FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agents</th>
<th>FDA Labeled Indications</th>
<th>Dosing and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esbriet® (pirfenidone) tablet, capsule</td>
<td>Indicated for the treatment of idiopathic pulmonary fibrosis (IPF)</td>
<td>Recommended dosage: 801 mg three times daily taken with food after 14-day titration</td>
</tr>
<tr>
<td>Ofev® (nintedanib) capsule</td>
<td>Indicated for the treatment of idiopathic pulmonary fibrosis (IPF)</td>
<td>Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food</td>
</tr>
</tbody>
</table>

CLINICAL RATIONALE

Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive fibrosing interstitial pneumonia of unknown origin occurring primarily in older adults and is limited to the lungs. IPF is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). IPF is characterized by fibroblast foci, featuring vigorous replication of mesenchymal cells and disposition of extracellular matrix. It is thought that repeated episodes of acute lung injury, due to unknown stimulus, leads to wound healing and fibrosis, with loss of lung function. The natural progression can vary with some patients remaining stable for extended periods of time; some having steady, but rapid progression and some patients experiencing acute exacerbations. Historically, a diagnosis of IPF has been associated with a poor prognosis with many only living for 3-5 years post diagnosis. The estimated prevalence of IPF within the United States has been difficult to establish due to the historical lack of a uniform definition, evolving diagnostic criteria, difference in case finding methodologies and study designs. The range is between 14-63 per 100,000 population with an annual incidence of approximately 7-16 per 100,000 population. The lower end of the incidence range includes patients with a more narrow definition of IPF. Patients were required to meet all major and minor American Thoracic Society and European Respiratory Society (ATS/ERS) criteria and had to have definite UIP patterns on high-resolution computed tomography (HRCT) scans. The upper end of the incidence range included patients that met the narrow definition requirements, along with patients with HRCT features of possible UIP.

Guidelines suggest that IPF be considered in adult patients with unexplained chronic exertional dyspnea, presents with cough, bibasilar inspiratory crackles, and finger clubbing. The diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity), either the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (SLB) OR specific combinations of HRCT patterns and histopathological patterns in patients subjected to SLB. Guidelines also recommend serological testing to exclude connective tissues disease.
An accurate diagnosis of IPF is a difficult and challenging process. The accuracy of the diagnosis increases with an integrated multidisciplinary approach. This includes dynamic discussion between pulmonologists, radiologists, and pathologists (when appropriate) who are experienced in the diagnosis of interstitial lung disease (ILD). The 2018 update of the 2011 guidelines provides a new diagnostic algorithm and schema for correlating histologic and radiologic findings in patients with suspected IPF. Aspects of this algorithm included criteria for four diagnostic categories for patterns of UIP based on HRCT findings (UIP, pattern, probable UIP pattern, indeterminate pattern, and alternative diagnosis) and four levels of certainty for histopathologic diagnosis (UIP, probable UIP, indeterminate for UIP, and alternative diagnosis). Below in Table 4 and 5 are the current guidelines on diagnosis IPF with HRCT and SLB.

Table 4. High-Resolution Computed Tomography Scanning Patterns

<table>
<thead>
<tr>
<th>UIP</th>
<th>Probable UIP</th>
<th>Indeterminate for UIP</th>
<th>Alternative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural and basal predominant; distribution is often heterogeneous</td>
<td>Subpleural and basal predominant; distribution is often heterogeneous</td>
<td>Subpleural and basal predominant</td>
<td>Subpleural and basal predominant</td>
</tr>
<tr>
<td>Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis</td>
<td>Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis</td>
<td>Subtle reticulation; may have mild GGO or distortion (&quot;early UIP pattern&quot;)</td>
<td>Subtle reticulation; may have mild GGO or distortion (&quot;early UIP pattern&quot;)</td>
</tr>
<tr>
<td>May have mild GGO</td>
<td>May have mild GGO</td>
<td>CT features and/or distribution of lung fibrosis that do not suggest any specific etiology (&quot;truly indeterminate&quot;)</td>
<td>CT features and/or distribution of lung fibrosis that do not suggest any specific etiology (&quot;truly indeterminate&quot;)</td>
</tr>
</tbody>
</table>

Findings suggestive of another diagnosis, including:
- CT features:
  - Cysts
  - Marked mosaic attenuation
  - Predominant GGO
  - Prune-like micronodules
  - Centrilobular nodules
  - Nodules
  - Consolidation
- Predominant distribution:
  - Peribronchovascular
  - Perilymphatic
  - Upper or mid-lung
- Other:
  - Pleural plaques (consider asbestosis)
  - Dilated esophagus (consider CTD)
  - Distal clavicular erosions (consider RA)
  - Extensive lymph node enlargement (consider other etiologies)
  - Pleural effusions, pleural thickening (consider CTD/drugs)

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; GGO = ground-glass opacities; RA = rheumatoid arthritis; UIP = usual interstitial pneumonia.

*Variants of distribution: occasionally diffuse, may be asymmetrical.

1Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.
UIP is characterized on HRCT by the presence of honeycombing, traction bronchiectasis, and traction bronchiolectasis, which may have concurrent fine reticulation and ground-glass opacification. Honeycombing is must be present for a definitive HRCT diagnosis of UIP. Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters (3–10 mm but occasionally larger). It is usually subpleural and is characterized by well-defined walls. Traction bronchiectasis/bronchiolectasis is another key feature of IPF and ranges from subtle irregularity and non-tapering to marked airway distortion and varicosity. Ground-glass opacifications superimposed on a fine reticular pattern represents fibrosis and may be seen in patients with IPF. The distribution of UIP on HRCT is characteristically basal and peripheral, though often patchy. The presence of coexistent pleural abnormalities (noted in the alternative diagnosis section in table 4 above) should lead to consideration of an alternative diagnosis. If HRCT patterns show probably or indeterminate UIP, the 2018 guidelines recommend surgical lung biopsy to make a definitive diagnosis. In patients whose HRCT does not demonstrate a UIP pattern, the surgical lung biopsy may still demonstrate UIP pattern on histopathology. Figure 8 below shows the algorithm for diagnosis with the updated guidelines.

<table>
<thead>
<tr>
<th>UIP</th>
<th>Probable UIP</th>
<th>Indeterminate for UIP</th>
<th>Alternative Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing)</td>
<td>• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF</td>
<td>• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause*</td>
<td>• Features of other histologic patterns of IIPs e.g., absence of fibroblast foci or loose fibrosis in all biopsies</td>
</tr>
<tr>
<td>• Predominant subpleural and/or paraseptal distribution of fibrosis</td>
<td>• Absence of features to suggest an alternative diagnosis</td>
<td>• Some histologic features from column 1, but with other features suggesting an alternative diagnosis†</td>
<td>• Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)</td>
</tr>
<tr>
<td>• Patchy involvement of lung parenchyma by fibrosis</td>
<td>Or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fibroblast foci</td>
<td>Honeycombing only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Absence of features to suggest an alternate diagnosis</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Definition of abbreviations: IIP = idiopathic interstitial pneumonias; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; UIP = usual interstitial pneumonia.

Grumolates, hyaline membranes (other than when associated with acute exacerbation of IPF, which may be the presenting manifestation in some patients, prominent airway-centered changes, areas of interstitial inflammation lacking associated fibrosis, marked chronic fibrosing pleuritis, organizing pneumonia. Such features may not be overt or easily seen to the untrained eye and often need to be specifically sought.

Features that should raise concerns about the likelihood of an alternative diagnosis include a cellular inflammatory infiltrate away from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centers, and a distinctly bronchiocentric distribution that could include extensive peribronchial metaplasia.
Prior to the simultaneous approvals of Esbriet (pirfenidone) and Ofev (nintedanib), there was no FDA approved pharmacologic therapy for idiopathic pulmonary fibrosis. The updated ATS/ERS/JRS/ALAT (American Thoracic Society), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) clinical practice guidelines address nintedanib and pirfenidone treatment for IPF. The guidelines suggest that clinicians use nintedanib or pirfenidone in patients with IPF (conditional recommendation, moderate confidence in estimates of effects). As with other interventions, the available evidence focuses on patients with IPF with mild to moderate impairment in pulmonary function tests; it is unknown whether the therapeutic benefits would differ in patients with a more severe impairment in pulmonary function testing or those with other comorbidities. The evidence does not allow suggestions about the optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing drug therapy.\(^5\)

Currently, there are neither head-to-head trials comparing the two agents nor are there any studies using the two in combination for therapy. Neither agent showed a significant mortality benefit compared to placebo.

**Safety**\(^1,2\)

Neither Esbriet nor Ofev have any FDA labeled contraindications.

**REFERENCES**


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<table>
<thead>
<tr>
<th>IPF suspected*</th>
<th>Histopathology pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIP</td>
</tr>
<tr>
<td>HRCT pattern</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UIP</td>
</tr>
<tr>
<td></td>
<td>Probable UIP</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
</tr>
<tr>
<td></td>
<td>Alternative diagnosis</td>
</tr>
</tbody>
</table>

Figure 8. Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns.

**IPF** is the likely diagnosis when any of the following features are present:
- Moderate-to-severe traction bronchiectasis (defined as mid traction bronchiectasis/bronchiolectasis in four or more lobes involving the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man over age 60 years or in a woman over age 50 years
- Extensive (>30%) retraction on HRCT and an age >70 years
- Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- Multidisciplinary discussion reaches a confident diagnosis of IPF.

**Indeterminate**
- Without an adequate biopsy to reliably be IPF
- With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and additional consultation.

* UIP: usual interstitial pneumonia; dx: diagnosis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; Non-IPF dx = usual interstitial pneumonia.


Idiopathic Pulmonary Fibrosis Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Idiopathic Pulmonary Fibrosis Prior Authorization (PA) Program is to promote appropriate selection of patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies. Criteria will approve doses that are at or below the maximum FDA labeled dose. Doses above the program set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized. When the quantity is above the FDA limit, the prescriber must submit documentation in support of therapy for the higher dose for the intended diagnosis.

TARGET AGENTS
Esbriet® (pirfenidone)
Ofev® (nintedanib)

QUANTITY LIMIT TARGET AGENTS- RECOMMENDED LIMITS

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity per Day Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esbriet (pirfenidone)</td>
<td>45550060000120</td>
<td>M, N, O, or Y</td>
<td>6 capsules</td>
</tr>
<tr>
<td>267 mg capsules</td>
<td>45550060000325</td>
<td>M, N, O, or Y</td>
<td>6 tablets</td>
</tr>
<tr>
<td>267 mg tablets</td>
<td>45550060000345</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>801 mg tablets</td>
<td>45550060000120</td>
<td>M, N, O, or Y</td>
<td></td>
</tr>
<tr>
<td>Ofev (nintedanib)</td>
<td>45554050200120</td>
<td>M, N, O, or Y</td>
<td>2 capsules</td>
</tr>
<tr>
<td>100 mg capsules</td>
<td>45554050200130</td>
<td>M, N, O, or Y</td>
<td>2 capsules</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. ONE of the following:
   A. The patient has a diagnosis of idiopathic pulmonary fibrosis (IPF) AND ALL of the following:
      I. The patient has not had a significant environmental exposure known to cause pulmonary fibrosis (e.g. drugs, asbestos, beryllium, radiation, raising birds/livestock, and metal dusts)
      AND
      II. The patient has no known explanation for interstitial lung disease (e.g. radiation, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis, and cancer)
      AND
      III. The patient has undergone serological testing to exclude any connective tissue disease known to cause interstitial lung disease (e.g. scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis)
      AND
      IV. The patient does not have clinical evidence of active infection (e.g. bronchitis/bronchiolitis, pneumonia, and sinusitis)
      AND
      V. ONE of the following:
A. ALL of the following:
   1. The patient has usual interstitial pneumonia (UIP) patterns on high-resolution computed tomography (HRCT) scans [containing BOTH of the following features: 1) subpleural, basal predominance 2) honeycombing with or without traction bronchiectasis]

   AND

   2. The patient does NOT have the presence of any of the following on HRCT:
      A. CT features (i.e. cysts, marked mosaic attenuation, predominant ground glass opacities, profuse micronodules, centrilobular nodules, nodules, consolidation)
      B. Predominant distribution (i.e. peribronchovascular, perilymphatic, upper or mid-lung)
      C. Pleural plaques
      D. Dilated esophagus
      E. Distal clavicular erosions
      F. Extensive lymph node enlargement
      G. Pleural effusions, pleural thickening

   AND

   3. A pulmonologist and a radiologist, both experienced in the diagnosis of interstitial lung disease, have been consulted with and both determine that the patient has definitive IPF

OR

B. ALL of the following:
   1. The patient has probable UIP patterns on HRCT (i.e. subpleural, basal predominance; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis; may have mild ground-glass opacities)

   AND

   2. ONE of the following:
      A. The patient has had a surgical lung biopsy that demonstrates UIP pattern on histopathology [containing ALL of the following 4 features: 1) Dense fibrosis with architectural distortion [i.e. destructive scarring and/or honeycombing] 2) predominantly subpleural and/or paraseptal distribution of fibrosis 3) presence of patchy involvement of lung parenchyma by fibrosis 4) presence of fibroblast foci]

   OR

      B. The patient has had a surgical lung biopsy that demonstrates probable UIP pattern on histopathology [containing ONE of the following features: 1) some of the features listed for UIP patterns on histopathology noted above but to an extent that precludes a definite diagnosis AND absence of features to suggest an alternative diagnosis; OR 2) honeycombing alone].

   AND

   3. The patient does NOT have the presence of any of the following:
A. Features of other histologic patterns of idiopathic interstitial pneumonia (e.g. absence of fibroblast foci or loose fibrosis) in all biopsies
B. Histological findings indicative of an alternative diagnosis (e.g. hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, lymphangioleiomyomatosis)

AND

4. A pulmonologist, radiologist, and a pathologist all experienced in the diagnosis of interstitial lung disease have been consulted with and determined that the patient has definitive IPF

OR

C. ALL of the following:
   1. The patient has indeterminate UIP patterns on HRCT (i.e. subpleural, basal predominance; subtle reticulation [may have mild ground-glass opacities or distortion]; CT features and/or distribution of lung fibrosis that do not suggest any specific etiology)
   AND
   2. The patient has had a surgical lung biopsy that demonstrates UIP pattern on histopathology [containing ALL of the following 4 features: 1) Dense fibrosis with architectural distortion [i.e. destructive scarring and/or honeycombing] 2) predominantly subpleural and/or paraseptal distribution of fibrosis 3) presence of patchy involvement of lung parenchyma by fibrosis 4) presence of fibroblast foci]
   AND
   3. The patient does NOT have the presence of any of the following:
      A. Features of other histologic patterns of idiopathic interstitial pneumonia (e.g. absence of fibroblast foci or loose fibrosis) in all biopsies
      B. Histological findings indicative of an alternative diagnosis (e.g. hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, lymphangioleiomyomatosis)
   AND
   4. A pulmonologist, radiologist, and a pathologist all experienced in the diagnosis of interstitial lung disease have been consulted with and determined that the patient has definitive IPF

OR

B. The patient has another FDA approved indication for the requested agent

AND

2. ONE of the following:
   A. The patient is NOT currently being treated with another agent included in this prior authorization program
   OR
   B. The patient is currently being treated with another agent included in this prior authorization program AND will discontinue prior to starting the requested agent

AND

3. The patient does not have any FDA labeled contraindications to the requested agent

AND

4. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
OR
B. ALL of the following:
   I. The requested quantity (dose) is greater than the program quantity limit
      AND
   II. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
      AND
   III. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

OR
C. ALL of the following:
   I. The requested quantity (dose) is greater than the program quantity limit
      AND
   II. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
      AND
   III. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months

Renewal Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent
   AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. pulmonologist, radiologist, pathologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis
   AND
4. ONE of the following:
   A. The patient is NOT currently being treated with another agent included in this prior authorization program
      OR
   B. The patient is currently being treated with another agent included in this prior authorization program AND will discontinue prior to continuing the requested agent
   AND
5. The patient does not have any FDA labeled contraindications to the requested agent
   AND
6. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
      OR
   B. ALL of the following:
      I. The requested quantity (dose) is greater than the program quantity limit
         AND
II. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
   AND
III. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
   OR
C. ALL of the following:
   I. The requested quantity (dose) is greater than the program quantity limit
      AND
   II. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
      AND
   III. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months