

## PHARMACY / MEDICAL POLICY – 5.01.555

## Pharmacologic Treatment of Interstitial Lung Disease

Effective Date: Sept. 1, 2024

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Replaces: N/A


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5.01.522 Advanced Therapies for Pharmacological Treatment of Pulmonary Arterial Hypertension

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## Introduction

Idiopathic means “unknown cause.” Idiopathic pulmonary fibrosis (IPF) is a lung (pulmonary) condition in which the lungs become scarred (fibrosis). Usually only one person in a family develops IPF. In a very small number of cases, IPF can develop in family members. When this happens, it’s called familial pulmonary fibrosis.

Because of the scar tissue, the lungs are not able to move oxygen into the bloodstream very well. The usual symptoms are a shortness of breath and a dry cough. It’s a progressive condition, meaning it gets worse over time. IPF usually affects people between 50 and 70 years old. There is no cure for IPF, but certain drugs can slow the progression to help maintain breathing capacity. This policy describes when medications for IPF and other diseases that cause fibrosis of the lungs may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

Drug	Medical Necessity
<p><b>Idiopathic Pulmonary Fibrosis (IPF)</b></p> <ul style="list-style-type: none"> <li>Ofev (nintedanib) oral</li> </ul>	<p><b>Ofev (nintedanib) may be considered medically necessary for the treatment of idiopathic pulmonary fibrosis (IPF)* when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>IPF was diagnosed in accordance with the 2000 ATS/ERS criteria (see <a href="#">Table</a> below)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Prescribed by or in consultation with a pulmonologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced vital capacity (FVC) <math>\geq</math> 50% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>DLCO (carbon monoxide diffusing capacity) between 30-79% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>High-resolution computed tomography (HRCT) performed within the last 12 months</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The dose is limited to 300 mg per day (taken as 150 mg twice daily)</li> </ul> <p><b>Note:</b> *Individuals must have a confirmed diagnosis of IPF.</p>
<p><b>Idiopathic Pulmonary Fibrosis (IPF)</b></p> <ul style="list-style-type: none"> <li>Generic pirfenidone</li> <li>Brand pirfenidone</li> <li>Esbriet (pirfenidone) oral</li> </ul>	<p><b>Brand pirfenidone and Esbriet (pirfenidone) may be considered medically necessary for the treatment of idiopathic pulmonary fibrosis (IPF)* when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>IPF was diagnosed in accordance with the 2000 ATS/ERS criteria (see <a href="#">Table</a> below)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Prescribed by or in consultation with a pulmonologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced vital capacity (FVC) <math>\geq</math> 50% of the predicted value</li> </ul> <p><b>AND</b></p>



Drug	Medical Necessity
	<ul style="list-style-type: none"> <li>• DLCO (carbon monoxide diffusing capacity) between 30-79% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• High-resolution computed tomography (HRCT) performed within the last 12 months</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual has tried generic pirfenidone and had an inadequate response or intolerance</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The dose is limited to 2,403 mg per day (taken as 801 mg three times daily)</li> </ul> <p><b>Note:</b> *Individuals must have a confirmed diagnosis of IPF.</p> <p><b>Generic pirfenidone may be considered medically necessary for the treatment of idiopathic pulmonary fibrosis (IPF)* when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>• Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• IPF was diagnosed in accordance with the 2000 ATS/ERS criteria (see <a href="#">Table</a> below)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Prescribed by or in consultation with a pulmonologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Forced vital capacity (FVC) <math>\geq</math> 50% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• DLCO (carbon monoxide diffusing capacity) between 30-79% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• High-resolution computed tomography (HRCT) performed within the last 12 months</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The dose is limited to 2,403 mg per day (taken as 801 mg three times daily)</li> </ul>



Drug	Medical Necessity
	<p><b>Note:</b> *Individuals must have a confirmed diagnosis of IPF.</p>
<p><b>Systemic sclerosis-associated interstitial lung disease (SSc-ILD)</b></p> <ul style="list-style-type: none"> <li>Actemra (tocilizumab) SC</li> <li>Tyenne (tocilizumab-aazg) SC</li> <li>Ofev (nintedanib) oral</li> </ul>	<p><b>Actemra (tocilizumab) SC and Tyenne (tocilizumab-aazg) SC may be considered medically necessary for interstitial lung disease associated with systemic sclerosis (SSc-ILD), when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>SSc is diagnosed in accordance with the 2013 ACR/EULAR classification criteria (see <a href="#">Table</a> below)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The medication is prescribed by or in consultation with a pulmonologist or a rheumatologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced vital capacity (FVC) is <math>\geq 55\%</math> of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>DLCO (carbon monoxide diffusing capacity) is <math>\geq 45\%</math> of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The diagnosis is confirmed by high-resolution computed tomography (HRCT)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The dose is limited to 162 mg given once every week as a subcutaneous injection</li> </ul> <p><b>Ofev (nintedanib) may be considered medically necessary for interstitial lung disease associated with systemic sclerosis (SSc-ILD), when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>SSc is diagnosed in accordance with the 2013 ACR/EULAR classification criteria (see <a href="#">Table</a> below)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Ofev is prescribed by or in consultation with a pulmonologist or a rheumatologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced vital capacity (FVC) is <math>\geq 40\%</math> of the predicted value</li> </ul>



Drug	Medical Necessity
	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>DLCO (carbon monoxide diffusing capacity) is between 30-89% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The diagnosis is confirmed by high-resolution computed tomography (HRCT)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The dose is limited to 300 mg per day (taken as 150 mg twice daily)</li> </ul> <p><b>Note:</b> *Individuals must have a confirmed diagnosis of SSc.</p>
<p><b>Chronic Fibrosing Interstitial Lung Diseases (ILDs)</b></p> <ul style="list-style-type: none"> <li>Ofev (nintedanib) oral</li> </ul>	<p><b>Ofev (nintedanib) may be considered medically necessary for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype* when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>DLCO (carbon monoxide diffusing capacity) is between 30-79% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced vital capacity (FVC) <math>\geq</math> 45% of the predicted value</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The diagnosis is confirmed by high-resolution computed tomography (HRCT)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Ofev is prescribed by or in consultation with a pulmonologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The dose is limited to 300 mg per day (taken as 150 mg twice daily)</li> </ul> <p><b>Note:</b> *Progressive phenotype is characterized by an increasing extent of fibrosis on high-resolution computed tomography (CT), decline in lung function, worsening of symptoms and quality of life, and early death despite current therapy.</p>



Drug	Medical Necessity
<p><b>Pulmonary hypertension associated interstitial lung disease (PH-ILD)</b></p> <ul style="list-style-type: none"> <li>• Tyvaso (treprostinil) oral inhalation solution</li> <li>• Tyvaso DPI (treprostinil) oral inhalation powder</li> </ul>	<p><b>Tyvaso (treprostinil) oral inhalation solution and Tyvaso DPI (treprostinil) oral inhalation powder may be considered medically necessary for the treatment of pulmonary hypertension associated interstitial lung disease (PH-ILD), when ALL the following conditions are met:</b></p> <ul style="list-style-type: none"> <li>• Individual is 18 years of age or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual has pulmonary hypertension (WHO Group 3) confirmed by right heart catheterization</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual has interstitial lung disease confirmed by high-resolution computed tomography (HRCT)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual is able to ambulate and complete a 6-Minute Walk Distance (6MWD) test of <math>\geq 100</math> meters <ul style="list-style-type: none"> <li>○ Record of the baseline 6MWD test is necessary for the initial review</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Medication is prescribed by or in consultation with a pulmonologist</li> </ul>

<b>ATS/ERS/JRS/ALAT Criteria for the Diagnosis of Idiopathic Pulmonary Fibrosis</b>
<ol style="list-style-type: none"> <li>1. IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP (Usual Interstitial Pneumonia)</li> <li>2. The diagnosis of IPF requires: <ol style="list-style-type: none"> <li>a. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)</li> <li>b. The presence of a UIP pattern on high-resolution computed tomography (HRCT) in individuals not subjected to surgical lung biopsy (Biopsy may not be feasible in certain individuals due to their risk for the procedure)</li> <li>c. Specific combinations of HRCT and surgical lung biopsy pattern in individuals subjected to surgical lung biopsy</li> </ol> </li> <li>3. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD</li> </ol>



## ATS/ERS/JRS/ALAT Criteria for the Diagnosis of Idiopathic Pulmonary Fibrosis

(Published in Am J Respir Crit Care Med Vol 198, Iss 5, pp e44-e68, Sep 1, 2018. Available without membership or subscription at <http://www.thoracic.org/statements/interstitial-lung-disease.php> Accessed August 5, 2024)

## ACR/EULAR Classification Criteria for Identifying Individuals with Systemic Sclerosis (SSc)

1. Systemic sclerosis (SSc; scleroderma) is a heterogeneous disease whose pathogenesis is characterized by three hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix.
2. The diagnosis of SSc requires:
  - a. The individual has skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints.OR
  - b. Presence of the following symptoms with a total score of  $\geq 9$  points:
  - c. Puffing fingers (2 points) **OR** bilateral skin thickening/ Sclerodactyly of the fingers (4 points)
  - d. Digital tip ulcers (2 points) **OR** fingertip pitting scars (3 points)
  - e. Telangiectasia (2 points)
  - f. Abnormal nailfold capillaries (2 points)
  - g. Pulmonary arterial hypertension or interstitial lung disease (2 points)
  - h. Raynaud's phenomenon with absence of antinuclear antibody (ANA) confirmed by laboratory testing (3 points)
  - i. Presence of any of the following SSc-related autoantibodies: anticentromere, anti-topoisomerase I or anti-RNA polymerase III (3 points)

(Published in Ann Rheum Dis 2013; 72:1742-1755. Available at:

[https://ard.bmj.com/content/72/11/1747?int\\_source=trendmd&int\\_medium=cpc&int\\_campaign=usage-042019](https://ard.bmj.com/content/72/11/1747?int_source=trendmd&int_medium=cpc&int_campaign=usage-042019)

Accessed August 5, 2024)

Drugs	Investigational
<b>Actemra (tocilizumab), Generic pirfenidone, Brand pirfenidone, Esbriet (pirfenidone), Ofev (nintedanib), Tyenne (tocilizumab-aazg), Tyvaso (treprostinil), Tyvaso DPI (treprostinil)</b>	<b>Combination therapy with Ofev (nintedanib) plus generic pirfenidone, brand pirfenidone, or Esbriet (pirfenidone) is considered investigational.</b>  <b>Combination therapy with Actemra (tocilizumab) or Tyenne (tocilizumab-aazg) plus Ofev (nintedanib) for treatment of SSc-ILD is considered investigational.</b>



Drugs	Investigational
	Use of these agents for the treatment of interstitial lung diseases other than described above is considered investigational.

Approval	Criteria
<b>Initial authorization</b>	<p>Actemra (tocilizumab), generic pirfenidone, brand pirfenidone, Esbriet (pirfenidone), Ofev (nintedanib), and Tyenne (tocilizumab-aazg) can be approved for 1 year.</p> <p>Tyvaso (treprostinil) and Tyvaso DPI (treprostinil) can be approved for 6 months.</p>
<b>Re-authorization criteria</b>	<p>Future re-authorization of Actemra (tocilizumab), generic pirfenidone, brand pirfenidone, Esbriet (pirfenidone), Ofev (nintedanib), and Tyenne (tocilizumab-aazg) depends on the clinical benefit/response shown at the time of re-authorization where:</p> <ul style="list-style-type: none"> <li>Chart notes documenting decrease in FVC are not greater than 10% from previous year</li> </ul> <p>Future re-authorization of Tyvaso (treprostinil) and Tyvaso DPI (treprostinil) depends on the clinical benefit/response shown at the time of re-authorization where:</p> <ul style="list-style-type: none"> <li>Individual shows a positive increase on the 6MWD test as compared to the baseline 6MWD test</li> </ul>

## Coding

Code	Description
<b>HCPCS</b>	
J3262	Injection, tocilizumab (Actemra), 1 mg
J7686	Treprostinil (Tyvaso), inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg
Q5135	Injection, tocilizumab-aazg (tyenne), biosimilar, 1 mg (new code effective 10/1/2024)





## Related Information

### Benefit Application

Generic pirfenidone, brand pirfenidone, Esbriet (pirfenidone), Ofev (nintedanib), and Tyvaso DPI (treprostinil) are managed through the pharmacy benefit. Actemra (tocilizumab), Tyenne (tocilizumab-aazg), and Tyvaso (treprostinil) are managed through both the pharmacy benefit and medical benefit.

## Evidence Review

### Ofev (nintedanib)

Ofev (nintedanib) is a tyrosine kinase receptor inhibitor (TKI) indicated for the treatment of idiopathic pulmonary fibrosis (IPF). A Phase III replicate trial (INPULSIS-1 and INPULSIS-2) demonstrated the efficacy of nintedanib versus placebo in individuals with idiopathic pulmonary fibrosis. The trial was conducted for 52 weeks and enrolled 1066 individuals who were diagnosed with IPF within the previous five years. Criteria for eligibility included having a FVC greater than 50% of the predicted value, a diffusion capacity of the lung for carbon monoxide (DLCO) between 30 – 79% of the predicted value, and a chest high resolution computed tomography (HRCT) within the last twelve months. The primary outcome for both trials was the annual rate of decline in FVC (milliliters/year). Secondary outcomes were the time to the first acute exacerbation and change from baseline score on the St. George's Respiratory Questionnaire (SGRQ) - a subjective measuring tool for quality of life.

Individuals receiving nintedanib 150mg BID as monotherapy achieved a significant decrease in annual FVC decline when compared to placebo at a reduction of 125.5ml/year (95% CI, 77.7-172.8,  $p < 0.001$ ) in INPULSIS- 1 and 93.7ml/year (95% CI, 44.8- 142.7,  $p < 0.001$ ) in INPULSIS- 2. While IMPULSIS- 1 did not show significant reduction in the time until first exacerbation, IMPULSIS -2 did demonstrate some significant decrease with a hazard ratio of 0.38 (95%CI, 0.19-0.77,  $p = 0.005$ ). When comparing changes in SGRQ scores from baseline, there were decreases in both trials indicating an improvement in quality of life (QOL). However, once again only IMPULSIS- 2 demonstrated significance at -2.69 (95% CI, -4.95 to -0.43;  $p = 0.02$ ).



The TOMORROW Phase II trial was similar in design and primary outcomes. As opposed to the phase III trials that did demonstrate efficacy, the phase II trial did not show significance in regard to decreased annual FVC decline when compared to placebo. However, it was noted that with nintedanib 150mg twice daily, there was a trend towards a general reduction in annual FVC decline at 68.4% ( $p= 0.06$ ). This prompted the current therapeutic dose recommended today of 150mg BID with a lower dose of 100mg showing some efficacy with less potential for adverse events. Secondary outcomes of this trial were incidences of acute exacerbations per 100 individual-years and difference in the mean SGRQ score from baseline. The number of acute exacerbations was significantly lower in the nintedanib group compared to placebo with a relative risk of 0.16 (95% CI, 0.03- 0.70;  $p= 0.02$ ). Similar to phase III trials, there was a significant decrease in the SGRQ score from baseline of 0.66 ( $p= 0.007$ ).

The most common adverse events noted in the registrational clinical trials were gastrointestinal (GI) in nature. In the phase II trials, individuals receiving nintedanib 150mg BID experienced at least one episode of diarrhea (55%), nausea (23%), and vomiting (13%) during the duration of the study and these events were responsible for most of the discontinuations in the treatment group. Individuals participating in IMPULSIS- 1 and -2 had similar adverse events, with diarrhea (61.5% and 63%) and nausea (23% and 26%) being the most prominent, and discontinuations of 4.5% and 4.3% in each trial, respectively.

Nintedanib has also been associated with elevated liver enzymes in both phase II and III trials. Some individuals experienced clinically significant increase (three times the upper limit of normal) in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Because nintedanib is metabolized partially by the liver, its use should be monitored for mild liver impairment and avoided in those with moderate to severe impairment. Liver enzymes should be monitored at baseline, prior to initiating nintedanib therapy and monitored periodically afterwards. Dose reduction and/or discontinuation of nintedanib resulted in a normalization of liver enzymes with no chronic liver impairment.

Nintedanib has not been studied in individuals with severe renal and moderate to severe hepatic impairment (Child Pugh score B or C). Currently there are no guidelines for the treatment of individuals with severe renal impairment, but mild to moderate renal insufficiencies do not require any dose adjustments as less than 1% of the starting dose is excreted by the kidneys. Nintedanib should not be recommended for individuals with moderate to severe hepatic impairment.



## Esbriet (pirfenidone)

Esbriet (pirfenidone) is a novel antifibrotic agent that has been recently approved for the treatment of idiopathic pulmonary fibrosis (IPF) after being previously removed from the market due to the lack of efficacy data. Since its removal, three more phase III trials were conducted: CAPACITY 004 & 006 and ASCEND. These were double blinded, randomized, placebo controlled, international and multi-center trials. Treatment consisted of pirfenidone 2403mg/daily compared to placebo. In the CAPACITY 004 trial, a lower 1197mg/day dose was used to examine any dose response relationship. Pirfenidone has shown mixed results in its efficacy, which is defined as a decrease in disease progression. The usual measurement is the change in FVC over time. In the three studies, treatment duration either lasted between 52 and 72 weeks. Enrolled individuals had either a clinical or radiographic diagnosis of IPF with other causes ruled out. Baseline characteristics were generally balanced amongst all groups. The population age was between 40 – 80 years old with the mean age of 67 years. A majority of the individuals were white males with some form of smoking history. The mean baseline FVC was 72% across all treatment groups.

Both CAPACITY 004 and ASCEND showed significant results in regard to percent predicted FVC after the trial period from baseline. CAPACITY 004 had an absolute mean FVC difference of 4.4% between pirfenidone 2403mg daily versus placebo after 72 weeks. ASCEND demonstrated an absolute mean FVC difference of 4.8% between pirfenidone 2403mg daily and placebo after 72 weeks. The impact of the 0.4% difference between the two trials is not known. CAPACITY 006 was the only trial out of the three that did not meet its primary endpoint. There was no association between differences in predicted FVC and certain secondary outcomes. These include but are not limited to the University of California at San Diego Shortness of Breath Questionnaire (SOBQ) for dyspnea, World Health Organization Quality of Life score, and mortality. Secondary outcomes in all three trials were noted to be exploratory and not make a claim for efficacy in the prescribing information.

The most common adverse effects noticed in all three trials were nausea (36%) and rash (30%). The mean exposure time to pirfenidone across all three trials was 62 weeks with the maximum duration being 118 weeks. Longer term safety risks have yet to be established. At the daily recommended dose of 2403mg, there were slightly higher discontinuations in treatment due to adverse effects than compared with placebo (15% vs. 10%).<sup>1,2</sup>

In three of the Phase III trials, there were higher incidences of photosensitivity reactions usually within the first 6 months of initiating treatment.

Elevated liver enzymes have also been associated with pirfenidone. Across the three phase III trials, there were higher incidences of alanine aminotransferase (ALT) or aspartate



aminotransferase (AST) elevations (3 times the upper limit of normal [ULN]) in pirfenidone treatment versus placebo (3.7% vs. 0.8%). These effects were reversible with dose reduction or discontinuation of the treatment. No further complications or liver failure were noted.

In a trial comparing the pharmacokinetics of pirfenidone in individuals with normal renal function to either mild, moderate, or severe renal impairment, there was an increase in overall systemic exposure of 1.4, 1.5, and 1.2 fold, respectively. Pirfenidone should be used with caution in individuals that have mild, moderate, or severe renal impairment, and adverse effects should be monitored closely with therapeutic adjustments, if needed.

Phase III data has shown that while the side effect profile of pirfenidone can vary to be gastrointestinal (GI) or dermatologic in nature, the symptoms can be treated with supportive therapy or avoidance of prolonged sun exposure and other concomitant photosensitive drugs.

## **Actemra (tocilizumab)**

Actemra (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of multiple inflammatory conditions such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, and giant cell arteritis. Early studies had also suggested that inhibition of IL-6 might reduce skin fibrosis in individuals with systemic sclerosis and preserve lung function.

The clinical efficacy of tocilizumab was assessed in a phase 3 multicenter, randomized, double-blind, placebo-controlled study in individuals with SSc (Study WA29767). A phase 2/3 multicenter, randomized, double-blind, placebo-controlled study in individuals with SSc (Study WA27788) provided supportive information. Study WA29767 (NCT02453256) enrolled adult individuals with SSc defined by the 2013 ACR/EULAR classification criteria for SSc, with onset of disease (first non-Raynaud symptom) of  $\leq 5$  years, modified Rodnan Skin Score (mRSS) of  $\geq 10$  and  $\leq 35$  at screening, elevated inflammatory markers (or platelets), and active disease based on at least one of the following: disease duration  $\leq 18$  months, increase in mRSS  $\geq 3$  units over 6 months, involvement of one new body area and an increase in mRSS of  $\geq 2$  over 6 months, or involvement of two new body areas within the previous 6 months, or presence of at least one tendon friction rub. Study WA27788 (NCT01532869) enrolled adult individuals with SSc with onset of disease  $\leq 5$  years, mRSS of  $\geq 15$  and  $\leq 40$  at screening, active disease, and elevated inflammatory markers or platelets. Individuals in both studies were not permitted to use biologic agents (such as TNF antagonists), alkylating agents, or cyclophosphamide.

In Study WA29767, 212 individuals were randomized in a 1:1 ratio to receive weekly SC injections of 162 mg of tocilizumab or placebo during the 48-week, double-blinded, placebo-



controlled period. Rescue treatment was allowed during the treatment period after 16 weeks for >10% percent predicted FVC (ppFVC) decline or after 24 weeks for worsening skin fibrosis. The primary efficacy endpoint was changed from baseline at Week 48 in mRSS. Change from baseline in FVC at Week 48 was a key secondary endpoint.

In the overall population of Study WA29767, there was not a statistically significant difference in the mean change from baseline to Week 48 in mRSS (primary endpoint) in individuals receiving tocilizumab compared to placebo (difference: -1.73; 95% CI: -3.78, 0.32). There also was not a statistically significant effect on the primary endpoint of mRSS in Study WA27788.

In the overall population of Study WA29767, individuals treated with tocilizumab, as compared to placebo treated individuals, were observed to have less decline from baseline in ppFVC and observed FVC at 48 weeks. FVC results from Study WA27788 were similar.

Of the 212 individuals who were randomized in Study WA29767, 68 individuals (65%) in the tocilizumab arm and 68 individuals (64%) in the placebo arm had SSc-ILD at baseline, as confirmed by a visual read of high resolution computed tomography (HRCT) by blinded thoracic radiologists. The mean ppFVC at baseline for individuals with SSc-ILD identified by HRCT was 79.6% (median 80.5%). Post-hoc analyses were performed to evaluate results.

within the subgroups of individuals with and without SSc-ILD.

The ppFVC and observed FVC results in the overall population were primarily driven by results in the SSc-ILD subgroup. In the SSc-ILD subgroup, the differences in mean changes from baseline to Week 48 for tocilizumab, as compared to placebo, were 6.47% and 241 mL for ppFVC and observed FVC, respectively.

The results of the key FVC secondary endpoints from Study WA29767 support a conclusion of effectiveness of tocilizumab in reducing the rate of progressive loss of lung function in the study population. However, in settings where a trial does not provide evidence of an effect on the primary endpoint, the estimated magnitude of effect on other endpoints should be interpreted with caution, and comparisons to results of other products and studies may be misleading.

The most common adverse reactions (incidence of at least 5%) reported with tocilizumab are upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions.



## Tyvaso (treprostinil) Inhalation Solution and Tyvaso DPI (treprostinil)

Tyvaso (treprostinil) is a prostacyclin mimetic indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and for pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. For the treatment of PH-ILD Tyvaso was evaluated in the INCREASE study which was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 individuals with PH-ILD. Enrolled study individuals predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

Individuals in the INCREASE study were randomized (1:1) to either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of individuals randomized to Tyvaso titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of individuals randomized to Tyvaso reaching a dose of 12 breaths, 4 times daily during the study.

The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Individuals receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ( $p=0.004$ ) using Hodges-Lehmann estimate. The treatment effect on 6MWD at Week 16 was consistent for various subgroups, including etiology of PH-ILD, disease severity, age, sex, baseline hemodynamics, and dose.

Time to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to a cardiopulmonary indication, decrease in 6MWD  $>15\%$  from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation. Treatment with Tyvaso in individuals with PH-ILD resulted in numerically fewer hospitalizations. The numbers of reported deaths were the same for both treatment groups. Overall, treatment with Tyvaso demonstrated a statistically significant increase in the time to first clinical worsening event (log-rank test  $p=0.041$ ), and a 39% overall reduction in the risk of a clinical worsening event (HR=0.61 [95% CI: 0.40, 0.92]).

The most common adverse reactions (incidence  $\geq 4\%$ ) reported with Tyvaso are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea, and syncope.



In a 3-week, open-label, single-sequence, safety and tolerability study (BREEZE) conducted in 51 individuals on stable doses of Tyvaso Inhalation Solution who switched to a corresponding dose of Tyvaso DPI, the most commonly reported adverse events on Tyvaso DPI during the 3-week treatment phase included cough (35.3%), headache (15.7%), dyspnea (7.8%), and nausea (5.9%). Individual tolerability, as assessed by incidence of new adverse events following transition to Tyvaso DPI, was consistent with the expected known safety profile of Tyvaso Inhalation Solution.

## **2015 Update**

A primary literature search from January 1, 2014, to October 31, 2015, did not identify any new evidence requiring changes to this policy. This policy was reviewed by the Pharmacy and Therapeutics Committee November 19, 2015.

## **2016 Update**

Addition of new and revised recommendations, as well as annual policy maintenance. This policy was reviewed by the Pharmacy and Therapeutics Committee February 25, 2016.

## **2017 Update**

Recent data do not indicate a need for change to the above medical necessity criteria.

## **2018 Update**

Primary literature search from January 1, 2016, to January 20, 2018, was conducted. Added initial approval duration and re-authorization criteria taken from a recent review article found. No other references were found that would impact this policy.

## **2019 Update**

Primary literature search from January 1, 2018, to February 28, 2019, was conducted. No references were found that would impact this policy.



## 2020 Update

Primary literature search from January 1, 2019 to January 8, 2020, was conducted. No references were found that would impact this policy other than addition of Ofev(nintedanib) for SSc-ILD.

## 2021 Update

Reviewed prescribing information for all drugs in policy and reviewed the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) clinical practice guidelines on the diagnosis of IPF. No changes were identified that would impact policy statements.

## 2022 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search through February 28, 2022. No references were found that would impact this policy.

## 2023 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search. Updated criteria for brand pirfenidone and brand Esbriet (pirfenidone) oral to require trial of a generic pirfenidone first.

## 2024 Update

Reviewed prescribing information for all drugs in policy. Added Tyenne (tocilizumab-aazg) SC coverage criteria for the treatment of certain individuals with interstitial lung disease associated with systemic sclerosis (SSc-ILD).

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27. Tyvaso DPI (treprostinil) oral inhalation powder prescribing information. United Therapeutics Corp.; Research Triangle Park, NC. Revised May 2022.
28. Tyenne (tocilizumab-aazg) prescribing information. Fresenius Kabi USA, LLC.; Lake Zurich, IL. Revised March 2024.

## History

Date	Comments
12/08/14	New policy, add to the Prescription Drug section. Considered medically necessary when criteria are met.
12/08/15	Annual Review. Policy updated with literature review; no change in policy statements.
04/01/16	Annual Review, approved March 8, 2016. Policy updated with new and revised recommendations.
07/07/17	Policy moved into new format, no changes to policy statement.
09/01/17	Annual Review, approved August 22, 2017. A literature search was conducted from 4/2/16 to 8/18/17. No new studies were found that would require changes to this policy.
02/01/18	Annual Review, approved January 30, 2018. Primary literature search from 1/1/16 to 1/20/18. Added initial approval duration and re-authorization criteria per new referenced found.
04/01/19	Annual Review, approved March 19, 2019. Updated literature search. No changes.
02/01/20	Annual Review, approved January 14, 2020. Added criteria for use Ofev (nintedanib) for SSc-ILD.
07/01/20	Interim Review, approved June 9, 2020. Changed policy title from Pharmacologic Treatment of Idiopathic Pulmonary Fibrosis to Pharmacologic Treatment of Interstitial Lung Disease. Added coverage criteria to Ofev for the treatment of chronic fibrosing interstitial lung diseases (ILDs). Added a dose limit of 300 mg per day for Ofev and 2,403 mg per day for Esbriet. Updated criteria for Ofev and Esbriet for the treatment of IPF adding age, prescriber specialty and dose limit. Updated criteria for Ofev for the treatment of SSc-ILD adding DLCO range and dose limit.



Date	Comments
06/01/21	Interim Review, approved May 11, 2021. Added criteria for Actemra (tocilizumab) for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD). Added criteria for Tyvaso (treprostinil) for the treatment of pulmonary hypertension associated interstitial lung disease (PH-ILD). Added HCPCS codes J3262 and J7686.
11/01/21	Annual Review, approved October 5, 2021. Updated the investigational table to clarify that use of these agents for the treatment of interstitial lung diseases other than described is considered investigational.
05/01/22	Annual Review, approved April 11, 2022. No changes to policy statement.
07/01/22	Interim Review, approved June 27, 2022. Added generic pirfenidone to policy with identical coverage criteria as brand Esbriet (pirfenidone) for the treatment of IPF.
10/01/22	Interim Review, approved September 12, 2022. Added brand pirfenidone (no trade name) to policy with identical coverage criteria as brand Esbriet (pirfenidone) for the treatment of IPF. Added Tyvaso DPI (treprostinil) oral inhalation powder with the identical coverage criteria as Tyvaso (treprostinil) oral inhalation solution for the treatment of pulmonary hypertension associated interstitial lung disease (PH-ILD).
05/01/23	Annual Review, approved April 24, 2023. Updated criteria for brand pirfenidone and brand Esbriet (pirfenidone) oral to require trial of a generic pirfenidone first. Changed the wording from "patient" to "individual" throughout the policy for standardization.
09/01/24	Annual Review, approved August 13, 2024. Added Tyenne (tocilizumab-aazg) SC coverage criteria for the treatment of certain individuals with interstitial lung disease associated with systemic sclerosis (SSc-ILD).
10/01/24	Coding update. Added Q5135.
10/11/24	Minor correction made to Tyenne (tocilizumab-aazg) in 2024 update section.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

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