BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/22/15**
SECTION: DRUGS	**LAST REVIEW DATE: 2/21/19**
	LAST CRITERIA REVISION DATE: 2/21/19
	ARCHIVE DATE:

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

Criteria:

- **Criteria for initial therapy:** Esbriet (pirfenidone) or Ofev (nintedanib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Requesting provider is a Pulmonologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of idiopathic pulmonary fibrosis (IPF) by **ONE** of the following:
    - Findings on high-resolution computed tomography (HRCT), performed within the last 12 months, indicating usual interstitial pneumonia (UIP), a copy of HRCT must be submitted (See Table 1)
    - If performed, a surgical lung biopsy demonstrating usual interstitial pneumonia (UIP), a copy must be submitted (See Tables 2 & 3)
    - Specific HRCT and lung biopsy combinations, as per histopathological criteria for UIP pattern and HRCT and biopsy patterns, in patients with surgical lung biopsy, a copy of HRCT & biopsy results must be submitted (See Table 4)
4. Excluded other known causes of interstitial lung disease (ILD):
    - Such as domestic and occupational environmental exposures, connective tissue disease, and drug toxicity, etc.
5. Individual is a nonsmoker or has been abstinent from smoking for at least six weeks
6. Pulmonary function tests with evidence of **EITHER** of the following: (a copy of tests must be submitted)
    - Most recent tests show **BOTH** of the following:
        - FVC is ≥ 50% of the predicted value
        - DLCO is 30-79% of predicted value
    - Longitudinal changes in the last six month show **EITHER** of the following:
        - Decline in absolute FVC of 5-10%
        - Decline in absolute DLCO of 10-15%
7. **ALL** of the following baseline tests have been completed before initiation of treatment:
    - Liver function testing within the last 30 days
    - Renal function testing within the last 30 days
    - For **Ofev**: a pregnancy test in a woman of child bearing age, unless is using effective contraception

Initial approval duration: 6 months

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

- **Criteria for continuation of coverage (renewal request):** Esbriet (pirfenidone) or Ofev (nintedanib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a Pulmonologist

  2. Individual's condition has responded while on therapy
     - Response is defined as:
       - Significant improvement in %FVC over baseline
       - Absolute decline in FVC is less than 10%
       - Absolute decline in DLCO is less than 15%
       - Improved or no decline in symptoms for cough or shortness of breath

  3. Individual has been adherent with the medication

  4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
     - Significant adverse effect such as:
       - Liver toxicity
       - Photosensitivity reaction
       - Severe and persistent GI reactions

  5. There are no significant interacting drugs

  Renewal duration: 12 months

Description:

Esbriet (pirfenidone) & Ofev (nintedanib) are approved for the treatment of idiopathic pulmonary fibrosis (IPF), a specific form of chronic progressive interstitial lung disease of the lower respiratory tract in which lung tissue becomes scarred or fibrotic over time. IPF is a progressive disease characterized by an irreversible decline in pulmonary function, worsening of pulmonary symptoms, and progressive fibrosis on high-resolution computed tomography (HRCT). As a result, patients with IPF experience shortness of breath, cough, and have difficulty participating in everyday physical activities. The exact cause of IPF is not known, but associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

Esbriet (pirfenidone) exact mechanism of action is unknown, however, pirfenidone has anti-inflammatory and anti-fibrotic activity. Pirfenidone exerts anti-inflammatory effects by interfering with the production of transforming growth factor (TGF)-beta (involved in cell growth) and tumor necrosis factor (TNF)-alpha (involved in inflammation). It acts as an antifibrotic agent by altering the expression, synthesis, and possibly accumulation of collagen. Esbriet (pirfenidone) is available as 267 mg capsule or tablet and 801 mg tablet.

Ofev (nintedanib) is a tyrosine kinase inhibitor that reduces fibroblast activity by binding to receptors for various growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

fibroblast growth factor (FGF). These pathways are implicated in the scarring of lung tissue. It blocks intracellular signaling, preventing proliferation, migration, transformation of fibroblasts implicated in IPF pathogenesis.

Idiopathic Pulmonary Fibrosis (IPF)

- Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis (CFA), is a specific and the most common type of idiopathic chronic, fibrosing interstitial pneumonia (IIP)
    - IIPs are spontaneously occurring diffuse parenchymal lung diseases
    - Other IIPs include nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), lymphocytic interstitial pneumonia (LIP), and cryptogenic organizing pneumonia (COP)
    - IIPs are classified based on their histopathologic appearances

- IPF is a fatal lung disease with a variable and unpredictable course, in which progression occurs slowly in the majority of patients; a minority of patients experience rapid progression or stable disease, some experience episodes of acute respiratory worsening despite previous stability
    - The prognosis of IPF is poor, with only 20-30% of individuals are alive five years after diagnosis
    - Hospitalizations for respiratory problems are common and are frequently associated with death
    - No medication has been found to cure IPF, but nintedanib and pirfenidone, have been shown to slow disease progression, as evidenced by smaller decline in FVC, compared to placebo in adult patients with IPF

- Cigarette smoking is most strongly associated with IPF
    - Exposure to stone, metal, wood, and organic dusts has also been suggested as a risk factor as well as gastroesophageal reflux disease

- High resolution computed temography (HRCT) should be obtained in all patients suspected of having IPF
    - The presence of certain specific HRCT features in the appropriate clinical setting, may be sufficient to establish the diagnosis

- The characteristic HRCT features of IPF include peripheral (subpleural), bibasilar reticular opacities associated with architectural distortion, including honeycomb changes and traction bronchiectasis
    - While honeycombing is essential to making a definite diagnosis, it may be absent

- When the results of the clinical evaluation, laboratory testing, and HRCT do not allow for a confident diagnosis of IPF, lung biopsy may be indicated
    - When performed, lung biopsy results need to be correlated with the HRCT findings
    - For patients who require histopathologic confirmation of IPF, a surgical biopsy is preferred over transbronchial lung biopsy (TBLB)

- The diagnosis of IPF requires exclusion of other known causes of interstitial lung disease (ILD) AND either definite features of UIP on HRCT or certain combinations of HRCT and lung biopsy features of UIP
    - The histologic hallmark and chief diagnostic criterion for UIP is a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci, and honeycomb changes

- A UIP-like pattern of injury can also be seen in other fibrotic lung diseases, such as those associated with rheumatic diseases, chronic hypersensitivity pneumonitis, drug-toxicity, and pneumoconioses, such as asbestosis

- There is no staging system for assessing the severity of IPF
  - Patients progress from mild to moderate to severe respiratory limitation
  - Disease severity is assessed on the basis of symptoms, HRCT, and pulmonary function testing
  - Surrogate markers for the disease include forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO)
  - Use of the FVC as an efficacy measure is both supported and discouraged in the literature while the DLCO is considered a standard predictor of survival

- Moderate disease is characterized by:
  - Nonproductive cough
  - Dyspnea on moderate exertion
    - Supplemental oxygen may be needed with exertion
  - Mild-to-moderate pulmonary function abnormalities:
    - A reduced FVC (50-70% of predicted)
    - A reduced DLCO (45-65% of predicted)
    - And/or $P(A\text{-}a)O_2$ (21-30 mmHg)

- Advanced disease is characterized by:
  - Dyspnea on mild exertion (walking < 300 feet or climbing more than one flight of stairs)
  - Oxygen desaturation (≥ 4%) during a six-minute walk test
  - Requires supplemental oxygen at rest and/or with exertion
  - Moderate to severe pulmonary function abnormalities:
    - Reductions in FVC (< 50% of predicted)
    - Reductions in DLCO (< 50% of predicted)
    - $P(A\text{-}a)O_2$ difference elevated (> 30 mmHg)

- Clinical features associated with increased risk of mortality include:
  - Level of dyspnea
  - Increasing degree of dyspnea
  - Absolute decrease in FVC by $\geq$ 10%
  - Absolute decrease in DLCO by $\geq$ 15%
  - DLCO < 40% of predicted
  - Oxygen desaturation to $\leq$ 88% during a 6-minute walk test (6MWT)
  - Extent of honeycombing on HRCT
  - Worsening fibrosis on HRCT

- IPF is defined by the American Thoracic Society in the following manner:
  - a) exclusion of other known causes of interstitial lung disease (connective tissue disease, drug toxicity, domestic and occupational environmental exposure such as asbestos or beryllium exposure, hypersensitivity pneumonitis, systemic sclerosis, scleroderma, SLE, rheumatoid

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

arthritis, radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, HIV, viral hepatitis, or cancer) **and**
- b) presence of usual interstitial pneumonia (UIP) pattern evidenced by HRCT alone or by a combination of surgical lung biopsy and HRCT

Definitions:

Idiopathic Pulmonary Fibrosis Criteria from the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association

- Exclusion of other know causes of interstitial lung disease (for instance, domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
- Presence of a usual interstitial pneumonia (UIP) pattern on HRCT in patients without surgical lung biopsy, as evidenced by sub-pleural, basal predominance; reticular abnormality; honeycombing with or without traction bronchiectasis; and absence of any features inconsistent with UIP pattern. (See Table 1)
- Specific HRCT and lung biopsy combinations, as per histopathological criteria for UIP pattern and HRCT and biopsy patterns, in patients with surgical lung biopsy. (See Tables 2, 3, 4)

HRCT Criteria for UIP Pattern:

Table 1: HRCT Criteria for UIP Pattern

Pattern	Features
UIP – need all 4 features	•Sub-pleural, basal predominance •Reticular abnormality •Honeycombing with or without traction bronchiectasis •Absence of feature listed in Inconsistent with UIP (see below)
Possible UIP – need all 3 features	•Sub-pleural, basal predominance •Reticular abnormality •Absence of feature listed in Inconsistent with UIP (see below)
Inconsistent with UIP – any of 7 features	•Upper or mid-lung predominance •Peribronchovascular predominance •Extensive ground glass abnormality (extent > reticular abnormality) •Profuse micronodules (bilateral, predominantly upper lobes) •Discrete cysts (multiple, bilateral, away from areas of honeycombing) •Diffuse mosaic attenuation/air-trapping (bilateral, in 3 or more lobes) •Consolidation in bronchopulmonary segment(s) / lobe(s)

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

Histologic features of UIP:

Table 2: Histologic features of UIP	
Key feature	• Dense fibrosis causing remodeling of lung architecture with frequent honeycomb fibrosis • Fibroblastic foci typically scattered at the edges of dense scars • Patchy lung involvement • Frequent subpleural and parseptal distribution
Pertinent negative	• Lack of active lesions of other interstitial diseases (such as sarcoidosis or Langerhans cell histiocytosis) • Lack of marked interstitial chronic inflammation • Granulomas are inconspicuous or absent • Lack of substantial inorganic dust deposits such as asbestos bodies (except for carbon black pigment) • Lack of marked eosinophilia

Histological Criteria for UIP Pattern:

Table 3: Histologic Criteria for UIP Pattern from biopsy specimen	
	Criteria
UIP Pattern – need all 4 criteria	• Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a predominantly sub-pleural/paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see Not UIP Pattern)
Probable UIP Pattern	• Evidence of marked fibrosis/architectural distortion, +/- honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see Not UIP Pattern) OR • Honeycomb changes only
Possible UIP Pattern – need all 3 criteria	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (see UIP Pattern) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see Not UIP Pattern)

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

Not UIP Pattern – need any of the 6 criteria	• Hyaline membranes • Organizing pneumonia • Granulomas • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Combination of HRCT & Surgical Lung Biopsy (determined with multidisciplinary discussion):

Table 4: Combination of HRCT and Biopsy for Diagnosis of IPF		
HRCT Pattern	Surgical Lung Biopsy Pattern	Diagnosis of IPF
UIP	UIP Probable UIP Possible UIP Not classifiable fibrosis	Yes
	Not UIP	No
Possible UIP	UIP Probable UIP	Yes
	Possible UIP Not classifiable fibrosis	Probable
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP Possible UIP Not classifiable fibrosis Not UI P	No
Shaded areas show combination of HRCT and biopsy patterns that lead to a diagnosis of IPF.		

American Thoracic Society and European Respiratory Society (ATS/ERS):

Table 5: ATS/ERS Criteria for Diagnosis of IPF in the absence of surgical lung biopsy	
Major Criteria	• Exclusion of other known causes of ILD (certain drug toxicities, environmental exposure, and connective tissue diseases) • Abnormal PFT that include evidence of restriction (reduced VC, often with an associated increase in FEV1/FVC) and impaired gas exchange (increased $P(A\text{-}a)O_2$, decreased PaO_2 with rest or exercise, or decreased DLCO) • Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans • Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

Minor Criteria	• Age > 50 years • Insidious onset of otherwise unexplained dyspnea on exertion • Duration of illness > 3 months • Bibasilar, inspiratory crackles (dry or Velcro-type in quality)
Presence of all Major with as at least 3 of the Minor criteria increases likelihood of a correct clinical diagnosis of IPF	

Resources:

Esbriet (pirfenidone) product information accessed 01-24-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2e8c3537-36d7-4de5-9b5c-7a624b9a9e6e

Ofev (nintedanib) product information accessed 01-24-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=da1c9f37-779e-4682-816f-93d0faa4cfc9

Raghu G, Collard HR, Egan JJ, et al.: An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Resp Crit Care Med 2011; 183(6):788-824.

OFEV Formulary Submission Dossier Boehringer Ingelheim Pharmaceuticals, Inc. Oct. 30th 2014.

Esbriet Formulary Submission Dossier (unavailable as of 1-09-2015).

Esbriet. Package Insert. Reference ID 3643926. Accessed 10-17-2014.

Esbriet. Package Insert. Revised by manufacturer 09/2015. Accessed 12-14-2016.

Esbriet. Package Insert. Revised by manufacturer 01/2017. Accessed 05-05-2017, 12-21-2017.

Ofev®. Package Insert. Reference ID: 3643917. Accessed 10-20-2014.

Ofev®. Package Insert. Revised by manufacturer on 08/2016. Accessed 12-14-2016.

Ofev®. Package Insert. Revised by manufacturer on 08/2017. Accessed 12-21-2017.

UpToDate: Clinical manifestations and diagnosis of idiopathic pulmonary fibrosis. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-manifestations-and-diagnosis-of-idiopathic-pulmonary-fibrosis?source=search_result&search=idiopathic%20pulmonary%20fibrosis&selectedTitle=2~103

UpToDate: UpToDate: Treatment of idiopathic pulmonary fibrosis. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-idiopathic-pulmonary-fibrosis?source=search_result&search=idiopathic%20pulmonary%20fibrosis&selectedTitle=1~103

ESBRIET® (pirfenidone) oral capsule and oral tablet
OFEV® (nintedanib) oral capsule (cont.)

UpToDate: Idiopathic interstitial pneumonias: Clinical manifestations and pathology. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/idiopathic-interstitial-pneumonias-clinical-manifestations-and-pathology?source=see_link

UpToDate: Approach to the adult with interstitial lung disease: Diagnostic testing. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/approach-to-the-adult-with-interstitial-lung-disease-diagnostic-testing?source=search_result&search=idiopathic%20pulmonary%20fibrosis&selectedTitle=8~103

BlueCross BlueShield of Arizona

An Independent Licensee of the Blue Cross and Blue Shield Association

Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

BlueCross BlueShield of Arizona

An Independent Licensee of the Blue Cross and Blue Shield Association

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.