Retrospective Analysis of Medication Utilization and Clinical Outcomes in Patients With Idiopathic Pulmonary Fibrosis Treated With Nintedanib or Pirfenidone

Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine
Volume 13: 1–7

DOI: 10.1177/1179548419834922

Anastasia Y Ipatova[1], Pamela H Koerner[2], Richard T Miller[1], Francis Staskon[3] and Melanie Radi[1]

[1]Clinical and Professional Services, AllianceRx Walgreens Prime, Pittsburgh, PA, USA.
[2]Division of Pharmacy Practice, School of Pharmacy, Duquesne University, Pittsburgh, PA, USA.
[3]Health Analytics, Research, and Reporting, Walgreen Co, Deerfield, IL, USA.

ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease which results in thickening and scarring of the interstitial tissue. As the only 2 Food and Drug Administration (FDA)-approved medications on the market, it is valuable to compare the impact of nintedanib and pirfenidone on clinical outcomes. Records of patients who started nintedanib or pirfenidone between calendar years 2015 and 2016 at a national specialty pharmacy were retrospectively reviewed. Data collection was derived from patient management applications and statistical data analysis was completed in SAS (SAS Institute Inc®). The nintedanib population contained 2605 patients and of the population completing clinical assessment surveys (n = 1343), 46% of respondents (n = 612) reported no adverse events, with the remaining 54% reporting at least 1 adverse event. Average proportion of days covered (PDC) was 84.2% (SD = 17.0). Average final monthly copay for this group was $235. The pirfenidone population had 1322 patients, and of the surveyed population (n = 764), 58% of respondents (n = 445) reported no adverse events, with the remaining 42% reporting at least 1 adverse event. Average PDC was 83.4% (SD = 17.3). Average final monthly copay for this group was $339. Outcomes in the studied IPF population were similar for nintedanib and pirfenidone.

KEYWORDS: nintedanib, pirfenidone, idiopathic, respiratory, pulmonary

RECEIVED: May 23, 2018. **ACCEPTED:** September 25, 2018.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Anastasia Y Ipatova, AllianceRx Walgreens Prime, 130 Enterprise Drive, Pittsburgh, PA 15275, USA. Email: ipatovaa@duq.edu

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease which results in thickening and scarring of the interstitial tissue.[1,2] Loss of normal lung tissue leads to restricted ventilation, impaired gas exchange, respiratory symptoms, exercise limitations, decreased quality of life, and ultimately death.[3] The earliest signs and symptoms are non-specific and patients commonly present with advanced disease years after the onset of initial symptoms.[4] The median survival following diagnosis is 3 to 5 years.[5] Diagnosis of IPF requires exclusion of other known causes of interstitial lung disease (ILD), a usual interstitial pneumonia (UIP) pattern on high-resolution computerized tomography (HRCT) in patients without surgical lung biopsy, and specific combinations of HRCT and surgical lung biopsy in patients who undergo biopsy.[1,4]

The exact prevalence of IPF is unknown with estimates ranging from 2 to 29 people per 100 000 in the general population.[1,2] A rising incidence in diagnosis has been observed, thought to be due to improved capacity diagnosing IPF using HRCT.[5] IPF primarily presents in older adults in their 50s and 60s and tends to affect men more than women.[2,4,6] Potential risk factors of IPF include environmental and occupational exposures, gastroesophageal reflux disease, and genetic factors.[1,4] Clinical presentation includes gradual onset of chronic dyspnea, non-productive cough without attributable causes, "velcro" crackles, and finger clubbing.[4]

Treatment options for IPF include both non-pharmacologic and pharmacologic approaches. The former consists of smoking cessation, pulmonary rehabilitation, maintaining healthy weight, vaccinations to prevent complications, and possible lung transplantation.[1,4,7] In addition to oxygen therapy, Food and Drug Administration (FDA)-approved pharmacologic therapies for IPF are limited to nintedanib and pirfenidone.[8]

Nintedanib inhibits receptor tyrosine kinases including those thought to be involved in IPF.[9] Although the mechanism of action of pirfenidone in the treatment of IPF has not been established, pirfenidone is thought to exhibit antifibrotic activity by inhibiting transforming growth factor beta and tumor necrosis factor alpha.[5,10] Both medications have been shown to slow disease progression in mild-moderate disease.[8–10] As the only 2 FDA-approved medications indicated to treat IPF, it is valuable to compare the impact of nintedanib and pirfenidone on medication utilization and clinical outcomes.

Methods

Study sample

The study sample consisted of patients prescribed either nintedanib or pirfenidone between January 2015 and December 2016 at a national specialty pharmacy. In addition, these patients participated in an enhanced clinical program initiated

in January 2016. Patients needed to be at least 18 years of age to be included in the study.

Study design

The study used a 2-year retrospective cohort design to examine patient characteristics, patient-reported side effects, discontinuation rates, medication adherence for nintedanib or pirfenidone, and patient copay amounts by payer categorizations. Descriptive statistics on utilization patterns were generated for each year of the study individually and reflect patterns within the given calendar year, including discontinuation rates per drug, patient-reported side effects, and final patient copay values. Due to initiation of the enhanced clinical program in January 2016, patient-reported side effect data were only available for this calendar year.

Modeling of patient adherence was not conducted within calendar years, but rather as a 6-month follow-up to the initial fill per patient (from January 2015 to July 2016). The outcome proportion of days covered (PDC) was defined by the total number of days where the medication was available on hand divided by the total days in the observation period (180 days) and reported as average adjusted PDC. This 6-month PDC was used as the main outcome for either the model on mean percentage value or coded as adherent for those with at least 80% PDC in the logistic model as described below. To enter into the adherence comparisons, patients had to have at least 2 or more prescription dispenses for either nintedanib or pirfenidone medication within the study period, and also have supply of medication after the 89th day of the observation period. This last requirement eliminated those patients who discontinued therapy or switched pharmacies early on. For a small count of individuals, cash was used rather than any primary insurance coverage and these individuals were eliminated from the models (n = 5 for pirfenidone and n = 7 for nintedanib) to avoid poor reliability and bias.

Linear or logistic models of adherence to either nintedanib or pirfenidone were constructed from the set of pharmacy utilization variables (patient demographics, pharmacy primary and secondary insurance types, and final patient copay per fill). Specifically, patient age at the first medication fill, patient sex, and census region designation were included as categorical variables representing age of at least 65 years or not, being female vs male, and residing in the Midwest census region or not. There were 139 patients that used both medications in the study period. These patients who switched medications throughout the study period were included in descriptive statistics but were not included in the analysis due to the small population size and potentially confounding patient adherence in the first 6 months with switching patterns. For the patient copay analysis, primary insurance plans were grouped into either government or commercial categories, and secondary insurance plans as either government, commercial (Patient Assistance Program [PAP]—manufacturer copay cards, PAP—charitable organizations), or none (including a small number of fills with Government coverage). Patient copay values represent the patients' final paid values (actual out-of-pocket amount) after primary and secondary insurance coverages were applied, and were summed per patient based on the fills within the first 180 days. The total final copay value was then divided by the total revenue per patient (to adjust for the range of dollar values) and this fraction was then divided by the number of fills included in the 180-day period. Hence, the copay variable is the average percent of revenue representing the patient final copay contribution within a given 180-day time segment. Patients' insurance coverage also had potential to change over time. For the 44 affected patients (0.01%), this was accounted for in the models by adjusting which insurance plan type they were grouped into. This adjustment was determined by the insurance category that provided coverage for most of the dispenses in the first 180 days. Most of these insurance adjustments were when the first dispense was a different insurance category than the remaining fills.

Results

Demographics

A total of 3927 patients were eligible after exclusion of 2 patients less than 18 years of age. The study populations were similar across the 2 medications ($P < .001$). Most of the patients (76%) were 65 years old or greater and 61% of total IPF patients were male.

The nintedanib population had 2605 patients in the 2-year study period. These patients consisted of 60% men (n = 1573) and 40% women (n = 1032), with 76% (n = 1978) over the age of 65. Insurance coverage of medication dispenses in 2015 and 2016 included 66% (n = 1797) patients with government coverage, 34% (n = 929) with commercial coverage, and n = 20 paid cash at some point in time.

The pirfenidone population had 1322 patients in the 2-year study period. These patients consisted of 63% men (n = 834) and 37% women (n = 488), and 77% (n = 1024) were over the age of 65. Insurance coverage of medication dispenses in 2015 and 2016 included 73% (n = 1028) patients with government coverage and 27% (n = 381) with commercial coverage, and n = 16 paid cash at some point in time. Patient counts do not reflect unique patients per drug group due to patient switches between drugs and between health insurances (Table 1).

Adverse events

Of the nintedanib population completing clinical assessment surveys in 2016 (n = 1343), 46% of respondents (n = 612) reported no adverse events at each completed assessment, with the remaining 54% reporting at least 1 adverse event. Of the reported adverse events (n = 2644), 53% (n = 1394) were diarrhea, 16% (n = 420) were nausea/vomiting, 5% (n = 144) were

Table 1. Demographics.

	NINTEDANIB	PIRFENIDONE	TOTAL	*P*-VALUE
Study sample size	2605	1322	3927	
Sex				<.0007
Male	1573 (60%)	834 (63%)	2407 (61%)	
Female	1032 (40%)	488 (37%)	1520 (39%)	
Within drug *P*-value	$P < .0001$	$P < .36$		
Age group				<.0001
<65	627 (24%)	298 (23%)	925 (24%)	
⩾65	1978 (76%)	1024 (77%)	3002 (76%)	
Within drug *P*-value	$P < .0003$	$P < .15$		

abdominal pain, and 9% (n = 240) were "other." Diarrhea is a known side effect of nintedanib and was reported by 38% (n = 509) of assessed patients, compared with 62% of patients in clinical trials.[8]

Of the 2016 surveyed pirfenidone population (n = 764), 58% of respondents (n = 445) reported no adverse events at each completed assessment, with the remaining 42% reporting at least 1 adverse event. Of the reported adverse events (n = 978), 17% (n = 166) were nausea/vomiting, 16% (n = 154) were diarrhea, 10% (n = 98) were fatigue, 9% (n = 86) were decreased appetite, 6% (n = 62) were dyspepsia, 6% (n = 59) were rash, 5% (n = 49) were headache, and 10% (n = 97) were "other." Remaining adverse events were all below 5% frequency (Table 2).

Financial burden

Average final monthly copay for the nintedanib group was $235 (SD = $551) with a range between $0 and $8104. Mean primary monthly insurance copay was $496 (SD = $656) in the government group and $384 (SD = $1351) in the commercial group, and reduced to an average final copay of $318 (SD = $567) and $71 (SD = $464), respectively, after application of secondary coverage.

Average final monthly copay for the pirfenidone group was $339 (SD = $586) with a range between $0 and $4449. Primary monthly insurance copay was $673 (SD = $721) in the government group and $358 (SD = $956) in the commercial group, and reduced to an average final copay of $431 (SD = $630) and $88 (SD = $330), respectively, after application of secondary coverage (Table 3).

Discontinuations

A decrease in patient discontinuation frequency was observed in both groups from 2015 to 2016. Discontinuation rates among the nintedanib group decreased from 50.8% in 2015 to 40.1% in 2016 with the average duration of treatment 94.0 days (SD = 67.2) in 2015 and 84.5 days (SD = 60.1) in 2016 prior to discontinuation. Discontinuation rates among the pirfenidone group decreased from 43.7% in 2015 to 39.8% in 2016 with the average duration of treatment being 80.0 days (SD = 58.3) in 2015 and 71.7 days (SD = 57.4) in 2016 prior to discontinuation (Table 4).

Adherence

For the full sample, PDC in the nintedanib group was 84.2% (SD = 17.0), and 71.3% of patients were adherent with a PDC ⩾ 80%. PDC in the pirfenidone group was 83.4% (SD = 17.3) with 70.0% of patients having a PDC greater than 80%.

Models of mean PDC and adherent patients for nintedanib. For the model of mean PDC, 356 patients were included to examine the association between the outcome mean PDC and patient demographics (age, sex, and census region), pharmacy primary and secondary insurance types, and average final patient copay over revenue. For this model, there was a mean PDC of 84.9% ($F = 4.53$; $P < .0001$; $R^2 = 0.09$). Of the included variables, sex ($P < .004$) and secondary insurance type ($P < .01$) were significant for predicting adherence. Specifically, men had a higher PDC (87.9%) compared with women (82.6%), and post hoc comparisons indicated charitable organization coverage had higher adherence than no secondary coverage (charitable organization coverage mean PDC = 90.7; commercial insurance coverage mean PDC = 81.7; no secondary coverage mean PDC = 83.4).

Results of the logistic model indicated that 73.9% of patients were adherent with PDC ⩾ 80% (n = 356) over the 180-day observation period from first fill. As with the prior model, variables were fixed in the following order—standardized copay

Table 2. Adverse events reported for 2016.

	NINTEDANIB (N = 1343)		PIRFENIDONE (N = 764)	
	PATIENTS[a]	REPORTED EVENTS	PATIENTS	REPORTED EVENTS
Abdominal pain	86	144	19	32
Bruising/bleeding	11	18	1	1
Constipation	20	27	10	13
Cough	17	23	10	13
Decreased appetite	58	87	52	86
Diarrhea	509	1394	77	154
Dizziness	13	18	19	25
Dyspepsia	22	25	41	62
Fatigue	37	53	60	98
Headache	42	59	30	49
Insomnia	4	5	12	16
Joint pain	3	3	2	5
Nausea/vomiting	198	420	78	166
Oxygen	10	10	8	8
Photosensitivity	5	7	23	45
Rash	17	31	33	59
Upper respiratory tract infection	9	10	4	13
Weight loss	44	70	16	36
Other	162	240	64	97
None	1281[b]	5920	724[c]	3734

aPatients may have completed multiple assessments and may have reported more than 1 adverse event.
b612 patients reported "none" per assessment completed.
c456 patients reported "none" per assessment completed.

ratio, sex, age, sex-by-age interaction, census region, primary insurance category, and secondary insurance category, followed by the interaction between the copay ratio and secondary insurance categories, and producing a significant model ($R^2 = 0.13$; $\chi^2 = 32.5$, $P < .001$). As with the linear model results, both sex ($P < .02$) and secondary insurance type ($P < .01$) were significant on predicting adherence for those with day's supply above 90. Women were about half as likely to be adherent as men (odds ratio [OR] = 0.53, 95% confidence interval [CI]: [0.27, 0.89]) and those with secondary insurance provided through charitable organizations were nearly 3 times more adherent than those with no secondary insurance (OR = 2.92, 95% CI: [1.46, 5.84]). Mean adherence rates were 69.5% for women compared with 81.2% for men. Mean adherence rates of those with charitable organization coverage were greater (mean PDC = 85.9%) compared with commercial payers (mean PDC = 70.7%) or no secondary coverage (mean PDC = 67.7%). Age was marginally significant ($P < .06$) with those younger than 65 (mean PDC = 81.3%) being more adherent than those older than 65 (mean PDC = 69.4%).

Models of mean PDC and adherent patients for pirfenidone. For the model of mean PDC, 177 patients were included to examine the association between the outcome mean PDC and patient demographics (age, sex, and census region), pharmacy primary and secondary insurance types, and average final patient copay over revenue. For this significant model, there was a mean PDC of 83.4% ($F = 2.43$, $P < .002$; $R^2 = 0.10$). Only secondary insurance type was significant ($P < .02$) of the examined variables. Specifically, post hoc comparisons indicated that the secondary insurance provided by charitable organization coverage had a significantly higher ($P < .02$) adherence (mean PDC = 89.3%) than no secondary coverage (mean PDC = 81.0%), with commercial coverage mean adherence at 71.7%.

Table 3. Financial and adherence data from 2015 to 2016.

NINTEDANIB	PRIMARY INSURANCE COPAY			FINAL PATIENT COPAY	
	PATIENT COUNT[a]	MEAN ($)	RANGE ($)	MEAN ($)	RANGE ($)
Insurance coverage	2726	454	0-11 236	235	0-8104
Government	1797	496	0-3886	318	0-3254
No secondary insurance	905	231	0-3254	231	0-3254
Government	29	529	0-2942	122	0-1359
PAP—charitable organizations	1062	755	0-3886	459	0-3182
Commercial	929	384	0-10 433	71	0-8104
No secondary insurance	558	84	0-8104	84	0-8104
Commercial	477	678	0-11 236	75	0-6660
PAP—charitable organizations	257	490	0-8813	2	0-50
PAP—manufacturer copay cards	27	545	25-2792	103	0-2302
Cash	20	10 368[b]	N/A	10 368[b]	N/A
PIRFENIDONE	**PRIMARY INSURANCE COPAY**			**FINAL PATIENT COPAY**	
	PATIENT COUNT[a]	MEAN ($)	RANGE ($)	MEAN ($)	RANGE ($)
Insurance coverage	1409	581	0-6864	339	0-4449
Government	1028	673	0-4544	431	0-2891
No secondary insurance	499	279	0-2901	279	0-2891
Government	8	478	5-1167	246	0-1167
PAP—charitable organizations	680	923	0-6814	564	0-2822
Commercial	381	358	0-6864	88	0-4450
No secondary insurance	274	70	0-6758	70	0-2359
Commercial	170	742	0-6864	242	0-4449
PAP—charitable organizations	34	585	24-2937	203	0-2906
PAP—manufacturer copay cards	57	929	30-7800	2	0-5
Cash	16	9828[b]	N/A	9828[b]	N/A

PAP, Patient Assistance Program.
aPatient counts do not reflect unique patients per drug group due to patient switches between drugs and between health insurances.
bAverage wholesale price for 2016 reported (Micromedex© REDBOOK).

There were more patients adherent with PDC ⩾ 80% (n = 122) than non-adherent (n = 55) over the 180-day observation period from first fill. Model variables were fixed in the following order: mean adherence, standardized copay ratio, sex, age, sex-by-age interaction, census region, primary insurance category, and secondary insurance category, followed by the interaction between the copay ratio and secondary insurance categories, producing a significant model ($R^2 = 0.16$; $\chi^2 = 21.3$, $P < .02$). Specifically, the secondary insurance type was significant on predicting adherence with those with secondary coverage provided by charitable organizations as the most adherent (mean PDC = 88.3%) compared with commercial payers (mean PDC = 66.8%) or no secondary coverage (mean PDC = 39.2%). The post hoc comparison between these payer types indicated that the secondary coverage provided by charitable organizations was significantly higher compared with those with no coverage (OR = 3.76, 95% CI: [1.56, 8.99]).

Discussion

Patient populations of those using nintedanib and pirfenidone were similar between the 2 medications, with comparable distributions of age and sex. Both medications produced adverse events as expected in the literature of clinical studies.[9,10] The most commonly reported adverse events in the nintedanib

Table 4. Discontinuations in 2015 and 2016.

	2015		2016	
	NINTEDANIB	PIRFENIDONE	NINTEDANIB	PIRFENIDONE
Total patient discontinuations (%)	773 (50.8)	270 (43.7)	291 (40.1)	178 (39.8)
Average duration of treatment (SD)	94.0 (67.2)	80.0 (58.3)	84.5 (60.1)	71.7 (57.4)

group included diarrhea (54%), nausea/vomiting (16%), and abdominal pain (5%). The pirfenidone group also exhibited a variety of gastrointestinal-symptom-related adverse events including nausea/vomiting (17%), diarrhea (16%), fatigue (10%), loss of appetite (9%), and dyspepsia (6%). Patient-reported adverse events may also play a clinically significant role in influencing medication utilization where gastrointestinal-symptom-related events have the potential to interfere with 2 and 3 times daily dosing of medication. In the nintedanib group, the high prevalence of diarrhea may be an influencing factor on adherence. To offset its effects, the manufacturer provides loperamide and patient education materials in its welcome kits. FDA-approved pirfenidone dosing includes a 2-week titration up to the full maintenance dose intended to reduce gastrointestinal symptoms; however, the full maintenance dose of 3 tablets 3 times per day has potential for pill burden that might affect patient compliance.

Most of the patients (73%) had government insurance coverage, as would be expected with a population predominantly (76%) greater than 65 years of age and therefore eligible for Medicare. Patients in the commercial coverage groups of nintedanib and pirfenidone showed lower monthly copay averages ($88 and $71, respectively) when compared with the government coverage group ($318 and $431, respectively), potentially due to the secondary commercial coverage in the form of manufacturer copay cards available to non-government-sponsored insurance holders. Adherence, however, was not associated with the lower final copay values, and this variable was not significant in the adherence models. According to the adherence models used for both medications, patients were likely to have significantly higher adherence based on payer type. Specifically, there was a significant association for patients using charitable organization secondary coverage having greater adherence than those using commercial coverage. In the nintedanib group, the sex variable was also significant in predicting adherence, with men (mean PDC = 87.9%) displaying significantly higher ($P < .02$) PDC than women (mean PDC = 82.6%).

Overall mean adherence was similar in both medication groups, with a PDC of 84.2% in the nintedanib group and 83.4% in the pirfenidone group. Both populations contained most of the adherent patients, with 70.0% of patients exhibiting greater than 80% PDC in the nintedanib group and 71.3% of patients with greater than 80% PDC in the pirfenidone group. Lower adherence rates in this IPF population may be due to a variety of factors including side effect intolerance, complexity of dosing regimen, and unpredictable disease progression leading to hospitalizations.[4]

Discontinuation rates decreased across the study period in both groups. Possibly, pulmonary specialists became more familiar with the proper utilization of these new-to-market medications over the duration of 2015 which may have changed medication prescribing or management that stabilized patient utilization over 2016. Alternatively, the enhanced clinical program that is launched in January of 2016 and offered standardized adverse event education and management may have supported a decreased discontinuation rate throughout 2016.

Limitations

Limitations of this study include that clinical assessment data were not available prior to 2016, when a new data collection program was implemented. In addition, this study used voluntary self-reported data. Furthermore, because patients were not matched across voluntary responses such as adverse events and discontinuation reasons, correlations were not made directly in the statistical analysis. Therefore, we are unable to differentiate discontinuations due to insurance changes or medication tolerability, and an 89-day cutoff was used for PDC calculation inclusion to eliminate patients who may have switched pharmacies in this period. Finally, all data were derived from 1 national pharmacy and may not be representative of the entire IPF population.

Conclusions

Outcomes in the studied IPF population were similar for nintedanib and pirfenidone. Adherence was significantly influenced in favor by secondary insurance coverage type, specifically in the form of charitable organization coverage, which may have eased financial burden to some capacity. In both medication populations, adherence was significantly higher in those patients with secondary charitable coverage than those with secondary commercial coverage or no secondary coverage at all. Copay value, on the other hand, did not show a significant association for adherence. The nintedanib population adherence was also significantly impacted by sex, with women about half as likely to be adherent as men.

Real-world self-reported adverse events in both groups were proportionally reflective of clinical trial results, albeit at lower rates. Occurrence of gastrointestinal-symptom-related adverse events in both medications supports manufacturer-recommended

dosing and titrations for these medications. Patient education regarding proper side effect management will remain pertinent in promoting patient adherence and influencing outcomes. Continued utilization of nintedanib and pirfenidone in the IPF population will help further establish the place in therapy for these medications, as well as impact patient outcomes through developed prescribing patterns and adverse event management.

Acknowledgements

At the time of the study, all authors currently affiliated with AllianceRx Walgreens Prime were employees of Walgreens Specialty Pharmacy.

Author Contributions

AYI, PHK, and RTM conceived the project, designed the analysis, and collected the data. FS contributed analysis tools and performed the data analysis. MR provided clinical and research support. All authors discussed the results and contributed to the final manuscript.

REFERENCES

1. Raghu G, Collard HR, Egan JJ, et al. 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.
2. Idiopathic Pulmonary Fibrosis. National Organization for Rare Disorders (NORD) web site. https://rarediseases.org/rare-diseases/idiopathic-pulmonary-fibrosis/. Accessed January 23, 2017.
3. Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. *Clin Epidemiol*. 2013;5:483-492. doi:10.2147/CLEP.S54815.
4. Insight In IPF Web site. About IPF. https://www.insightsinipf.com/science-of-ipf/. Accessed January 23, 2017.
5. Puglisi S, Torrisi SE, Vindigni V, et al. New perspectives on management of idiopathic pulmonary fibrosis. *Ther Adv Chronic Dis*. 2016;7:108-120.
6. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. *N Engl J Med*. 2001;345:517-525. doi:10.1056/NEJMra003200.
7. National Institutes of Health. What is idiopathic pulmonary fibrosis. http://www.nhlbi.nih.gov/health/health-topics/topics/idiopathic-pulmonary-fibrosis. Accessed September 20, 2016.
8. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192:e3-e19.
9. DailyMed. Ofev nintedanib capsule. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=da1c9f37-779e-4682-816f-93d0faa4cfc9. Accessed January 23, 2017.
10. DailyMed. Esbriet pirfenidone capsule. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0ab861c2-d5ca-4f92-854c-6477971a1b38. Accessed January 23, 2017.