Idiopathic Pulmonary Fibrosis (IPF) Drugs
Pulmonary-1 Drug Class: Pulmonary Miscellaneous Subclass

Executive Summary

- **For the MTF Formulary Management Document with the formulary recommendation from the May 2017 P&T Committee meeting, see http://www.health.mil/DoDPTResources.**
- IPF is a difficult-to-diagnose disease that has limited therapeutic options. Two recently approved IPF agents provide the first pharmacotherapeutic advances for this disease. Nintedanib (Ofev) and Pirfenidone (Esbriet) work by different mechanisms of action, and each come with unique safety risks.
- The mechanism of action in each agent is not fully understood, but for patients who are able to tolerate adverse effects, and for an as-yet unpredictable cohort of IPF sufferers, these two drugs may provide a delay in disease progression. Unfortunately, no matter the agent selected, the decline will continue for most patients.
- While neither agent is curative, their simultaneous FDA approval in 2014 was based on the potential for nintedanib and pirfenidone to reduce the rate of the inexorable decline in lung function in IPF.
- Guidelines place value in these therapies for the potential decline in disease progression, and the opportunity these agents provide patients and providers to bridge to future pharmaceutical advances as well as potentially curative therapies that are available today, such as lung transplantation.
- Meta-analyses suggest that pirfenidone and nintedanib effectively slow the decline in FVC over 52 weeks; overall, based on the available data, there is no difference between the two. Noted differences in adverse events include photosensitivity and rash with pirfenidone, but more significant GI issues and reduced tablet burden with nintedanib.
- Although the efficacy is underwhelming from a pure statistical viewpoint, nintedanib and pirfenidone are the first therapies to show any benefit for endpoints, such as lung capacity, in a disease with limited options. Additionally, data that has come to light since initial FDA approval show potential for benefit in endpoints beyond lung function, such as hospital exacerbations and survival benefit.

Background

- Prior authorization criteria were recommended at the August 2015 DoD P&T Committee meeting (implemented in February 2017) for both agents to ensure appropriate patient selection, avoidance of active tobacco use, consultation with relevant specialist, and avoidance of combining the agents. Renewal PA criteria are in place to ensure continued benefit from the selected agent.
- IPF is a rare, chronic, progressive, interstitial lung disease of unknown etiology that affects approximately 150,000 patients in the United States, with an additional 50,000 diagnosed annually. Demographically, males predominate and diagnosis occurs between the fifth and seventh decade of life. Progression of the disease is variable among individuals, ranging from a rapid decline to a steady decrement in lung function that can last several years. Progressive fibrosis ultimately leads to death with a median survival of 3 to 5 years after diagnosis. Approximately 40,000 patients diagnosed with IPF succumb to the disease per year.
- Presenting signs and symptoms typically include dyspnea, and non-productive cough. Patients often report feeling tired and have a gradual unintended weight loss. Physical signs include clubbing of the fingers and toes.
- The diagnosis requires a high index of clinical suspicion. Often clinical symptoms predate confirmatory lung function testing and x-ray findings; a unique pattern on high resolution CT scan is a characteristic of IPF. When the diagnosis is not clear, pathology from lung tissue biopsy may be necessary. Multidisciplinary teams of respiratory physicians, radiologists, and interstitial lung disease specialist nurses are involved in managing these patients.
- Treatment options are intended to reduce symptoms and signs, improve quality of life, slow disease progression, and increase survival. Lung transplantation is the only currently available therapy that significantly changes trajectory of the disease. Until nintedanib and pirfenidone were approved, there were no FDA recommended or approved therapies specifically targeting IPF. Therapies that had been considered the standard of care in the past, such as corticosteroids, N-acetylcysteine or triple therapy (prednisone, azathioprine, and N-acetylcysteine), were harmful when studied in clinical trials. Newer therapies, such as ambrisentan and imatinib, have also failed to show benefit and are not recommended in latest guidelines.
- Drug development has been limited by factors to include the small number of patients with the disease, diverse disease phenotypes, and several unanswered questions such as how disease should be measured, ability of a clinical trial to capture symptom progression, and relevant biomarkers.

- Therapeutic options can currently include pulmonary rehabilitation, corticosteroids, immunosuppressants, n-acetylcysteine, and acid reflux therapy. Discussion of these other treatment options will not be included in this review. Additionally, patients can potentially benefit from oxygen therapy, surgery, and lifestyle changes such as smoking cessation.
- Table 1 includes the drugs in the class and dosing information.

Table 1. Drugs in the Class

Pulmonary-1 Drug Class: Miscellaneous Pulmonary Subclass – IPF Drugs		
Generic	**pirfenidone**	**nintedanib**
Brand	**Esbriet**	**Ofev**
Manufacturer	Genentech/Roche	Boehringer Ingelheim
Approval Mo/Yr	15 Oct 2014	
Formulation	267 mg caps and tabs; 801 mg tablets	100 and 150 mg caps
Dose/Frequency	801 mg PO TID, dose reduce by 267 mg PRN	150 mg PO BID, dose reduction to 100 mg PRN
Indication	Treatment of idiopathic pulmonary fibrosis	

Clinical Practice Guidelines

- The American Thoracic Society (ATS), through a cooperative assessment with several other international organizations, provides guidance on the diagnosis and treatment of IPF. Requirements for diagnosis of IPF include exclusion of other known causes of interstitial lung disease, presence of a pattern of usual interstitial pneumonia on high resolution CT (HRCT), and/or a specific combination of HRCT findings and lung biopsy findings.
- The ATS statement from 2015 advises that accuracy of the diagnosis is improved when the decision is made collaboratively between pulmonary specialists, radiologists, and pathologists. The group also identifies the fact that this may contribute to difficulties in research studies, as some trials are based on individual providers diagnosing IPF, while other studies rely on a centrally read imaging.
- The statement from the ATS acknowledges the difficulties faced with diagnosing IPF, and the incremental benefit IPF therapies have typically provided. The group identifies endpoints for assessing the disease and highlights vital capacity (VC) as one of the factors that can be used to assess response to therapy. A favorable response can be defined as a >10% increase in VC over 3-6 months. A stable response is within a 10% change, positively or negatively from baseline, in VC over 3-6 months. A >10% decrease in VC over that same time period is identified as a failure to respond.
- Secondary endpoints used to assess efficacy include 6-minute walk time distance, acute exacerbation events, lung transplantation, respiratory related hospitalizations, progression-free survival, and death. These are often limited by issues such as whether the acute exacerbation is specifically related to IPF. Similarly, these patients have comorbidities and may be impacted by other disease states, some of which may have overlapping complications from a pulmonary perspective. IPF-specific exacerbations are of special interest, as they may be complicated by significant mortality, approaching 50% at 30 days post event, as well as large reductions in lung function.
- Many trials will assess change in forced vital capacity (FVC), typically centering around 10%, and change in carbon monoxide diffusing capacity (DLCO). Clinical practice will similarly monitor these two parameters over time to determine progression of the disease.
- The ATS statement does not specifically recommend any one treatment as superior. While there is no guidance on sequential therapies, both nintedanib and pirfenidone are conditionally recommended. The ATS statement identifies conditional recommendations as recognizing that different choices will be appropriate for individual patients and providers should help each patient arrive at a management decision consistent with his or her values and preferences. Providers should explicitly interpret that although drug therapy may slow rate of loss of lung function, this may also not necessarily make an individual patient feel better.
- Other groups, such as the NICE UK, identify selected patients (those with FVC of 50-80%, as was studied in pivotal trials) as possibly having a modest but measurable effect on slowing decline in lung function.

Efficacy

- Available meta-analyses suggest that pirfenidone and nintedanib effectively slow the decline in FVC over 52 weeks and that overall, based on the available data, there is no difference between the two. For secondary endpoints, nintedanib showed no effect on progression-free survival or 6-minute walk time distance. Acute exacerbations were defined differently in the studies with nintedanib compared to pirfenidone and were not included in the meta-analyses. Both agents are typically identified as effective for the indication for which they have been approved.
- The meta-analyses included the studies used to gain FDA approval. There have been no head-to-head studies and the two drugs have been only been compared versus placebo.
- For the clinical trials with pirfenidone and nintedanib, the study designs include differences in length of time analyzed, diagnosis inclusion criteria (FVC, FEV/FVC, DLCO) and endpoint definitions (acute exacerbations). The trials all had similar age groups studied, gender breakdowns, and race characteristics.
- Nintedanib had 3 studies that included 1,231 patients. One study was a dose range finding study, and the other two were phase 3 studies. For pirfenidone, the initial trials were two phase 3 studies. The FDA required a third study as one of the initial studies, PIPF-006, but there were mixed results. The three pirfenidone studies comprised 779 patients. See Table 2 for a summary of the clinical trials with nintedanib and pirfenidone.
- The FDA found that nintedanib had convincing benefit in FVC, supported by numerical trends in favor of mortality, and other secondary efficacy measures. Pirfenidone was found to have benefit in FVC for two of three studies, and numerical trends in favor of mortality, and other secondary efficacy measures.
- The efficacy of both agents at lower doses than recommended in the package inserts is even further limited. This is an important finding as many patients require dose modification through reductions or discontinuations due to adverse events.

Table 2: Clinical Trial Summary for the IPF Drugs

Drug	Study	Tx vs PBO (n)	FVC % or mL Δ from BL to Endpoint (absolute difference)	P value
pirfenidone (Esbriet)	ASCEND	278 vs 277	-3.7% vs -6.6% (2.9)	p<0.01
	PIPF-004*	174 vs 174	-8.0% vs -12.4% (4.4)	p=0.01
	PIPF-006*	171 vs 173	-9.0% vs -9.6% (0.6)	p=0.501
nintedanib (Ofev)	TOMORROW	86 vs 85	-60 vs -191 (131 mL)	p=0.014
	INPULSIS 1	309 vs 204	-115 vs -240 (125 ml)	p <0.001
	INPULSIS 2	329 vs 219	-114 vs -207 (94 ml)	p <0.001

*PIPF 004, 006 are 72-week trials; other trials are 52 weeks

Safety

- In regards to safety, common adverse events were similar between the pirfenidone and nintedanib, despite the different mechanisms of action. Pirfenidone has a longer safety exposure for a subset of patients, approaching 5 years or more. Development of nintedanib was started later, but overall has nearly the same number of patients exposed as pirfenidone.
- Warnings and precautions for nintedanib include hepatic impairment, elevated liver enzymes, gastrointestinal disorders, embryo-fetal toxicity, arterial thromboembolic events, bleeding events, and GI perforation. For pirfenidone, elevated liver enzymes, photosensitivity/rash, and GI disorders are of concern.
- Common adverse effects for nintedanib center on GI issues such as diarrhea, nausea, vomiting, and abdominal pain. Pirfenidone similarly often has issues with nausea, but uniquely has a photosensitivity/rash issue that can occur more frequently.
- Both agents have significant discontinuation rates, pirfenidone at 14.6% versus 9.6% (placebo) and nintedanib at 21% versus 15% (placebo). Dosage reductions also occur significantly often from gastrointestinal issues.

- Both have unique drug-drug interactions: nintedanib being affected by CYP450 3A4, 5, and 7, while pirfenidone is affected by CYP1A2.

Other Factors

- Significant differences between pirfenidone and nintedanib include dosing frequency and capsule burden. Nintedanib is dosed 150 mg twice daily. Currently pirfenidone, once maximum dose is reached, is given as three capsules three times daily. A pirfenidone dosage formulation of 801 mg tablets was recently approved, that will allow for dosing three times daily with one tablet. See Table 3 for a comparison of both products.

Table 3. Clinical Comparisons of IPF Drugs

Factor	Nintedanib (Ofev)	Pirfenidone (Esbriet)
Dosing	• 150 mg BID given approximately 12 hours apart • Take with food • Dose modifications are recommended for adverse events	• 801 mg (three 267-mg capsules/tabs or one 801 tablet) TID with food for a total of 2,403 mg/day • Administer doses at the same time daily • Titrate to the full dosage of nine capsules per day over a 14-day period
Storage	Store at 77F; permitted range of 59-86F	
Dose skip	Next dose administered at scheduled time	
Baseline Labs	Conduct liver function test & pregnancy test	Liver function test
Pregnancy Category	D	C
Lactation	Pirfenidone: Unknown if excreted in breast milk	
Pediatrics	None established	
Geriatrics	Overall, no differences in safety between younger and older subjects	
Clinical Trial Composition	>65 yo: 60.8%; >75 yo: 16.3%	>65 yo: 67%; >75 yo: 22%
Smokers	↓'d exposure which may alter efficacy; instruct pts to stop smoking prior to start & avoid when using	
Hepatic	Child Pugh Class A: 100 mg dose, Avoid in B/C	Caution in Child Pugh A/B; Avoid in C
Renal	Mild-mod impairment no Δ; avoid severe	Caution in mild to severe renal impairment

Conclusion

- Nintedanib and pirfenidone provide new mechanisms of action via an oral route to affect an endpoint that consensus guidelines consider useful for patients with mild to moderate severity confirmed IPF disease.
- Available data suggest these two drugs have similar efficacy when compared with placebo, providing a modest reduction in the expected decline that contributes to the rapid demise of the vast majority of IPF patients.
- Studies have mainly focused on patients with mild to moderate disease and are likely a subset of patients that may benefit from these agents. IPF patients have limited options for this devastating disease, with options previously considered standard of care being discarded as additional data has failed to support their use.
- There is no evidence to support switching among the agents, and there is no data from a clinical perspective to definitively aid in selecting patients for one agent over another.
- While pirfenidone and nintedanib appear safe over the short-term, there are significant numbers of patients who require dose reduction, temporary stoppage, or complete discontinuations.

References

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Abbreviations

The following abbreviations are used in this review:

ATS	American Thoracic Society
BL	baseline
FVC	forced vital capacity
GI	gastrointestinal
IPF	idiopathic pulmonary fibrosis
VC	vital capacity