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Drug Class Update: Interstitial Lung Disease (formerly Idiopathic Pulmonary Fibrosis)

Date of Review: June 2020

Date of Last Review: July 2015
Dates of Literature Search: 1/1/2015 - 2/1/2020

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Nintedanib (OFEV) received approval from the U.S. Food and Drug Administration (FDA) to treat chronic fibrosing interstitial lung diseases with a progressive phenotype and slow the rate of decline in pulmonary function in patients with interstitial lung disease associated with systemic sclerosis or scleroderma.

Research Questions:
1. What are the differences in efficacy or effectiveness between drugs approved by the FDA to treat idiopathic pulmonary fibrosis (IPF)?
2. What are the differences in adverse events between drugs approved by the FDA to treat IPF?
3. Are there specific populations based on demographic characteristics in which drug treatments for interstitial lung diseases like idiopathic pulmonary fibrosis are associated with greater harm or reduced effectiveness?

Conclusions:
- Four new high-quality systematic reviews and one high-quality clinical practice guideline were identified. Populations studied in patients with IPF were primarily limited to mild-to-moderate disease from the original Phase 3 clinical trials for nintedanib and pirfenidone, but also included several older pharmacological interventions used to manage IPF. Lastly, the new indication for nintedanib was reviewed.
- Few treatments studied in IPF have shown any effect on surrogate outcomes which can be linked through evidence to clinically meaningful outcomes such as mortality.[1]
- There is insufficient evidence to support any intervention for symptom management in IPF.[1]
- There is moderate quality evidence that pirfenidone and nintedanib are effective at improving some measures of lung function (e.g., absolute change in forced vital capacity [FVC]);[1,2] however, quality of evidence is low for more clinically meaningful outcomes (e.g., mortality, acute exacerbations, or dyspnea).[1] Several investigators of the identified systematic reviews expressed caution for broad recommendations for these drugs though one determined there is moderate quality evidence that pirfenidone reduced all-cause mortality, IPF-related mortality and improved progression-free survival.[3] Nintedanib was not evaluated in this systematic review.[3]

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- Another systematic review found insufficient evidence to support drugs specific for pulmonary hypertension in IPF patients.[4] Studies have included endothelin receptor antagonists (bosentan, ambrisentan, and macitentan) and sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor. Additionally, there is low quality evidence that adding a PDE5 inhibitor to nintedanib in patients with advanced IPF does not appear to provide significant benefit compared with nintedanib alone.[5]
- The American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society provided an update to their joint 2011 clinical practice guideline in 2015.[6] Strong recommendations were not made for any drug studied for treatment of IPF, although pirfenidone and nintedanib, which are currently the only approved drugs for IPF, received a conditional recommendation for use with moderate confidence in effect estimates.[6] This recommendation placed high value on potential benefit of nintedanib and pirfenidone on patient-important outcomes such as disease progression and lower value on potentially significant adverse effects and the expected cost of treatment.[6] No suggestions for or against combination regimens or sequential therapies were provided except for the recommendation against using prednisone in combination with azathioprine and N-acetylcysteine.[6]
- Nintedanib obtained an expanded indication by the FDA in September 2019 to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.[7] Nintedanib 150 mg twice daily was studied in a phase 3, 52-week, multi-centered, randomized, double-blind, placebo-controlled trial in 576 patients.[8] For the primary endpoint, the annual rate of change in FVC over a 52-week period was lower in the nintedanib group than in the placebo group (-52.4 mL/year vs. -93.3 mL/year; mean difference [MD], 41.0 mL/year; 95% Confidence Interval [CI], 2.9 to 79.0; p=0.04).[8] No statistically significant differences were found for the key secondary endpoints which included the patient's health-related quality of life (HRQoL), as assessed by the St. George's Respiratory Questionnaire (SGRQ), and their skin thickness, as assessed by the modified Rodnan skin score.[8] No differences in mortality were observed between the nintedanib and placebo groups through the entire trial period.[8] This study provides low quality evidence that nintedanib may slow disease progression with unknown impact on quality of life, skin thickness related to systemic sclerosis, and mortality.
- Nintedanib obtained an expanded indication by the FDA in March 2020 to treat chronic fibrosing interstitial lung diseases with a progressive fibrotic phenotype other than IPF.[7] Nintedanib 150 mg twice daily was studied in a phase 3, 52-week, multi-centered, randomized, double-blind, placebo-controlled trial in 663 patients.[9] The adjusted annual rate of decline in the FVC was −80.8 mL per year in the nintedanib group and −187.8 mL per year in the placebo group (between-group difference, 107.0 mL; 95% CI, 65.4 to 148.5; p<0.001).[9] No statistically significant differences were found for the secondary endpoints which included mortality, acute exacerbations, and overall health status as assessed by the self-administered King's Brief Interstitial Lung Disease questionnaire (K-BILD).[9] This study provides low quality evidence that nintedanib may slow disease progression with unknown impact on mortality and acute exacerbations.
- Warning labeling was updated for both nintedanib and pirfenidone regarding elevated liver enzymes based on case reports and post-marketing studies.[10] Regular monitoring of liver function tests is advised.[10]

Recommendations:

- Update clinical prior authorization (PA) criteria (see **Appendix 4**) to approve nintedanib for adults with interstitial lung disease associated with systemic sclerosis or patients with chronic fibrosing interstitial lung disease.
- No change in PDL status of drugs at this time.
- Broaden PDL class to cover drugs with approved indications for interstitial lung diseases, which includes idiopathic pulmonary fibrosis.

Summary of Prior Reviews and Current Policy

- Nintedanib and pirfenidone were evaluated in patients with mild-to-moderate IPF in placebo-controlled trials and were not compared with each other.[11,12] There is insufficient evidence to determine relative efficacy and safety between the two drugs.
- The placebo-controlled trials did not provide sufficient evidence to determine whether nintedanib had positive effect on mortality, but there was low quality evidence to suggest pirfenidone may decrease mortality in mild-to-moderate IPF patients when data were pooled across studies.[11,12] The data were not statistically significant, but there was a consistent trend toward improved mortality which was associated with slower decline in FVC.[12]
- Phase 3 placebo-controlled trials provided moderate quality evidence that both nintedanib and pirfenidone slow disease progression by reducing decline in FVC.[11,12] Endpoints studied included annual rate of decline in FVC, percent-predicted FVC from baseline and the dichotomous endpoint of absolute FVC decline of 10% or greater.[11,12]
- The nintedanib trials provided low quality evidence that nintedanib may improve quality of life, but the clinical relevance of the results were unclear.[11] The effect of nintedanib on acute exacerbations was inconsistent.[11]
- The pirfenidone trials provided low quality evidence that pirfenidone may slow decline in the 6-minute walk distance test, but the clinical relevance of this result was unclear.[12] Pirfenidone did not appear to improve dyspnea.[12]
- The primary adverse effects from both drugs were diarrhea, nausea, vomiting and abdominal pain.[11,12] Diarrhea was the most common adverse event leading to study discontinuation for nintedanib.[11] Both drugs were also associated with elevated liver enzymes (AST/ALT) which may require dose reduction or interruption in therapy.[11,12] Close monitoring of liver enzymes was advised by the FDA.[11,12]
- Based on this evidence, clinical prior authorization criteria were developed for both drugs that require a diagnosis of IPF; treatment prescribed by a pulmonologist; and an FVC greater than 50%. Concomitant use was prohibited. Renewal of treatment required evidence that IPF had not progressed too rapidly on therapy (defined as a 10% or greater decline in the percent predicted FVC in the previous 12 months).

Background:

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause occurring in adults predominantly over the age of 50 years.[6,13] The definition of IPF requires the exclusion of other forms of interstitial pneumonia and interstitial lung disease associated with environmental exposure, medication or systemic disease.[14] The prevalence of IPF is estimated between 14 and 27.9 cases per 100,000 persons.[13] Evidence shows that the number of people with IPF is increasing, although the reasons for this are unclear.[1]

IPF is associated with a poor prognosis; median survival is 2 to 3 years after diagnosis.[13] No cure for IPF has been identified. It is unknown if geographic, ethnic, cultural or racial factors play a role in IPF, but several potential risk factors have been identified: 1) environmental factors like smoking history of more than 20 packs per year, exposure to silicon, brass, steel, lead and wood dust, and farming or agricultural work; 2) genetic factors such as familial pulmonary fibrosis, mutations in genes that maintain the length of telomeres, mutations in the surfactant protein C gene and mutations in the mucin 5B promoter region; 3) gastro-esophageal reflux disorder; 4) viral infections, although the role in IPF is not clear; and 5) autoimmunity.[13,14] Diagnosis, evaluation and treatment of IPF requires a multidisciplinary approach, including general practice physicians, pulmonologists, radiologists and pathologists.[13]

The primary symptoms of IPF are unexplained chronic exertional dyspnea and a cough, which can have a considerable impact on day-to-day life.[1,14] IPF was once thought to progress at a steady, predictable rate, but it is now known that this is often not the case.[1] Many people with IPF deteriorate rapidly, while others may have periods of relative stability.[1] IPF is a difficult condition to manage, particularly in the later stages.[1]

Treatments aim to reduce symptoms and improve survival.[1] N-acetylcysteine (NAC) combined with prednisone and azathioprine was the treatment-of-choice for several years until a study found the triple therapy combination resulted in higher mortality and hospital admissions compared to placebo or NAC alone.[15] Two antifibrotic agents, nintedanib and pirfenidone, are the only two drugs with confirmed efficacy in slowing functional decline and disease progression in IPF patients. Both drugs received approval from the FDA in 2014 for the treatment of IPF. Although pirfenidone and nintedanib have both demonstrated efficacy in reducing rates of disease progression compared with placebo, these drugs do not cure IPF and patients continue to experience lung function decline while on treatment.[16-18] The long-term safety and tolerability of nintedanib and pirfenidone have been evaluated in open-label follow-up studies.[19,20] The safety profiles for both drugs included gastrointestinal adverse events, which are consistent with the known safety profile of the drugs from the phase 3 trials [16-18], and no new safety signals were observed.[19,20] Combined treatment with pirfenidone and nintedanib has been studied for safety and tolerability, but efficacy has not been established.[21,22] The frequency of common treatment-emergent adverse effects seen with either drug alone is higher when the two are combined, with mild to moderate nausea, vomiting and diarrhea being the most common.[21,22]

Non-pharmacologic treatment also plays a vital role in the management of patients with IPF.[13] Pulmonary rehabilitation in early stages of IPF has shown short-term improvement in walking distance, symptoms and quality of life.[13] Patients with resting hypoxemia should use long-term oxygen therapy based on chronic obstructive pulmonary disease and chronic respiratory failure studies.[13] Ultimately, lung transplantation is the most effective and reliable treatment for patients with IPF.[13] Lung transplantation 5-year survival ranges from 50-56% and 10-year survival rate is 30%.[13]

Clinically meaningful outcomes for IPF include mortality, morbidity [e.g., acute exacerbations or disease progression evaluated with surrogate endpoints of FVC or carbon monoxide diffusing capacity (DLCO)], symptom relief (e.g., dyspnea), functioning [e.g., 6-minute walking distance (6MWD) test], and quality of life. Validated instruments to assess clinically meaningful subjective outcomes and their minimum clinically important difference (MCID) are not clearly defined for IPF. An exception might be the SGRQ, a 50-item patient-administered questionnaire that assesses HRQoL in patients with respiratory disease.[23] The questionnaire is comprised of 3 domains: impact, symptoms and activity.[23] The symptoms domain addresses the frequency and severity of respiratory symptoms; the activity domain assesses activities that cause or are limited by breathlessness and the impact domain assesses a range of aspects around social functioning and the psychological impact of the disease.[23] Domain and total scores range from 0 to 100, with higher scores indicating worse HRQoL.[23] The suggested MCID for patients with IPF is a change of 4-5 points but this has not been validated in other interstitial lung diseases.[23]

Composite scoring systems have been developed utilizing physiological (e.g., FVC or DLCO) and radiographic variables in an attempt to provide more accurate prognostic information. However, this composite approach has not been tested in any prospective clinical trials to date and its clinical utility is unknown.[14] Although the 6MWD test is widely used in clinical practice, its prognostic value is limited due to lack of procedural standardization in patients with IPF. Some studies have suggested that desaturation (i.e., a decline in oxygen saturation to below 88%) during the 6MWD test is a marker for increased risk of mortality. Shorter walk distance and delayed heart-rate recovery after walk testing have been associated with an increased risk of subsequent mortality. However, it is unclear if desaturation, distance walked, and other variables measured during 6MWD test in this population are reproducible.[14]

Acute exacerbations are an especially relevant outcome that can be studied in clinic trials since 50% of patients admitted for an acute IPF exacerbation die during hospitalization.[13] Acute exacerbations are treated with high-dose corticosteroid therapy and broad-spectrum antibiotics despite the lack of conclusive evidence demonstrating their benefit.[13]

Utilization of pirfenidone and nintendanib is infrequent in the fee-for-service (FFS) population, with typically no more than one or two patients with claims each quarter.

Author: Gibler Date: June 2020

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

The Clinical Efficacy of Pulmonary Hypertension-Specific Agents in IPF (2020)[4]:
Pulmonary hypertension (PH) is common in patients with IPF and is associated with poor outcomes.[4] A systematic review with meta-analysis was performed to determine the clinical efficacy of PH-specific therapeutic agents for IPF patients.[4] The investigators used the following inclusion criteria: 1) published studies in peer-reviewed journals; 2) RCTs that compared pulmonary hypertension-specific agents with controls; 3) active interventions for one of the four PH-specific agent classes: endothelin receptor antagonists (ERAs), prostacyclin analogues, soluble guanylate cyclase stimulators, or PDE5 inhibitors; 4) patients diagnosed with IPF according to international guidelines; and 5) clinical outcomes and adverse events data available.[4] The primary outcome studied was all-cause mortality.[4] Risk of bias was assessed using the following criteria: sequence generation/ allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias.[4] Risk of bias was labeled as high, low, or unclear. A total of 43 eligible articles were selected, and of these, 10 studies reported at least one primary (all-cause mortality) or secondary outcome (lung function, quality of life, functioning, adverse events) that could be combined into a meta-analysis.[4] The number of patients in the trials ranged from 24 to 616. The active interventions were ERAs in 6 trials (bosentan in 4; ambrisentan in one; macitentan in one) and a PDE5 inhibitor in 4 trials (sildenafil in all).[4] One study included idiopathic nonspecific interstitial pneumonia as well as IPF, and another study included results from a combined therapy of nintedanib and sildenafil.[4] One trial was judged to be high risk of bias because it was non-blinded to participants, researchers and outcome assessment.[4]

Data regarding the effects of PH-specific agents on all-cause mortality in IPF patients were available in 8 trials.[4] All-cause mortality did not differ between the PH-specific agent group and the control group (placebo or no treatment) [hazard ratio (HR) 0.99; 95% CI, 0.92 to 1.06; p=0.71; moderate heterogeneity: I^2 =30%; p=0.19].[4] Even after excluding one outlier study based on sensitivity analysis, all-cause mortality did not differ between the groups, although the heterogeneity decreased (HR 0.99; 95% CI, 0.92 to 1.06; p=0.78; I^2 =0%).[4] Because the result for the primary outcome was not statistically significant, a subgroup analysis planned *a priori* was performed. When the analysis was restricted to patients treated with ERAs or PDE5 inhibitors, all-cause mortality did not differ between the groups (HR 1.09; 95% CI, 0.63 to 1.86; p=0.77; I^2 =56% for ERAs and HR 0.98; 95% CI, 0.92 to 1.06; p=0.67; I^2 =0% for the PDE5 inhibitor sildenafil).[4] All-cause mortality also did not differ based on sample size (≥200 vs. <200), age (≥65 y vs. <65 y), mean FVC (≥60% vs. <60%), or mean DLCO (≥30% vs. <30%).[4]

Seven trials reported data on changes in FVC and DLCO from baseline.[4] Change in FVC did not differ between the PH-specific agent group and the control group (MD 0.69% predicted; 95% CI, -0.36 to 1.74%; p=0.20; I^2 =0% for FVC % predicted, and MD 0.06 L; 95% CI -0.11 to 0.25 L; p=0.48; I^2 =0% for FVC L).[4] The decline in patient-predicted DLCO also did not differ in the PH-specific agent group and the control group (MD 0.81%; 95% CI, -0.24 to 1.87; p=0.13; I^2 =0%).[4] Mean change in DLCO also did not differ.[4] Three trials reported quality of life for IPF patients as measured by the St. George Respiratory Questionnaire (SGRQ) total score, a disease-specific instrument used in IPF.[4] Pooled estimates showed a statistically significant improvement in the SGRQ total score in the PH-treatment group compared to controls (MD -3.16 points; 95% CI, -5.34 to -0.97 points; p=0.005; I^2 =0%).[4] However, no differences between the 2 groups were found from 2 trials that reported the Borg dyspnea index score after walk test (MD 0.23 points; 95% CI, -1.21 to 1.68 points; p=0.75; I^2 =69%) or from 3 trials that reported change in the 6-minute walk distance test (MD -2.16 m; 95% CI, -8.00 to 3.68 m; p=0.47; I^2 =22%).[4] Serious adverse events were also similar between the study and control groups (RR 0.97; 95% CI, 0.82 to 1.15; p=0.74; I^2 =17%).[4]

The investigators concluded that this systematic review provides insufficient evidence to support PH-specific agents in IPF patients.[4]

<u>The Clinical Effectiveness and Cost-effectiveness of Treatments for IPF</u> (2015)[1]:

The Health Technology Assessment program, part of the National Institute for Health Research, produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the U.K. National Health Service (NHS).[1] The objective of this report was to evaluate the clinical effectiveness and cost-effectiveness of the different treatment strategies used within the NHS for IPF through systematic reviews of the evidence.[1] The report was funded by the National Institute for Health Research.[1] For the systematic review of clinical effectiveness, studies were eligible for inclusion if the patients had a confirmed diagnosis of IPF and the interventions under study were currently used to manage symptoms or modify IPF.[1] Randomized clinical trials were eligible for inclusion.[1] Where appropriate, the studies were combined in a meta-analysis and heterogeneity was assessed.[1] A network meta-analysis (NMA) focusing on pharmacological treatments for IPF which assessed FVC end points was undertaken on 10 studies.[1] The FVC end point was measured on two continuous scales, and the NMA used the standardized mean difference approach.[1] Systematic literature searches were undertaken to identify full economic evaluations of interventions to manage IPF, and to assess the HRQoL for people with IPF.[1] Studies reporting HRQoL in people with IPF were eligible for inclusion if they used either generic preference-based measures or the SGRQ.[1] Cost-effectiveness results from this report will not be discussed because the economic modelling is relevant to the UK setting.

Eight hundred and fourteen references were identified by searches for clinical effectiveness.[1] Ten studies of patients with mild to moderate IPF were included, of which 1 evaluated azathioprine, 3 evaluated NAC (alone or in combination), 4 evaluated pirfenidone, 1 evaluated nintedanib, and 1 evaluated sildenafil.[1] Study quality was generally good with a low risk of bias.[1]

In a small RCT, treatment with azathioprine and prednisolone led to an improvement in survival compared with placebo and prednisolone when an age-adjusted analysis was used (HR 0.26; 95% CI, 0.08 to 0.88), suggesting a 64% reduction in the risk of death with azathioprine.[1] The likely inclusion of participants with non-specific interstitial pneumonia may explain this treatment effect, and the small sample size and potential risk of bias in this study should be considered when interpreting these data.[1] There was no effect on lung function (MD in % predicted FVC at 12 months: 4.8%; p=0.87; MD in % predicted DLCO at 12 months: 6.4%; p=0.70).[1] Follow-up was 12 months.[1]

Nintedanib 300 mg daily was more favorable than placebo on some measures of lung function (absolute change in FVC from baseline for nintedanib -0.06 L [95% CI, -0.13 to 0.01] vs. placebo -0.23 L [95% CI, -0.30 to -0.16]; MD 0.17 L; p=0.001; absolute change in % predicted FVC for nintedanib -1.04% [95% CI, -2.98% to

0.91%] vs. placebo -6.00% [95% CI, -8.01 to -4.00%]; MD 4.96%; p<0.001), rates of acute exacerbations (nintedanib 2.4 per 1000 patient years vs. placebo 15.7 per 1000 patient years [RR 0.16; 95% CI, 0.03 to 0.70; p=0.02]) and the number of all-cause deaths (nintedanib 7 vs. placebo 9); however, the primary outcome of annual rate of decline in FVC was not statistically significantly different between groups in a 54-month study (nintedanib -0.06 L [95% CI, -0.14 to 0.02 L] vs. placebo -0.19 L [95% CI, -0.26 to -0.12 L]; MD 0.13 L; p=0.06).[1]

Treatment with NAC was evaluated in 3 studies. In 2 studies, NAC 600 mg was administered orally three times daily in combination with azathioprine and prednisolone; NAC was studied as a single agent at 352.4 mg diluted with saline to a total volume of 4 mL and nebulized twice daily in the third study.[1] Follow-up was approximately 12 months in these studies.[1] Study results were mixed, with no benefit from triple therapy on change in FVC compared with placebo in one study (-0.24 L vs. -0.23 L, respectively [MD -0.01 L; 95% CI, -0.14 to 0.11; p=0.85]); however, there was a benefit on FVC when triple therapy was compared with double therapy (placebo, azathioprine plus prednisolone) in another study (2.27 L vs. 2.10 L, respectively [MD 0.18 L; 95% CI, 0.03 to 0.32; p=0.02]).[1] Inhaled single-therapy NAC did not have a statistically significant effect compared with a control.[1] Secondary outcomes (e.g., HRQoL, 6MWD and DLCO) were reported, similarly with mixed results across the 3 studies.[1] The 2 studies with triple-therapy interventions had a low risk of bias; however, the study using nebulized NAC had an unclear risk of bias.[1]

Pirfenidone was studied in 4 RCTs, and meta-analysis of FVC shows that pirfenidone appears to demonstrate an effect when compared with placebo treatment (MD 0.24 L; 95% CI, 0.06 to 0.41; p=0.008; I^2 45%).[1] However, caution is required in interpreting these data as the outcomes pooled were different, and as a consequence a standardized mean difference analysis was undertaken; in addition, the timing of assessment of these outcomes varied (from 48 weeks to 72 weeks).[1] A random-effects meta-analysis demonstrated a favorable effect of pirfenidone on the proportion of patients with a decline in FVC of 10% or more (RR 0.62; 95% CI, 0.41 to 0.93; p=0.02; I^2 57%).[1] Results for secondary outcomes were generally seen to be less favorable to pirfenidone. Differences in mean change from baseline in the percent predicted DLCO at 72 weeks was not statistically different between pirfenidone and placebo (MD 0.68; 95% CI, -0.87 to 3.22; p=0.6).[1] In addition, no differences were found between pirfenidone and placebo in the 6MWD.[1] The rate of acute exacerbations was studied in 2 trials but results were mixed, favoring pirfenidone over placebo in one trial and placebo over pirfenidone in the other trial.[1] Health-related quality of life outcomes were not reported.

One study assessed sildenafil for those with moderate to severe IPF; the patients in this study also had evidence of pulmonary hypertension.[1] Results on the primary outcome, a 20% improvement on the 6MWD test, were not statistically significant between the sildenafil and placebo groups (10% vs. 7%, respectively; p=0.39).[1] Results for secondary outcomes were mixed, with some favoring sildenafil (quality of life and DLCO) and others favoring placebo (incidence of acute exacerbations and FVC).[1] This study followed participants for 12 weeks and had an unclear risk of bias.[1]

Adverse events from the pharmacological interventions were generally mild to moderate and were reasonably well balanced between the treatment and placebo arms across the studies.[1] Severe adverse events appeared to be more common in one study in those treated with triple therapy.[1]

The fixed-effects NMA found only nintedanib and pirfenidone to have a statistically significant improvement in FVC over placebo.[1] A head-to-head comparison of nintedanib versus pirfenidone showed a trend favoring nintedanib, but this was not statistically significant.[1] Caution is required in the interpretation of the results of the NMA.

The investigators concluded that the current evidence suggests that there are few treatments that have any effect on surrogate outcomes which can be linked through evidence to patient-related outcomes such as mortality.[1] There is overall a scarcity of studies on interventions in symptom management. Pirfenidone

and nintedanib appear to be clinically effective; however, general recommendations cannot be made in terms of their cost-effectiveness owing to limitations in the evidence base.[1] Limitations to this report include there being few direct comparisons of treatments identified.[1] An indirect comparison through an NMA was performed; however, caution is recommended in the interpretation of these results.

The Effectiveness and Safety of Pirfenidone, Nintedanib and N-acetylcysteine for the Treatment of Idiopathic Pulmonary Fibrosis (2016)[2]:
A systematic review of the effectiveness and safety of pirfenidone, nintedanib and NAC for treatment of IPF versus placebo was performed.[2] Lack of head-to-head RCTs of treatment interventions drove the decision to systematically review placebo-controlled high-quality RCTs of at least 6 months' duration.[2] Patients enrolled in the study were suffering from IPF diagnosed by high-resolution computed tomography or biopsy.[2] Data from included studies were extracted and checked for study characteristics and duration, doses of medications, disease characteristics, age, gender, smoking habits, smoking history, FVC, DLCO, 6MWD, time since diagnosis, weight and Jadad score.[2] The Jadad score was used to assess the quality of the studies, and a score of 3 or more was required to be included in the meta-analysis.[24] The risk of publication bias was assessed by applying the funnel plot and Egger's test.[2] Significant moderate to high levels of heterogeneity were considered for I^2 greater than 50%.[2] Result were obtained from 3847 IPF patients from 12 RCTs.[2] Funnel plot analysis did not find publication bias for the analysis of the impact of pirfenidone, nintedanib and NAC on all the investigated outcomes.[2] Of note, in conflict of interest disclosure, nearly all of the authors of this systematic review had financial associations with Boehringer Ingelheim Pharmaceuticals, the manufacturer of nintedanib.[2]

The meta-analysis of these trials found that both pirfenidone or nintedanib, but not NAC, improved the standardized mean difference (SMD) of change from baseline in FVC (pirfenidone 0.26 L; 95% CI, 0.15 to 0.37; I^2 29%; nintedanib 0.37 L; 95% CI, 0.26 to 0.48; I^2 16%; NAC 0.1 L; 95% CI, -0.11 to 0.30; I^2 10%) versus placebo. The risk difference (RD) for FVC decline of 10% or more favored pirfenidone and nintedanib, but not NAC (pirfenidone RD -0.10%; 95% CI, -0.14 to -0.06; I^2 4%; nintedanib RD -0.12%; 95% CI, -0.21 to -0.03; I^2 66%; NAC RD -0.06%; 95% CI, -0.20 to 0.08; I^2 63%), versus placebo.[2] Nintedanib, but not pirfenidone nor NAC reduced acute exacerbations (nintedanib RD -0.05%; 95% CI, -0.10 to -0.01; I^2 59%; pirfenidone RD -0.01%; 95% CI, -0.05 to 0.03; I^2 51%; NAC RD 0.03%; 95% CI, -0.04 to 0.09; I^2 70%) compared with placebo.[2] Data on the 6MWD variable were not suitable for performing an unbiased meta-analysis.[2]

Pirfenidone and nintedanib did not increase the RD of serious adverse events (SAE) (pirfenidone 0.00; 95% CI, -0.02 to 0.02; I^2 0%; nintedanib -0.02; 95% CI -0.06 to 0.03; I^2 0%) versus placebo, while NAC slightly increased risk for SAE but was not statistically significant (RD 0.12; 95% CI, -0.05 to 0.29; I^2 80%).[2] Nintedanib, but not pirfenidone nor NAC, protected against both overall and respiratory-specific risk of death (nintedanib -0.03; 95% CI, -0.06 to -0.001; I^2 28%; pirfenidone -0.01; 95% CI, -0.02 to 0.00; I^2 24%; NAC 0.03; 95% CI, -0.02 to 0.08; I^2 18%) compared with placebo.[2] The most common adverse events associated with the administration of FDA-approved doses of pirfenidone were rash (30.34%), nausea (25.68%), cough (19.42%), dizziness (17.98%), headache (16.05%), anorexia (13.00%), dyspepsia (12.68%), dyspnea (11.08%) and insomnia (10.43%), whereas those associated with approved doses of nintedanib were diarrhea (60.68%), nausea (24.34%), cough (12.86%), nasopharyngitis (12.86%), vomiting (11.62%) and decreased appetite (11.07%).[2] However, overall 40% of very common (i.e., ≥10%) and 87% of common (i.e., ≥1% to 10%) adverse events were also observed with similar frequency in the placebo arms. [2]

Overall, approved doses of pirfenidone and nintedanib, but not NAC, reduced progression of IPF in terms of improved SMD change from baseline in FVC and the RD of FVC decline compared with placebo, but with a safety profile similar to that of placebo.[2]

The Effectiveness and Safety of Pirfenidone for Idiopathic Pulmonary Fibrosis (2015)[3]:
The aim of another systematic review and meta-analysis was to assess the efficacy and safety of pirfenidone on several physiological and clinical outcomes in IPF (including mortality, acute exacerbations and worsening of IPF).[3] Studies were eligible for inclusion if they limited their investigation to adults age 18 years or older with IPF, were RCTs that compared pirfenidone with placebo, and studied at least one clinical outcome.[3] The included outcomes in the analysis were: 1)

change in all-cause mortality; 2) change in IPF-related mortality; 3) progression-free survival (PFS); 4) decrease in predicted FVC; 5) worsening of idiopathic pulmonary fibrosis; 6) acute exacerbation; 7) change in 6MWD test; 8) and adverse effects.[3]

A total of 557 studies were identified, but only 5 RCTs included in 4 publications met inclusion criteria and were analyzed.[3] **Table 1** summarizes the findings following the GRADE approach. Absolute values were not reported for each of the outcomes.

Table 1. Summary of findings from Studies of Pirfenidone for IPF.[3]

Outcome	Relative Effect (95% CI)	Participants	Quality of Evidence (GRADE)
All-cause mortality	RR 0.53 (0.32 to 0.88)	N=1247 (3 RCTs)	Moderate
Progression-free Survival	RR 0.82 (0.73 to 0.92)	N=728 (3 RCTs)	Moderate
Acute Exacerbation	RR 0.59 (0.19 to 1.84)	N=235 (2 RCTs)	Low
Worsening of IPF	RR 0.64 (0.50 to 0.83)	N=1615 (5 RCTs)	Moderate
Change in 6MWD	RR 0.74 (0.64 to 0.86)	N=1236 (3 RCTs)	High
Change in aminotransferases	RR 2.26 (1.33 to 3.83)	N=764 (5 RCTs)	Moderate

Abbreviations: CI = confidence interval; RCT = randomized clinical trial; RR = risk ratio; 6MWD = 6-minute Walk Distance test.

Three RCTs (1247 patients) were identified that reported the effect of pirfenidone and mortality.[3] The meta-analysis included 623 patients in the intervention group and 624 in the placebo group.[3] Pirfenidone decreased all-cause mortality and IPF-related mortality at week 52 relative to placebo (see Table 1).[3] Quality of evidence was downgraded to moderate because of indirectness of this outcome.[3]

Five RCTs were identified that reported the effect of pirfenidone and PFS.[3] Pooled data from all studies were evaluated at week 52.[3] When PFS was not reported at week 52, data were extracted to 52 weeks from Kaplan-Meier curves.[3] The meta-analysis included 850 patients in the pirfenidone group and 863 in the placebo group.[3] Pirfenidone decreased PFS at week 52 compared with placebo (see Table 1).[3] Quality of evidence was downgraded to moderate because of indirectness.[3]

Four RCTs reported acute exacerbation of IPF.[3] The meta-analysis included 235 patients in the pirfenidone group and 139 in the placebo group.[3] Pirfenidone did not improve acute exacerbations of IPF compared with placebo (see Table 1).[3] Quality of evidence was downgraded to low because of indirectness and imprecision between results.[3]

Three RCTs reported worsening of IPF as a secondary endpoint, a composite outcome that included acute IPF exacerbations, IPF-related death, lung transplantation or respiratory hospitalization.[3] The meta-analysis included 786 patients in the pirfenidone group and 728 in the placebo group.[3] Pirfenidone improved worsening of IPF compared with placebo (see Table 1).[3] Quality of evidence was downgraded to moderate because of indirectness.[3]

Five RCTs reported the effect of pirfenidone on FVC or vital capacity (VC).[3] In 3 RCTs, change in percentage of predicted FVC greater than 10% were reported.[3] The meta-analysis included 623 patients in the pirfenidone group and 624 patients in the placebo group.[3] Pirfenidone decreased the risk of greater than 10% change in FVC compared with placebo (see Table 1).[3] Quality of evidence was downgraded to moderate due to imprecision.[3]

Three RCTs reported the effect of pirfenidone on change in 6MWD.[3] The meta-analysis included 617 patients in the pirfenidone group and 619 patients in the placebo group.[3] Pirfenidone improved 6MWD compared with placebo (see Table 1).[3] The quality of evidence was rated as high.[3]

Five RCTs were identified that reported the effect of pirfenidone and adverse effects.[3] Pooled data from all studies were evaluated at the end of each trial.[3] The meta-analysis included 857 patients in the pirfenidone group and 766 in the placebo group.[3] Pirfenidone was not associated with severe adverse events (RR 1.02; 95% CI, 0.93 to 1.11; I^2 2%) compared with placebo.[3] However, other adverse events such as photosensitivity (RR 4.92; 95% CI, 2.10 to 11.53; I^2 57%) or change in aminotransferases (RR 2.26; 95% CI, 1.33 to 3.83; I^2 23%) were more frequent with pirfenidone compared with placebo.[3] The quality of evidence was graded as moderate because of imprecision.[3]

The investigators found pirfenidone results in statistically significant differences in physiologic and clinically meaningful outcomes such as reduction in all-cause mortality, IPF-related mortality, worsening and exacerbation of IPF and PFS.[3] As a result, they concluded that pirfenidone use should be considered not only for its benefit in pulmonary function tests but also for its impact on clinically meaningful outcomes.[3]

After further review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[25-29]

New Guidelines:

<u>The American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and the Latin American Thoracic Society (ALAT) (2015)</u>[6]:
This update of the 2011 guideline[14] was developed by a multidisciplinary committee of pulmonologists with recognized IPF expertise, general pulmonologists, a pulmonologist-methodologist, and allergist-methodologist, a general internist, a chest radiologist, a pulmonary pathologist, an information scientist, and a patient with IPF.[6] The committee worked with 5 health research methodologists who had expertise in evidence synthesis and the guideline development process. The Committee conducted systematic reviews and prepared the systematic evidence summaries following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[6]

Committee members signed a confidentiality agreement and disclosed all potential conflicts of interest.[6] All of the 8 pulmonologists with recognized IPF expertise were considered to either have major financial or intellectual conflicts based on disclosures or participation in IPF clinical studies.[6] Although they were permitted to participate in the discussions of the evidence with the rest of the committee, they were instructed to abstain from discussions related to the evidence to decision framework, formulating and grading recommendations, and voting on recommendations.[6] Adherence to the rules was strict, with one of the committee co-chairs responsible for monitoring the discussions for adherence to these rules.[6] The remaining 9 nonconflicted committee members were allowed unrestricted participation.[6]

This guideline does not provide recommendations for one treatment regimen over another. With the exception of the recommendation against using prednisone with azathioprine and N-acetylcysteine, the guideline does not provide suggestions for or against combination regimens or sequential therapies.[6] The committee suggested each recommendation be weighed individually (i.e., 2 recommendations with the same strong or conditional rating should not be considered equivalent recommendations), factoring in all components used to determine the grade of the recommendation, including the confidence in effect estimates, outcomes studied, desirable and undesirable consequences of treatment, cost of treatment, and feasibility of treatment.[6]

The committee selected outcomes of interest for each research question.[6] All outcomes were identified *a priori*, and the committee explicitly rated their relative importance from the perspective of a patient with IPF.[6] Ranking outcomes by their relative importance helped focus attention on clinically meaningful outcomes most relevant to patients and helped to resolve or clarify potential disagreements in decision making.[6] Examples of clinically meaningful outcomes were mortality or disease progression.[6] Disease progression can be measured using multiple outcome measures, and was defined by the committee as increasing respiratory symptoms, worsening pulmonary function test (PFT) results, progressive fibrosis on high-resolution computed tomography scan, acute respiratory decline, or death.[6] Changes over time in FVC or DLCO were considered indirect measures of disease progression.[6]

Data from identified studies with the same treatment were pooled and meta-analyses were reviewed.[6] Overall confidence in effect estimates for each outcome was assessed following the GRADE approach, based on the following criteria: risk of bias, precision, consistency, directness of the evidence, risk for publication bias, presence of dose-effect relationship, magnitude of effect, and assessment of the effect of plausible residual confounding or bias.[6] Each of the following factors was considered in development of each recommendation: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of intervention to stakeholders, and the feasibility of implementation.[6]

The recommendations were graded as "strong" or "conditional", according to the GRADE approach.[6] Conditional recommendations are synonymous with weak recommendations.[6] Conditional recommendations require clinicians to recognize that different treatment choices will be appropriate for individual patients based on their values and preferences.[6]

Recommendations:

1. The recommendation **against** the use of the following agents for the treatment of IPF is **strong**:
    a. Anticoagulation (warfarin) (low confidence in effect estimates).[6]
        i. This recommendation is based on lack of benefit (no change in FVC) and increased mortality (RR 4.73; 95% CI, 1.42 to 15.77) with warfarin (goal INR 2.0 – 3.0) versus placebo in patient with IPF.[6]
    b. Imatinib, a selective tyrosine kinase inhibitor against platelet-derived growth factor (PDGF) receptors (moderate confidence in effect estimates).[6]
        i. This recommendation is based on lack of efficacy and high cost of treatment. No differences in mortality or progression of IPF were found between imatinib and placebo in patients with IPF. Imatinib is associated with higher rates of adverse events than placebo in this population.
    c. Combination prednisone, azathioprine, and N-acetylcysteine (low confidence in effect estimates).[6]
        i. Immune suppression was considered an important part of IPF treatment, but studies have shown higher rates of mortality and hospitalization in IPF patients treated with the combination of prednisone, azathioprine and N-acetylcysteine versus placebo. In addition, no differences in FVC change or quality-of-life indices were found with this drug combination.[6]
    d. Selective endothelin receptor antagonist (ambrisentan) (low confidence in effect estimates).[6]
        i. A 52-week placebo-controlled RCT was stopped early for lack of benefit and high likelihood of harm with ambrisentan in IPF patients (HR 2.08; 95% CI, 0.75 to 5.76; low confidence). Patients who received ambrisentan also experience increased disease progression regardless of presence or absence of pulmonary hypertension.[6]

2. The recommendations **for** the use of the following agents for the treatment of IPF are **conditional**:

a. Nintedanib, a tyrosine kinase inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor, and PDGF receptors (moderate confidence in effect estimates).[6]
    i. Nintedanib was evaluated in 3 RCTs in patients with mild to moderate IPF. The first RCT was a phase 2 trial that did not find statistically significant differences in mortality between placebo and nintedanib 50 mg daily, 100 mg daily, 150 mg daily and 150 mg twice daily. The percentage of patients with more than 10% FVC decline at 12-month follow-up was lower with 150 mg twice daily versus placebo (p=0.004), but no difference was found between placebo and the other doses. However, fewer patients experienced IPF exacerbations with any dose of nintedanib compared to placebo (HR 0.16; 95% CI, 0.04 to 0.70). The other 2 identical phase 3 trials compared nintedanib 150 mg twice daily to placebo for 52 weeks and found no difference in mortality (RR 0.70; 95% CI, 0.44 to 1.11) or acute exacerbations of IPF (HR 0.64; 95% CI, 0.39 to 1.05); however, fewer patients treated with nintedanib had a more than 10% absolute decline in FVC (RR 1.16; 95% CI, 1.06 to 1.27) and annual rate of change in FVC was slower with nintedanib (MD 125.2 mL; 95% CI, 77.7 to 172.8 mL). More patients treated with nintedanib reported an adverse event (RR 1.07; 95% CI, 1.03 to 1.11) with diarrhea being the most prevalent.[6]
    ii. This recommendation places high value on potential benefit of nintedanib on patient-important outcomes such as disease progression and lower value on potentially significant adverse effects and the expected cost of treatment.[6]
    iii. The available evidence focuses on patients with IPF with mild to moderate impairment in PFTs, and it is unknown whether the therapeutic benefits would differ in patients with a more severe impairment.[6]
    iv. The evidence does not suggest an optimal duration of therapy, and it is unknown if there is loss in treatment effect with ongoing therapy.[6]
b. Pirfenidone, an oral antifibrotic drug shown to regulate profibrotic and proinflammatory cytokine cascades in vitro and reduce fibroblast proliferation and collagen synthesis in animal models of lung fibrosis (moderate confidence in effect estimates).[6]
    i. Pooled analyses of clinical trials suggest possible, but not statistically significant, improvement in mortality (RR 0.70; 95% CI, 0.47 to 1.02; moderate confidence), reduced rate of FVC decline (SMD, 0.23; 95% 0.06 to 0.41; high confidence), and increased rate of photosensitivity (high confidence), fatigue (moderate confidence), stomach discomfort (moderate confidence) and anorexia (high confidence) in patients treated with pirfenidone.[6]
    ii. This recommendation places high value on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value on potentially significant adverse effects and the cost of treatment.[6]
    iii. Given the different inclusion criteria for the pirfenidone trials, these results may not be applicable to patients with IPF with more severe impairment.[6]
    iv. The evidence does not suggest optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing therapy.[6]
c. Antacids (very low confidence in effect estimates).
    i. Background: gastroesophageal reflux disease (GERD) has been observed in up to 90% of patients with IPF. GERD is a risk factor for aspiration or microaspiration which could subsequently cause pneumonitis and has been postulated to cause or worsen IPF. Antacid use on a regular basis with proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA) may decrease risk for microaspiration-associated lung injury.[6]
    ii. An aggregate analysis of 3 RCTs of different pharmacological treatments on patient with IPF compared patients enrolled in the trials who were on a PPI/H2RA at baseline versus patients who were not on an antacid at baseline. The analysis showed a smaller decrease in FVC during the study period for those receiving antacid treatment at baseline (MD, 0.07 L; 95% CI, 0 to 0.14 L; p=0.05). A retrospective analysis of longitudinal cohorts suggested an association with survival for IPF patients who received antacids (hazard ratio [HR] 0.47; 95% CI, 0.24 to 0.93).[6]

iii. This recommendation places higher value on possible improved lung function and survival and the low cost of therapy and a lower value on the potential adverse effects of antacids (e.g., pneumonia).[6]

3. The recommendation **against** the use of the following agents for the treatment of IPF is **conditional**:
    a. Phosphodiesterase-5 inhibitor (sildenafil) (moderate confidence in effect estimates).[6]
        i. Sildenafil has been studied in 2 RCTs of patients with IPF. One placebo-controlled trial did not find a benefit with sildenafil on the primary outcome, which was the proportion of patients who showed more than 20% improvement in the 6MWD after 12 weeks of treatment. A pre-defined subgroup analysis of patients with documented right ventricular hypertrophy or right ventricular systolic dysfunction did find improvement in the primary outcome (mean distance, 99.3 m; 95% CI, 22.3 to 176.2 m). A second, smaller trial, which excluded patient with known pulmonary hypertension or right ventricular dysfunction, also did not find benefit with sildenafil on the 6MWD test. Pooled analysis of these two trials showed no benefit of sildenafil on mortality (RR 0.51; 95% CI, 0.1 to 2.72; low confidence) or acute exacerbation (RR 0.51; 95% CI, 0.04 to 3.22; low confidence).[6]
        ii. The committee felt there was a net harm with sildenafil therapy in IPF patients.[6]
    b. Endothelin receptor antagonists (ERA) (macitentan, bosentan) (low confidence in effect estimates).[6]
        i. Two RCTs examined the effect of bosentan versus placebo, whereas a single RCT tested macitentan versus placebo. In the first bosentan trial, no benefit was seen in mortality (RR 1.14; 95% CI, 0.24 to 5.54), although the data suggested potential improvement, which was not statistically significant, in the composite outcome of mortality and disease progression (RR 0.62; 95% CI, 0.37 to 1.05), as measured by PFTs or clinical status. A larger, follow-up study evaluated patients with biopsy-proven interstitial pneumonia, a pathologic diagnosis consistent with IPF. Despite these modifications in study design, bosentan did not show an effect on mortality (RR 1.25; 95% CI, 0.53 to 2.96) or disease progression (RR 0.86; 95% CI, 0.71 to 1.05). In a trial that evaluated macitentan, no difference was seen in patients treated with macitentan versus those who received placebo in mortality (RR 0.74; 95% CI, 0.13 to 4.33), mortality or disease progression (RR 1.02; 95% CI, 0.63 to 1.66), or change in FVC (MD 0.00; 95% CI, -0.16 to 0.16).[6]
        ii. This recommendation places relatively higher value on clinically meaningful outcomes and high cost of this medication and a relatively lower value on possible reduction of the risk of mortality or disease progression. Given the inconsistency of a composite outcome (mortality or disease progression) across trials and the imprecision in the estimate of effect, the committee recommended against this therapy.[6]
    c. N-acetylcysteine monotherapy (inhaled and oral) (low confidence in effect estimates).[6]
        i. A pooled analysis of 3 RCTs that examined NAC monotherapy in patients with IPF did not demonstrate statistically significant differences in mortality (RR 1.97; 95% CI, 0.50 to 7.71; low confidence), in change in FVC (high confidence), quality of life (moderate confidence), or adverse outcomes (low confidence). Two studies reported on 6-minute walk test distance and a statistically significant improvement was seen with NAC monotherapy (MD, 44.33 meters; 95% CI, 2.92 to 85.75; very low confidence).[6]
        ii. This recommendation places higher value on the potential risks, inconvenience of use, and cost of therapy and low value on possible improvement of outcomes with unclear clinical significance. The committee did not find sufficient evidence for differences in outcomes between inhaled versus oral administration on NAC, and so this recommendation applies to both interventions.[6]

In summary, the committee did not provide strong recommendations for use of any drug in IPF, although pirfenidone and nintedanib, which are the only currently approved drugs for IPF, received a conditional recommendation for use with moderate confidence in effect estimates.[6] No suggestions for or against combination regimens or sequential therapies were provided, excluding the recommendation against using prednisone in combination with azathioprine and N-acetylcysteine.[6]

Two additional guidelines for treatment of IPF were excluded due to poor quality.[13,30]

New Formulations or Indications:

Nintedanib: New Indication for Systemic Sclerosis-Associated Interstitial Lung Disease (9/6/2019)

Nintedanib was studied in a phase 3, multi-centered, randomized, double-blind, placebo-controlled, parallel-group trial in which 576 adult patients with systemic sclerosis and interstitial lung disease with fibrosis affecting more than 10% of the lungs received nintedanib 150 mg twice daily (n=288) or placebo (n=288) for at least 52 weeks.[8] Patients were required to have an FVC that was at least 40% of the predicted value and a DLCO that was 30 to 89% of the predicted value.[8] Patients with pulmonary hypertension were excluded.[8] The study was funded by Boehringer Ingelheim, the manufacturer of nintedanib.[8] All analyses were conducted in the patients who received at least one dose of the trial drug or placebo.[8] About half the patients had diffuse cutaneous systemic sclerosis, and half had limited cutaneous systemic sclerosis.[8] The median time since the onset of the first non-Raynaud's symptom was 3.4 years.[8] The mean age of the patients was 54.0 years, and the mean FVC and DLCO were 72.5% and 53.0% of the predicted value, respectively.[8] Among the patients who received at least one dose, 232 (80.6%) in the nintedanib group and 257 (89.2%) in the placebo group completed the 52-week intervention.[8]

The primary end point was the annual rate of decline in the FVC (mL/year), as assessed over the 52-week period.[8] Key secondary endpoints were absolute changes from baseline in the modified Rodnan skin score and the SGRQ total score at week 52.[8] Background information on the SGRQ was mentioned earlier in this class update.[8] The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis.[8] The minimal clinically important difference in modified Rodnan skin score in patients with ILD associated with systemic sclerosis has not been established but has been suggested to be 3 to 4 points.[8] Other secondary endpoints included the annual rate of decline in FVC and DLCO as a percentage of the predicted value and absolute changes in FVC from baseline to week 52.[8]

For the primary endpoint, the annual rate of change in FVC over a 52-week period was lower in the nintedanib group than in the placebo group (-52.4 mL/year vs. -93.3 mL/year; difference, 41.0 mL/year; 95% CI, 2.9 to 79.0; p=0.04).[8] Multiple-imputation sensitivity analyses for missing data yielded p-values ranging from 0.06 to 0.10.[8] The mean absolute change from baseline in FVC at week 52 was -54.6 mL in the nintedanib group and -101.0 mL in the placebo group (difference, 46.4 mL; 95% CI, 8.1 to 84.7).[8] The mean absolute change from baseline in the modified Rodnan skin score at week 52 was -2.17 in the nintedanib group and -1.96 in the placebo group (difference, -0.21; 95% CI, -0.94 to 0.53).[8] The mean absolute change from baseline in total score on the SGRQ at week 52 was 0.81 in the nintedanib group and 0.88 in the placebo group (difference, 1.69; 95% CI, -0.73 to 4.12).[8] These key secondary endpoints also did not differ between the groups based on different baseline characteristics.[8] The percentages of patients with any adverse event and any serious adverse event were similar in the nintedanib group and placebo group; however, the percentage of patients who had an adverse event that led to the discontinuation of the assigned intervention was higher in the nintedanib group than in the placebo group (16.0% vs. 8.7%).[8] Over the entire trial period, 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group died (HR 1.16; 95% CI, 0.47 to 2.84).[8]

Nintedanib obtained an expanded indication by the FDA in September 2019 to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.[7] This is the second indication for nintedanib, which was already approved treatment of IPF.

Nintedanib: New Indication for Treatment for Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype (3/9/2020)

Nintedanib was studied in a phase 3, multi-centered, randomized, double-blind, placebo-controlled trial in which 663 adult patients with physician-diagnosed fibrosing interstitial lung disease received nintedanib 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks.[9] Because nintedanib already had an indication for IPP, efforts were made to enroll patients with a progressive fibrotic phenotype other than IPF.[9] The study was funded by Boehringer Ingelheim, the manufacturer of nintedanib. Mean age of patients was 69 years and mean FVC was 69.0% of the predicted value.[9] Overall, 252 patients (75.9%) in the nintedanib group and 282 (85.2%) in the placebo group completed 52 weeks of treatment.[9] A total of 80 patients prematurely discontinued nintedanib (65 patients due to an adverse event) and a total of 49 patients prematurely discontinued placebo (34 patients due to an adverse event).[9] All analyses were conducted in the patients who received at least one dose of the trial drug or placebo.[9] The analysis was based on all data measurements obtained over the 52-week period, including those from patients who had discontinued nintedanib or placebo.[9] The mean duration of exposure over 52 weeks was 10.3 months in the nintedanib group and 11.2 months in the placebo group.[9]

The primary end point was the annual rate of decline in the FVC, as assessed over the 52-week period.[9] The secondary endpoints were the absolute change from baseline in the total score on the K-BILD questionnaire at week 52, the time until the first acute exacerbation of interstitial lung disease or death over the 52-week period, and the time until death over the 52-week period.[9] The K-BILD questionnaire is a self-administered health-status questionnaire that has been developed in patients with interstitial lung diseases.[9] It consists of 15 items in 3 domains: breathlessness and activities, psychological factors, and chest symptoms.[9] Domain and total scores range from 0 to 100, with higher scores representing better health status.[9] The minimal clinically important difference has not been established, but a change of between 4 and 8 points has been suggested to represent a meaningful change.[9]

For the primary endpoint, the adjusted rate of decline in the FVC over the 52-week period was −80.8 mL per year in the nintedanib group and −187.8 mL per year in the placebo group (between-group difference, 107.0 mL; 95% CI, 65.4 to 148.5; p<0.001).[9] At week 52, the adjusted mean absolute change from baseline in the total score on the K-BILD questionnaire was 0.55 points in the nintedanib group and -0.79 points in the placebo group (between-group difference, 1.34 points; 95% CI, -0.31 to 2.98).[9] The percentage of patients who either died or had an acute exacerbation of interstitial lung disease over the 52-week period was 7.8% in the nintedanib group and 9.7% in the placebo group (HR 0.80; 95% CI, 0.48 to 1.34).[9] The percentage of patients who died over the 52-week period was 4.8% in the nintedanib group and 5.1% in the placebo group (HR 0.68; 95% CI, 0.32 to 1.47).[9]

A greater percentage of patients in the nintedanib group than in the placebo group had adverse events leading to a permanent dose reduction (33.1% vs. 4.2%) and to discontinuation of either nintedanib or placebo (19.5% vs. 10.3%).[9] Fatal adverse events were less frequent in the nintedanib group than in the placebo group (3.3% vs. 5.1%).[9] The most frequent adverse event was diarrhea, which was reported in 222 patients (66.9%) in the nintedanib group and in 79 patients (23.9%) in the placebo group.[9]

Nintedanib obtained an expanded indication by the FDA in March 2020 to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.[7] This is the third indication for nintedanib, which was already approved treatment of IPF and patients with systemic sclerosis-associated interstitial lung disease.

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts.

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Nintedanib	OFEV	9-6-19	Warnings and Precautions	Elevated Liver Enzymes and Drug-induced Liver Injury
Pirfenidone	ESBRIET	7-31-19	Warnings and Precautions	Elevated Liver Enzymes and Drug-induced Liver Injury

Nintedanib:

Warnings and Precautions: Elevated Liver Enzymes and Drug-Induced Liver Injury (9/6/2019):[7,10]

Cases of drug-induced liver injury have been observed with nintedanib. In the clinical trials and post-marketing experience, serious and non-serious cases of drug-induced liver injury, including fatal severe liver injury, have been reported. Most hepatic events occur within the first 3 months of treatment. In clinical trials, administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in most cases. In IPF studies, most (94%) patients with ALT or AST elevations had elevations less than 5-times upper limit of normal (ULN) and most (95%) patients with bilirubin elevations had elevations less than 2-times ULN. In the SSc-ILD study, a maximum ALT or AST greater than or equal to 3-times ULN was observed for 4.9% of patients in the nintedanib group and for 0.7% of patients in the placebo group. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes.

Drug Interactions: Pirfenidone (11/9/2018)[7,10]

In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either drug. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone.

Pirfenidone:

Warnings and Precautions: Elevated Liver Enzymes and Drug-Induced Liver Injury (7/31/2019)[10,31]

Cases of drug-induced liver injury have been observed with pirfenidone. In post-marketing experience, serious and non-serious cases of drug-induced liver injury, including fatal severe liver injury, have been reported. Conduct baseline liver function tests (ALT, AST, and bilirubin) prior to the initiation of pirfenidone, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.

Randomized Controlled Trials:

Table 3. Key Inclusion Criteria for Randomized Controlled Trials.

Population	Idiopathic Pulmonary Fibrosis
Intervention	Nintedanib, pirfenidone
Comparator	Other active drug (e.g., nintedanib, pirfenidone, sildenafil, n-acetylcysteine, etc.)
Outcomes	Mortality, morbidity outcomes, symptoms, quality of life or functioning. Surrogate markers of lung function acceptable if validated (e.g., forced vital capacity; carbon monoxide diffusing capacity)
Timing	Multi-week study or longer
Setting	Outpatient

A total of 83 citations were manually reviewed from the initial literature search. After further review, 82 citations were excluded because of wrong study design (e.g., observational, post-hoc analysis), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstract is included in **Appendix 2**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Kolb, et al.[5] DB, PG, RCT N=274 13 countries Funded by Boehringer Ingelheim	1. Nintedanib 150 mg PO BID + sildenafil 20 mg PO TID 2. Nintedanib 150 mg PO BID + Placebo PO TID 1:1 24 weeks	-Age ≥40 y -IPF diagnosis -Recent chest CT and surgical lung biopsy specimens consistent with IPF diagnosis -Single-breath DLCO ≤35% of predicted value	Change from baseline in the SGRQ total score at week 12 SGRQ: *A 50-item questionnaire divided into 3 domains (impact, symptoms, activity) that assess health-related QoL in patients with respiratory disease. Total scores range from 0-100, with higher scores indicated worse QOL. The likely MCID for patients with IPF is a change of ≥4 points.*[5]	Week 12: 1. -1.28 points 2. -0.77 points MD -0.52 points (95% CI, -3.33 to 2.30 points) Week 24: 1. 0.23 points 2. 2.42 points MD -2.19 points (95% CI, -5.40 to 1.02 points) Conclusion: In patients with advanced IPF and DLCO ≤35% of the predicted value, nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone.

Abbreviations: BID = twice daily; DB = double blind; CI = confidence interval; CT = computed tomography; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; MCID = minimal clinically important difference; MD = mean difference; PC = placebo controlled; PG = parallel group; PO = by mouth; QoL = quality of life; RCT = randomized clinical trial; SGRQ = St. George's Respiratory Questionnaire; TID = three times daily.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
nintedanib esylate	OFEV	CAPSULE	N
pirfenidone	ESBRIET	CAPSULE	N
pirfenidone	ESBRIET	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

BACKGROUND: Nintedanib is an approved treatment for idiopathic pulmonary fibrosis (IPF). A sub- group analysis of a previously published trial suggested that sildenafil may provide benefits regarding oxygenation, gas exchange as measured by the diffusion capacity of the lungs for carbon monoxide (DLCO), symptoms, and quality of life in patients with IPF and severely decreased DLCO. That idea was tested in this trial.

METHODS: We randomly assigned, in a 1:1 ratio, patients with IPF and a DLCO of 35% or less of the predicted value to receive nintedanib at a dose of 150 mg twice daily plus sildenafil at a dose of 20 mg three times daily (nintedanib-plus-sildenafil group) or nintedanib at a dose of 150 mg twice daily plus placebo three times daily (nintedanib group) for 24 weeks. The primary end point was the change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 12 (the total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life). Secondary end points included measures of dyspnea and safety.

RESULTS: A total of 274 patients underwent randomization. There was no significant difference in the adjusted mean change from baseline in the SGRQ total score at week 12 between the nintedanib-plus-sildenafil group and the nintedanib group (−1.28 points and −0.77 points, respectively; p=0.72). A benefit from sildenafil treatment was not observed with regard to dyspnea as measured with the use of the University of California, San Diego, Shortness of Breath Questionnaire. No new safety signals were observed, as compared with previous trials.

CONCLUSIONS: In patients with IPF and a DLCO of 35% or less of the predicted value, nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone. No new safety signals were identified with either treatment regimen in this population of patients. (Funded by Boehringer Ingelheim; INSTAGE ClinicalTrials.gov number, NCT02802345.)

Appendix 3: Medline Search Strategy

1 exp Idiopathic Pulmonary Fibrosis/ 3587
2 nintedanib.mp. 822
3 pirfenidone.mp. 1158
4 2 or 3 1670
5 1 and 4 503
6 limit 5 to (english language and yr="2015 -Current" and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review" or systematic reviews as topic)) 83

Author: Gibler Date: June 2020

Drugs for Interstitial Lung Disease

Goal:

- Restrict use to populations with chronic interstitial lung disease in which the drugs have demonstrated efficacy with FDA approval.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Preferred Alternatives:

- No preferred alternatives at this time

Table 1. FDA-approved Indications.

Indication	Nintedanib	Pirfenidone
Idiopathic pulmonary fibrosis	X	X
Chronic fibrosing interstitial lung disease with a progressive phenotype	X	
Systemic sclerosis-associated interstitial lung disease	X	

Approval Criteria		
1. Is the claim for a drug with an FDA-approved interstitial lung disease indication as outlined in Table 1?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Is the treatment prescribed by a pulmonologist?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient a current smoker?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 12 months.

	Efficacy of approved drugs for IPF may be altered in smokers due to decreased exposure (see prescribing information).	

P&T/DUR Review: *6/20 (AG); 7/15*
Implementation: *7/1/20, 8/16, 8/25/15*