BlueCross BlueShield of Alabama

# Idiopathic Pulmonary Fibrosis Prior Authorization with Quantity Limit Criteria Program Summary

This prior authorization applies to Commercial, NetResults A series, NetResults F series and Health Insurance Marketplace formularies only.

**OBJECTIVE**

The intent of the Idiopathic Pulmonary Fibrosis Prior Authorization (PA) Program is to encourage 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 DRUGS**

**Esbriet** (pirfenidone)
**Ofev** (nintedanib)

**PRIOR AUTHORIZATION AND QUANTITY LIMIT TARGET DRUGS- RECOMMENDED LIMITS**

| Brand (generic) | GPI | Multisource Code | Quantity per Day Limit |
|---|---|---|---|
| Esbriet (pirfenidone) | | | |
| 267 mg capsules | 45550060000120 | M, N, O, or Y | 9 capsules/day |
| Ofev (nintedanib) | | | |
| 100 mg capsules | 45554050200120 | M, N, O, or Y | 2 capsules/day |
| 150 mg capsules | 45554050200130 | M, N, O, or Y | 2 capsules/day |

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

**Esbriet (pirfenidone) and Ofev (nintedanib) – INITIAL evaluation** will be approved when the following are met:

1. The patient has either the diagnosis of idiopathic pulmonary fibrosis (IPF) or another FDA approved diagnosis
   **AND**
2. If IPF, ALL of the following
   A. The patient is a non-smoker confirmed by biochemical testing
      **AND**
   B. 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**
   C. 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**

D. The patient does not have a diagnosis of any connective tissue disease known to cause interstitial lung disease (e.g. scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis)
**AND**
E. The patient does not have clinical evidence of active infection (e.g. bronchitis/bronchiolitis, pneumonia, and sinusitis)
**AND**
F. ONE of the following:
    i. If Ofev (nintedanib) is requested, the patient does not have moderate/severe hepatic impairment (Child-Pugh class B or C) or end-stage liver disease
    **OR**
    ii. If Esbriet (pirfenidone) is requested, the patient does not have severe hepatic impairment (Child-Pugh class C) or a history of end-stage renal disease requiring dialysis
**AND**
G. The prescriber has performed a baseline forced vital capacity (FVC) test
**AND**
H. The patient has a predicted FVC ≥50% and ≤90%
**AND**
I. The patient has a $FEV_1$/FVC ratio ≥0.80 and is not <0.8 after administration of a bronchodilator
**AND**
J. The patient has a carbon monoxide diffusion capacity (%DLco) of ≥30% and ≤90%
**AND**
K. ONE of the following:
    i. ALL of the following:
        a. The patient has usual interstitial pneumonia (UIP) patterns on high-resolution computed tomography (HRCT) scans [containing all of the following 3 features: 1) subpleural, basal predominance 2) reticular abnormality 3) honeycombing with or without traction bronchiectasis]
        **AND**
        b. The patient does NOT have the presence of any of the following on HRCT:
            1. Upper or mid-lung predominance
            2. Peribronchovascular predominance
            3. Extensive ground glass abnormality (extent > reticular abnormality)
            4. Profuse micronodules (bilateral, predominantly upper lobes)
            5. Discrete cysts (multiple, bilateral, away from areas of honeycombing)
            6. Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
            7. Consolidation in bronchopulmonary segments(s)/lobe(s)
        **AND**
        c. 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**

ii. ALL of the following:
    a. The patient has possible UIP patterns on HRCT (i.e. subpleural, basal predominance and reticular abnormality with absent honeycombing)
    **AND**
    b. The patient has had a surgical lung biopsy that demonstrates UIP pattern on histopathology [containing ALL of the following 3 features: 1) Evidence of marked fibrosis/architectural distortion, with or without honeycombing in a predominantly subpleural/paraseptal distribution 2) presence of patchy involvement of lung parenchyma by fibrosis 3) presence of fibroblast foci]
    **AND**
    c. The patient does NOT have the presence of any of the following:
        1. Hyaline membranes not associated with an acute exacerbation
        2. Organizing pneumonia not associated with an acute exacerbation
        3. Granulomas
        4. Marked interstitial inflammatory cell infiltrate away from honeycombing
        5. Predominant airway centered changes
        6. Other features suggestive of an alternative diagnosis
    **AND**
    d. 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

**AND**

3. The patient is receiving only one agent included in this prior authorization program at a time (Esbriet or Ofev)
**AND**
4. The patient does not have any FDA labeled contraindication(s) to therapy
**AND**
5. ONE of the following:
    A. The requested quantity (dose) is NOT greater than 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) is less than or equal to the FDA labeled dose
        **AND**
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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 FDA labeled dose
        **AND**

iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

**Length of Approval:** 12 months

| Agent | Contraindication(s) |
|---|---|
| Esbriet | None |
| Ofev | None |

**Renewal Evaluation** will be approved when ALL of the following are met:

1. The patient has been approved for the requested agent previously through the Prime Therapeutics PA process
   **AND**
2. If IPF, BOTH of the following:
   A. The patient is a non-smoker confirmed by biochemical testing
      **AND**
   B. The patient has not had a decline in percent predicted FVC of ≥10% OR ≥15% decline in %DLco
   **AND**
3. ONE of the following:
   A. If Ofev (nintedanib) is requested, the patient does not have moderate/severe hepatic impairment (Child-Pugh class B or C) or end-stage liver disease
      **OR**
   B. If Esbriet (pirfenidone) is requested, the patient does not have severe hepatic impairment (Child-Pugh class C) or a history of end-stage renal disease requiring dialysis
   **AND**
4. The patient is receiving only one agent included in this prior authorization program at a time (Esbriet or Ofev)
   **AND**
5. The patient does not have any FDA labeled contraindication(s) to therapy
   **AND**
6. ONE of the following:
   A. The requested quantity (dose) is NOT greater than 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) is less than or equal to the FDA labeled dose
         **AND**
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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 FDA labeled dose

**AND**

iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

**Length of Approval:** 12 months

| Agent | Contraindication(s) |
|---|---|
| Esbriet | None |
| Ofev | None |

**FDA APPROVED INDICATIONS AND DOSAGE[1,2]**

| Available Products | Indication | Dosing and Administration |
|---|---|---|
| Esbriet (pirfenidone) | Esbriet is a pyridone indicated for the treatment of idiopathic pulmonary fibrosis (IPF). | Recommended dosage: 801 mg (three capsules) three times daily taken with food after 14-day titration. |
| Ofev (nintedanib) | Ofev is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF). | Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food. |

**CLINICAL RATIONALE**

Idiopathic pulmonary fibrosis (IPF) is type of interstitial lung disease of unknown etiology.[3,7] It is a chronic, progressive disease that is limited to the lungs.[5,7,8] IPF is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).[4] Progressive scarring (fibrosis) of the lung's alveoli and consequent thickening of the alveoli walls causes a decline in lung function manifesting itself through cough, dyspnea, fatigue, and low blood oxygen levels.[5,7,8] The natural progression can be variant with some patients remaining stable for extended periods of time, some have steady but rapid progression yet others may experience an acute exacerbation.[4,6] Historically, a diagnosis of IPF has been associated with a poor prognosis with many only living for 3-5 years post diagnosis.[5,6] Male patients over the age of 50 tend to be the demographic most diagnosed with IPF.[8,9] The estimated prevalence of IPF within the United States is variant and difficult to establish due to the historical lack of a uniform definition, evolving diagnostic criteria, difference in case finding methodologies and study designs.[9] The range is between 14-63 per 100,000 population with an annual incidence of approximately 7-16 per 100,000 population.[9] The lower end of the range is linked to a more narrow definition needing to meet all major and minor American Thoracic Society and European Respiratory Society (ATS/ERS) criteria and required definite UIP patterns on high-resolution computed tomography (HRCT) scans. The upper end of the range equates to including those that met the narrow definition requirements along with patients who had HRCT features of possible UIP.[9] Translating this into overall prevalence, one estimate is approximately 50,000-70,000 people are living in the US with a diagnosis of IPF with approximately 15,000-20,000 new cases are diagnosed yearly.[15]

An accurate diagnosis of IPF is a difficult and challenging process. The accuracy of the diagnosis increases with an integrated multidisciplinary approach.[4,5,7] This includes dynamic discussion between pulmonologists, radiologists, and pathologists (when appropriate) who are experienced in the diagnosis of interstitial lung disease (ILD).[4,5,7] The latest guidelines provides a new diagnostic algorithm and schema for correlating histologic and radiologic findings in patients with suspected IPF.[5] Aspects of this algorithm included criteria for three levels of certainty for patterns of UIP based on HRCT findings (UIP, possible UIP, and inconsistent with UIP) and four levels of certainty for pathologic diagnosis (UIP, probable, possible, and not UIP).[4,5]

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), the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (SLB) and specific combinations of HRCT and SLB patterns in patients subjected to SLB.[4,5] Guidelines suggest that IPF be considered in adult patients with unexplained chronic

exertional dyspnea, presents with cough, bibasilar inspiratory crackles, and finger clubbing.[4] UIP is characterized on HRCT by the presence of reticular opacities, often associated with traction bronchiectasis. Honeycombing is common, and is critical for making a definite diagnosis. Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters on the order of 3–10 mm but occasionally as large as 2.5 cm. It is usually subpleural and is characterized by well-defined walls. Ground glass opacities are common, but usually less extensive than the reticulation. The distribution of UIP on HRCT is characteristically basal and peripheral, though often patchy. The presence of coexistent pleural abnormalities (e.g., pleural plaques, calcifications, significant pleural effusion) suggests an alternative etiology for UIP pattern. Micronodules, air trapping, nonhoneycomb cysts, extensive ground glass opacities, consolidation, or a peribronchovascular-predominant distribution should lead to consideration of an alternative diagnosis. If honeycombing is absent, but the imaging features otherwise meet criteria for UIP, the imaging features are regarded as representing possible UIP, and surgical lung biopsy is necessary 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. Below in Table 4 and 5 are the current guidelines on diagnosis IPF with HRCT and SLB.[5]

**TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN**

| UIP Pattern (All Four Features) | Possible UIP Pattern (All Three Features) | Inconsistent with UIP Pattern (Any of the Seven Features) |
|---|---|---|
| • Subpleural, basal predominance<br>• Reticular abnormality<br>• Honeycombing with or without traction bronchiectasis<br>• Absence of features listed as inconsistent with UIP pattern (*see* third column) | • Subpleural, basal predominance<br>• Reticular abnormality<br>• Absence of features listed as inconsistent with UIP pattern (*see* third column) | • Upper or mid-lung predominance<br>• Peribronchovascular predominance<br>• Extensive ground glass abnormality (extent > reticular abnormality)<br>• Profuse micronodules (bilateral, predominantly upper lobes)<br>• Discrete cysts (multiple, bilateral, away from areas of honeycombing)<br>• Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)<br>• Consolidation in bronchopulmonary segment(s)/lobe(s) |

*Definition of abbreviation*: UIP = usual interstitial pneumonia.

**TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN**

| UIP Pattern (All Four Criteria) | Probable UIP Pattern | Possible UIP Pattern (All Three Criteria) | Not UIP Pattern (Any of the Six Criteria) |
|---|---|---|---|
| • Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution<br>• Presence of patchy involvement of lung parenchyma by fibrosis<br>• Presence of fibroblast foci<br>• Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) | • Evidence of marked fibrosis / architectural distortion, ± honeycombing<br>• Absence of either patchy involvement or fibroblastic foci, but not both<br>• Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)<br>OR<br>• Honeycomb changes only‡ | • Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation<br>• Absence of other criteria for UIP (*see* UIP Pattern column)<br>• Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) | • Hyaline membranes*<br>• Organizing pneumonia*†<br>• Granulomas†<br>• Marked interstitial inflammatory cell infiltrate away from honeycombing<br>• Predominant airway centered changes<br>• Other features suggestive of an alternate diagnosis |

*Definition of abbreviations*: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.
* Can be associated with acute exacerbation of idiopathic pumonary fibrosis.
† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
‡ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

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.[17]

**Efficacy**

**Nintedanib** – pivotal trials

The clinical efficacy was studied in 1231 patients with IPF in one phase 2 (TOMORROW[10]) and two phase 3 (INPULSIS-1[11] and INPULSIS-2[11]) studies. These were randomized, double-blind, placebo-controlled studies comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks.

INPULSIS-1 and INPULSIS-2 were identical in design. Patients were randomized in a 3:2 ratio to either nintedanib 150 mg or placebo twice daily for 52 weeks. The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC).[11,12] TOMORROW was similar in design to INPULSIS trials. Patients were randomized in a 1:1 ratio to either nintedanib 150 mg or placebo twice daily for 52 weeks. The primary endpoint was the same as the INPULSIS trials (the annual rate of decline in FVC).[11,12]

Regarding the primary endpoint, there was a statistically significant reduction in the annual rate of decline of FVC (in mL) that was demonstrated in patients receiving nintedanib compared to patients receiving placebo based on the random coefficient regression model, adjusted for gender, height, and age. The treatment effect on FVC was consistent in all 3 studies. A prespecified pooled analysis (INPULSIS-1 and INPULSIS-2) of the primary end point showed a significant treatment effect [between group difference in the annual rate of FVC change, -109.9 mL (95% CI, 75.6 to -144.01)].[11,12]

As for secondary endpoints, in TOMORROW (investigator-reported) and INPULSIS-2 (adjudicated), the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving nintedanib compared to placebo. In INPULSIS-1 (adjudicated), there was no difference between the treatment groups. All-cause mortality did not show a statistically significant difference in pooled results from INPULSIS-1 and INPULSIS-2.[11,12] There was no significant difference between the nintedanib and placebo group in time to first investigator-reported acute exacerbation. There was no significant between-group difference in death from any cause, death from a respiratory cause, or death that occurred between randomized and 28 days after the last dose of the study drug.[11]

Smoking was associated with decreased exposure to Ofev, which may alter the efficacy profile of Ofev.[16]

**Pirfenidone** – pivotal trials

The efficacy of pirfenidone was evaluated in patients with IPF in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials (ASCEND[10], CAPACITY 004[13], and CAPACITY 006[14]). The primary endpoint was the same in all three trials differing in only the duration of the study. The primary endpoint was the change in percent predicted forced vital capacity (%FVC) from baseline to study end. The %FVC was measured at 52 weeks in ASEND, and at 72 weeks in CAPACITY 004 and CAPACITY 006.[13,14]

ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in idiopathic Pulmonary Fibrosis) was a randomized, double-blind, placebo-controlled 52-week trial comparing pirfenidone 2403 mg/day (n=278) versus placebo (n=277) in patients with IPF.[13] At week 52, the proportion of patients who had a decline of 10 percentage points or more in the %FVC or who had died was reduced by 47.9% in the pirfenidone group as compared with the placebo group [(46 patients (16.5%) vs 88 patients (31.8%); p<0.001], and the proportion of patients with no decline in the %FVC was increased by 132. 5% in the pirfenidone group [63 patients (22.7%) vs 27 patients (9.7%); p<0.001]. In ASCEND, a mean decline from baseline in FVC was 235 mL in the pirfenidone group and 428 mL in the placebo group (mean treatment difference, 193 mL; relative difference, 45.1%; p<0.001) at week 52.[13]

CAPACITY (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis Research of Efficacy and Safety Outcomes)[14] : CAPACITY 004 and CAPACITY 006 were nearly identical randomized, double-blind, placebo controlled trials with few exceptions, including an intermediate dose treatment arm in CAPACITY 004. CAPACITY 004 compared treatment with either pirfenidone 2403 mg/day (n=174) or pirfenidone 1197 mg/day (n=87) to placebo (n=174), while CAPACITY 006 compared pirfenidone 2403 mg/day (n=171) to placebo (n=173). In CAPACITY 004, pirfenidone successfully met the primary efficacy endpoint, with a significant reduction in the mean decline from baseline in %FVC compared with placebo at week 72 (-8.0% vs 12.4%; 35% relative difference; 4.4% absolute difference; p<0.001).[14] In CAPACITY 006, did not differ in the primary endpoint of mean decline from baseline in %FVC at week 72 (-9.0% vs -9.6%; 6.5% relative difference; absolute difference 0.6%; p=0.501).[14] CAPACITY 004, a reduction in the decline in FVC volume was also observed in patients receiving pirfenidone 2403 mg/day compared with placebo (mean treatment difference 157 mL) at Week 72.[14] There was no statistically significant difference in decline in FVC volume seen in CAPACITY 006.[14]

Survival was evaluated for pirfenidone compared to placebo in ASCEND, CAPACITY 004 and CAPACITY 006 as an exploratory analysis to support the primary endpoint (FVC). All-cause mortality was assessed over the study duration and available follow-up period, irrespective of cause of death and whether patients continued treatment. All-cause mortality did not show a statistically significant difference.

Decreased exposure has been noted in smokers using pirfenidone, which may alter the efficacy profile. Prescribing information indicates to instruct patients to stop smoking prior to treatment with pirfenidone and to avoid smoking when using pirfenidone.

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**[1,2,12,15]

Nintedanib:

Nintedanib has been associated with elevated liver enzymes. The safety and efficacy of Ofev in patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment have not been studied and is therefore not recommended for these patients.[16]

Pirfenidone:

Pirfenidone is not recommended for use in patients with severe hepatic impairment. It is also not recommended for use in patients with end stage renal disease on dialysis.

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