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 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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
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</table>
| Ofev® (nintedanib) or Esbriet® (pirfenidone) | Ofev® (nintedanib) or Esbriet® (Pirfenidone) may be considered medically necessary for the treatment of idiopathic pulmonary fibrosis (IPF)* when ALL the following conditions are met:  
- IPF was diagnosed within the last five years, in accordance with the 2000 ATS/ERS criteria (see table below) 
AND  
- Forced vital capacity (FVC) ≥ 50% of the predicted value 
AND  
- DLCO between 30-79% of the predicted value 
AND  
- HRCT performed within the last 12 months  
*Note: Patients must have a confirmed diagnosis of IPF. |

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

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)

2. The diagnosis of IPF requires:
   
a. Exclusion of other known causes of interstitial lung disease (ILD) (eg, domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)  

b. The presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy (Biopsy may not be feasible in certain patients due to their risk for the procedure)  

c. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

3. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD

### Drugs

<table>
<thead>
<tr>
<th>Investigational</th>
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<tbody>
<tr>
<td>Ofev® (nintedanib) and Esbriet® (pirfenidone)</td>
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### Approval

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Initial authorization</td>
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| Re-authorization criteria | Future re-authorization would depend on clinical benefit/response shown at the time of re-authorization where:  
  - Chart notes documenting decrease in FVC not greater than 10% from previous year |

### Coding

N/A

### Related Information

**Benefit Application**

This policy is managed by the Pharmacy benefit.

### Evidence Review
Comparison of Treatment Recommendations in the 2015 and 2011 ATS/ERS/JRS/ALAT Idiopathic Pulmonary Fibrosis Guidelines

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2015 Guideline</th>
<th>2011 Guideline</th>
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<tr>
<td><strong>New and Revised Recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-target tyrosine kinase inhibitor [nintedanib (OFEV)]</td>
<td>Conditional recommendation for use*</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Antifibrotic agent [pirfenidone (ESBRIET)]</td>
<td>Conditional recommendation for use*</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Anticoagulation [warfarin (COUMADIN)]</td>
<td>Strong recommendation against use*</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Combination corticosteroid (prednisone) + azathioprine + N-acetylcysteine</td>
<td>Strong recommendation against use†</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Selective endothelin receptor antagonist [ambrisentan (LETAIRIS)]</td>
<td>Strong recommendation against use†</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Single-target tyrosine kinase inhibitor [Imatinib (GLEEVEC)]</td>
<td>Strong recommendation against use*</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Dual endothelin receptor antagonists [macitentan (OPSUMIT), bosentan (TRACLEER)]</td>
<td>Conditional recommendation against use†</td>
<td>Strong recommendation against use*</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitor [sildenafil (REVATIO)]</td>
<td>Conditional recommendation against use*</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>Unchanged Recommendations</strong></td>
<td></td>
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</tr>
<tr>
<td>Anti-acid therapy</td>
<td>Conditional recommendation for use‡</td>
<td>Conditional recommendation for use‡</td>
</tr>
<tr>
<td>N-acetylcysteine monotherapy</td>
<td>Conditional recommendation against use†</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Antipulmonary hypertension therapy</td>
<td>Recommendation deferred</td>
<td>Conditional recommendation against use‡</td>
</tr>
<tr>
<td>Single vs. bilateral lung transplantation</td>
<td>Recommendation deferred</td>
<td>Not addressed</td>
</tr>
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</table>

* Moderate confidence in effect estimates
† Low confidence in effect estimates
‡ Very low confidence in effect estimates
**Ofev® (nintedanib)**

Ofev® (nintedanib) is a tyrosine kinase receptor inhibitor (TKI) indicated for the treatment of idiopathic pulmonary fibrosis (IPF). A recent Phase III replicate trial (INPULSIS-1 and INPULSIS-2) demonstrated the efficacy of nintedanib verses placebo in patients with idiopathic pulmonary fibrosis. The trial was conducted for 52 weeks and enrolled 1066 patients who were diagnosed with IPF within the previous five years. Criteria for eligibility included having a forced vital capacity (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.

Patients 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 regards 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 patient-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, patients 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
Patients 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 patients 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 patients with severe renal and moderate to severe hepatic impairment (Child Pugh score B or C). Currently there are no guidelines for the treatment of patients 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 patients 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 a few years ago 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 forced vital capacity (FVC) over time. In the three studies, treatment duration either lasted between 52 and 72 weeks. Enrolled patients 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 patients 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 regards 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 met 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%).

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 patients 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 patients 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.
2015 Update

A primary literature search from 1/1/14 to 10/31/15 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 1/1/16 to 1/20/18 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 1/1/18 to 2/28/19 was conducted. No references were found that would impact this policy.

References


17. OFEV® (nintedanib) prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT. October 2014.


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/08/14</td>
<td>New policy, add to the Prescription Drug section. Considered medically necessary when criteria are met.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature review; no change in policy statements.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Annual Review, approved March 8, 2016. Policy updated with new and revised recommendations.</td>
</tr>
<tr>
<td>07/07/17</td>
<td>Policy moved into new format, no changes to policy statement.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>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.</td>
</tr>
<tr>
<td>02/01/18</td>
<td>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.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Annual Review, approved March 19, 2019. Updated literature search. No changes.</td>
</tr>
</tbody>
</table>

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200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


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Tagalog (Tagalog):

ไทย (Thai):
ประกาศนี้มีข้อความที่สำคัญเกี่ยวกับการมีสิทธิ์หรือข้อจำกัดของสิทธิ์ในการสมัคร Premera Blue Cross และมีข้อมูลที่เกี่ยวข้องในกรณีที่คุณจะต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่ายในการสมัคร Premera Blue Cross และมีข้อมูลที่เกี่ยวข้องในกรณีที่คุณจะต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่ายในการสมัคร Premera Blue Cross และมีข้อมูลที่เกี่ยวข้องในกรณีที่คุณจะต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่ายในการสมัคร Premera Blue Cross และมีข้อมูลที่เกี่ยวข้องในกรณีที่คุณจะต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จ่าย การดำเนินการในลักษณะนี้สามารถทำให้คุณต้องจ่ายค่าใช้จysters