Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Idiopathic Pulmonary Fibrosis (Esbriet® / pirfenidone, Ofev® / nintedanib)

➢ **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6113KS-IPFB.pdf

Link to Drug List (Formulary):
https://www.bcbsks.com/drugs/

Professional
Original Effective Date: May 1, 2015
Revision Date(s): May 1, 2015; May 1, 2016; April 1, 2017; May 15, 2017; October 1, 2017; April 1, 2018
Current Effective Date: October 1, 2017

Institutional
Original Effective Date: May 1, 2015
Revision Date(s): May 1, 2015; May 1, 2016; April 1, 2017; May 15, 2017; October 1, 2017; April 1, 2018
Current Effective Date: October 1, 2017

State and Federal mandates and health plan member contract language, including specific provisions / exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

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)

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 267 mg tablets/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.

POLICY

Prior Authorization and Quantity Criteria for Approval

I. **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 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
      B. 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

C. 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
D. The patient does not have clinical evidence of active infection (e.g. bronchitis/bronchiolitis, pneumonia, and sinusitis)
AND
E. 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

Length of Approval: 12 months

Agent	Contraindication(s)
Esbriet	None
Ofev	None

II. **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. The requested agent has been clinically beneficial to the patient
   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

Brand (generic)	Quantity Limit
Esbriet (pirfenidone)	
267 mg capsules	6 capsules/day
267 mg tablets	6 tablets/day
801 mg tablets	3 tablets/day
Ofev (nintedanib)	
100 mg capsules	2 capsules/day
150 mg capsules	2 capsules/day

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 • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• 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 three or more lobes) • 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 • 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 fourth column)	• 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* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • 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]

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.

REVISIONS	
05-01-2015	Published 03-17-2015.
	This is a new stand-alone medical policy to the website from the New to Market Drugs policy formerly titled "Esbriet (pirfenidone) and Ofev (nintedanib)".
05-01-2016	Policy Published 04-29-2016. Policy Effective 05-01-2016.
	In Policy section: ▪ In Item I 2 F added “ONE of the following:” ▪ In Item I 2 F i added “If Ofev (nintedanib) is requested” and “or” to read “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”

	▪ In Item I 2 F ii added "If Esbriet (pirfenidone) is requested, the patient does not have severe hepatic impairment (Child-Pugh class C)," to read "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" ▪ In Item II 2 removed "ALL" and added "BOTH" to read "If IPF, BOTH of the following:" ▪ In Item II 3 added "ONE of the following:" ▪ In Item II 3 A added "If Ofev (nintedanib) is requested" and "or" to read "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" ▪ In Item II 3 B added "If Esbriet (pirfenidone) is requested, the patient does not have severe hepatic impairment (Child-Pugh class C)," to read "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"
	Rationale section updated
	References updated
04-01-2017	In Policy section: ▪ Added "Prior Authorization and Quantity Criteria for Approval" header ▪ In Item I removed: "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 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" ▪ In Item I G removed "and ≤90%" to read "The patient has a predicted FVC ≥50%" In Item II removed: "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 ▪ Added Quantity Limit chart, which had been erroneously left off the prior version.
	Rationale section updated
	References updated
05-15-2017	Policy published 06-09-2017. Policy retro-effective to 05-15-2017.
	In Description section: ▪ Updated FDA Approved Indications and Dosage chart to add Esbriet tablets
	In Policy section: ▪ Updated Quantity Limit chart to add Esbriet tablets
10-01-2017	In Policy section: ▪ In Item I 2 removed the following criteria: "A. The patient is a non-smoker confirmed by biochemical testing" "F. The prescriber has performed a baseline forced vital capacity (FVC) test G. The patient has a predicted FVC ≥50% H. The patient has a FEV1/FVC ratio ≥0.80 and is not <0.8 after administration of a bronchodilator I. The patient has a carbon monoxide diffusion capacity (%DLco) of ≥30% and ≤90%" ▪ In Item II removed "3. 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 added "The requested agent has been clinically beneficial to the patient". ▪ In Quantity Limits updated Esbriet 267 mg capsules from "9 capsules / day" to "6 capsules / day"
	Rationale section updated
	References updated

04-01-2018	Policy reviewed with no changes.

REFERENCES

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2. Ofev prescribing information. Boehringer Ingelheim. August 2016.
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10. Deleted.
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15. AMCP Dossier for Esbriet (pirfenidone). InterMune. October 28, 2014.
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17. American Thoracic Society Documents: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis- An Update of the 2011 Clinical Practice Guideline. Am J Resp Crit Care 2015; 192(2): e3-e19. Available at: http://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf .