverse Reactions	% of Patients (0 to 118 weeks)	
	Pirfenidone 2403mg/day (n = 623)	Placebo (n = 173)
Nausea	36%	16%
Abdominal pain	24%	15%
Diarrhea	26%	20%
Dyspepsia	19%	7%
Vomiting	13%	6%
Gastro-esophageal Reflux Disease	11%	7%

- The incidence of liver enzyme (ALT, AST) elevations > 3 x ULN was greater with pirfenidone than with placebo in patients participating in CAPACITY and ASCEND (3.7% vs. 0.8%, respectively). Rarely, these elevations were associated with a concomitant elevation in bilirubin. Such elevations have responded favorably to pirfenidone dose modification or discontinuation and there have been no cases of death due to liver failure or need for transplant associated with its use. Liver function tests should be conducted prior to the initiation of pirfenidone, then monthly for the first 6 months and every 3 months thereafter.

Adverse Reactions

Common adverse reactions	Incidence ≥ 5% and more commonly than placebo, includes: Gastrointestinal (various; see Table 6), rash, pruritus, photosensitivity, headache, insomnia, fatigue, asthenia, dizziness, anorexia, dysgeusia, weight loss, arthralgia, sinusitis, and upper respiratory tract infection.
Death/Serious adverse reactions	Pooled data from CAPACITY and ASCEND revealed 7 of 22 deaths in pirfenidone-treated patients were directly related to IPF; none of the remaining deaths were considered to be related to study treatment.
Discontinuations due to adverse reactions	At the recommended dosage of 2403mg/day, 14.6% of patients taking pirfenidone compared to 9.6% on placebo permanently discontinued treatment due to an adverse event. The most common adverse reactions leading to

	discontinuation were rash and nausea, while the most common reactions requiring temporary discontinuation or dose reduction were rash, nausea, diarrhea and photosensitivity.
Laboratory Abnormalities	Liver enzyme (ALT and/or AST) and bilirubin elevations may occur with pirfenidone therapy which may necessitate dose modification or treatment discontinuation. If ALT and/or AST are > 3 but ≤ 5 x ULN without symptoms or hyperbilirubinemia the full daily dosage of pirfenidone may be continued. Alternatively, the pirfenidone dose may be reduced or therapy can be interrupted until liver chemistries have normalized – at that time therapy can be resumed with re-titration to full dose as tolerated. If liver enzymes are > 3 but ≤ 5 x ULN with symptoms or hyperbilirubinemia OR if liver enzymes are > 5 x ULN, then pirfenidone should be permanently discontinued without subsequent re-challenge.

Drug-Drug Interactions[1,12]

- Consult the prescribing information prior to use of pirfenidone for potential drug interactions.
- Pirfenidone is metabolized 70 to 80% via CYP1A2, with minor contributions from CYP2C9, 2C19, 2D6 and 2E1.
- The concomitant administration of pirfenidone with strong CYP1A2 inhibitors such as fluvoxamine is not recommended; however, if co-administration is unavoidable, the dose of pirfenidone should be reduced to 267mg three times daily
- Pirfenidone dose reduction may be required when the drug is co-administered with a high dose of a moderate CYP1A2 inhibitor. For example, pirfenidone should be reduced to 534mg three times daily when co-administered with ciprofloxacin 750mg twice daily, but the usual maintenance dose of pirfenidone can be continued (with monitoring) if co-administered with lower doses of ciprofloxacin.
- Co-administration of pirfenidone with strong CYP1A2 inducers is not recommended due to an expected reduction in pirfenidone exposure and loss of efficacy.
- CYP1A2 induction caused by smoking significantly accelerates pirfenidone metabolism which may lead to loss of drug efficacy. Patients should be advised not to smoke while taking pirfenidone.
- Strong or moderate CYP1A2 inhibitors in combination with other drugs which inhibit other CYP isoenzymes involved in the metabolism of pirfenidone would have an unpredictable effect on clearance of the drug; these combinations should be discontinued or avoided during pirfenidone treatment.
- In a multiple dose study, concomitant administration of nintedanib and pirfenidone did not affect pirfenidone exposure; however, nintedanib AUC and C_{max} were respectively decreased 68.3 and 59.2%.

Risk Evaluation

As of October 2014	**Comments**
Sentinel event advisories	• None
Look-alike/sound-alike error potentials	• Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List):

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment

	Pirfenidone Esbriet				Prednisone Prednisolone Primidone Perphenazine Paliperidone Esgic

Dosing and Administration[1]

- Refer to the package insert for full dosing information.
- The recommended daily maintenance dose of pirfenidone is 2403mg (three 267mg capsules three times daily with food). Therapy with pirfenidone should be initiated at 267mg three times daily on days 1-7, increased to 534mg three times daily on days 8-14, then continued at 801mg three times daily from day 15 onward. Interruption of pirfenidone for ≥ 14 days warrants repeat of the 2 week titration schedule if the drug is to be re-initiated.
- Dose modifications may be required due to drug-drug interactions, liver function test abnormalities or serious side effects (see Safety).

Special Populations (Adults)[1]

	Comments
Elderly	• In clinical trials of pirfenidone, 714 patients were ≥ 65 years old and 231 were ≥ 75years. No differences in safety or effectiveness were found in the elderly necessitating dosage adjustments based upon age.
Pregnancy	• Pregnancy Category C
Lactation	• It is not known if pirfenidone is excreted in human breast milk. According to the PI, due to the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue pirfenidone, taking into account the importance of the drug to the mother.
Renal Impairment	• Based on a pharmacokinetic study in subjects with renal impairment, pirfenidone should be used with caution in patients with mild (CLcr 50-80ml/min), moderate (CLcr 30-50ml/min), or severe (CLcr < 30ml/min), where systemic exposure to the drug is increased approximately 1.4, 1.5, and 1.2 fold. The pharmacokinetics and safety of pirfenidone has not been studied in patients with end-stage renal disease on dialysis.
Hepatic Impairment	• Systemic exposure ($AUC_{0\text{-}inf}$) and peak plasma concentration (C_{max}) of pirfenidone was increased 1.6 and approximately 1.4 fold in subjects with moderate hepatic impairment (Child Pugh Class B) compared to those with normal hepatic function. Pirfenidone is not recommended in patients with severe hepatic impairment.
Pharmacogenetics/genomics	• There are no data identified in the FDA approved labeling http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm (accessed December 18, 2014)

Projected Place in Therapy [13, 14, 15, 16, 17]

- Approximately 100,000 people in the United States have IPF, a chronic and ultimately fatal lung disease characterized by a progressive loss of the ability of the lungs to function due to interstitial scarring. The cause of IPF is unknown and there is no cure. While some patients may experience periods of disease stability, the prognosis in IPF is poor: the estimated median survival is only two to five years after diagnosis (similar to that of non-small cell lung cancer). In FY14, 2150 patients in VA were identified through ICD-9 coding to have the diagnosis of IPF.

- In CAPACITY and ASCEND, pirfenidone reduced disease progression, improved exercise tolerance, and progression-free survival in patients with IPF. Treatment with pirfenidone was generally safe and was associated with an acceptable side-effect profile. No mortality benefit was demonstrated in individual trials and quality of life was not assessed; however, the ability to positively influence the progression of IPF is a major step forward in its management, as there were no effective pharmacological therapies for IPF prior to the 2014 FDA approvals of pirfenidone and another agent, nintedanib.
- Positive outcomes have resulted when pirfenidone was given to patients with mild- to moderate IPF; however, it is unclear to what extent pirfenidone is effective in patients with severe disease (FVC < 50%).
- There is little information to characterize the persistence of pirfenidone efficacy beyond one year.
- The use of pirfenidone relative to that of nintedanib, which has a different mechanism of action than pirfenidone, has not yet been determined. There is no evidence to support use of the drugs in combination and a significant drug interaction exists between the two agents.

References

1. Esbriet [prescribing information]. Brisbane, CA: InterMune, Inc.; October, 2014.
2. Noble PW, Albera C, Bradford WZ, et al. for the CAPACITY Study Group. Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomized Trials. Lancet 2011; 377: 1760-69 + supplementary appendix.
3. King TE, Bradford WZ, Castro-Bernardini S et al. for the ASCEND Study Group. A Phase 3 Trial of Pirfenidone in Patients with idiopathic Pulmonary Fibrosis. N Engl J Med; 370: 2083-92 + supplementary appendix.
4. American Thoracic Society, European Respiratory Society. Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment: International Consensus Statement. Am J Respir Crit Care Med 2000; 161: 646-64.
5. Raghu G, Collard HR, Egan JJ et al. for the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med 2011; 183: 788-824.
6. Ley B, Collard HR and King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2011; 183: 431-40
7. Wells AU and Ward S (2014) Pulmonary Function Tests in Idiopathic Pulmonary Fibrosis in Meyer KC and Nathan SD (Eds) Idiopathic Pulmonary Fibrosis: A Comprehensive Clinical Guide, pp 103-21 (New York), Humana Press.
8. 2010-2014 News Releases (Pirfenidone), Manufacturers website: https://www.intermune.com/. Accessed December, 2014.
9. Costabel U, Albera C, Bradford WZ et al. Analysis of Lung Function and Survival in RECAP: An Open-label Extension Study of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 198-205.
10. Taniguchi H, Ebina M, Kondoh Y et al. for the Pirfenidone Study Group in Japan. Pirfenidone in Idiopathic Pulmonary Fibrosis. Eur Respir J 2010; 35: 821-9 + supplementary appendix.
11. Valeyre D, Albera A, Bradford WZ et al. Comprehensive Assessment of the Long-term Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. Respirology 2014; 19: 740-7.
12. Ofev® (nintedanib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October, 2014.
13. Bouros D. Pirfenidone for Idiopathic Pulmonary Fibrosis (edit). Lancet 2011; 377: 1727-9.
14. Hunninghake GM. A New Hope for Idiopathic Pulmonary Fibrosis (edit). N Engl J Med 2014; 370: 2142-3.
15. Ryu JH, Moua T, Daniels CE et al. Idiopathic Pulmonary Fibrosis: Evolving Concepts. Mayo Clin Proc 2014; 89: 1130-42.
16. Wuyts WA, Antoniou KM, Borensztajn K et al. Combination Therapy: the Future of Management for Idiopathic Pulmonary Fibrosis? Lancet Respir Med 2014; 2: 933-42.
17. Raghu G and Selman M. Nintedanib and Pirfenidone: New Antifibrotic Treatments Indicated for Idiopathic Fibrosis Offer Hopes and Raise Questions. Am J Resp Crit Care Med 2015; 191: 252-3.

Prepared: December, 2014 Contact person: Michael Chaffman, Pharm.D., BCPS, National PBM Clinical Pharmacy Program Manager

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.