nintedanib (Ofev®); prifenidone (Esbriet®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO138

Description

Nintedanib (Ofev) is an orally administered tyrosine kinase inhibitor.
Pirfenidone (Esbriet) is an orally administered pyridine that is thought to exert antifibrotic properties by decreasing fibroblast proliferation and the production of fibrosis associated proteins and cytokines.

Length of Authorization

- Initial:
  - Esbriet: 12 months
  - Ofev: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
nintedanib (Ofev)	Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis-associated interstitial lung disease (SSc-ILD); Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype	100 mg capsules	60 capsules/30 days
		150 mg capsules	
pirfenidone (generic Esbriet)	Idiopathic Pulmonary Fibrosis (IPF)	267 mg capsules or tablets	270 capsules or tablets/ 30 days
		534 mg tablets	120 tablets/30 days
		801 mg tablets	90 tablets/30 days
pirfenidone (Esbriet)	Idiopathic Pulmonary Fibrosis (IPF)	267 mg capsules or tablets	270 capsules or tablets/ 30 days
		801 mg tablets	90 tablets/30 days

Initial Evaluation

I. **Nintedanib (Ofev) and prifenidone (Esbriet)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**

B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
C. Nintedanib (Ofev) and prifenidone (Esbriet) will not be used in combination with each other; **AND**
D. Provider attests the member is currently abstaining from any form of smoking; **AND**
E. Documentation of baseline assessment [forced vital capacity (%FVC) **OR** carbon monoxide diffusing capacity (DLCO) **OR** six-minute walking distance (6MWD)]; **AND**
F. A diagnosis of one of the following:
    1. **Idiopathic pulmonary fibrosis (IPF); AND**
        i. Member has a usual interstitial pneumonia pattern (UIP) confirmed by a high resolution computed tomographic (HRCT) scan or surgical lung biopsy; **AND**
        ii. The request is for generic pirfenidone tablets; **OR**
            a. The request is for generic pirfenidone capsules, and treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
            b. The request is for brand Esbriet; **AND**
                i. Treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **AND**
                ii. Treatment with generic pirfenidone capsules has been ineffective, not tolerated, or contraindicated; **OR**
        iii. If the request is Nintedanib (Ofev), treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
    2. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
        i. Request is for nintedanib (Ofev); **AND**
        ii. The diagnosis confirmed by a high resolution computed tomographic (HRCT) scan; **OR**
    3. Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND
        i. Request is for nintedanib (Ofev); **AND**
        ii. Member has fibrotic features in lungs confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
        iii. Member has clinical signs of progression (eg. decline in %FVC with worsening respiratory symptoms **or** increasing extent of fibrotic changes on chest imaging)

II. Nintedanib (Ofev) and prifenidone (Esbriet) are considered investigational when used for all other conditions, including but not limited to:
    A. Bronchiolitis Obliterans Syndrome (BOS)
    B. Lymphangioleiomyomatosis (LAM)

C. Non-Small Cell Lung Cancer (NSCLC)
D. Malignant Pleural Mesothelioma (MPM)
E. Esophagogastric Cancer
F. Thyroid Cancer
G. Breast Cancer
H. Ovarian Cancer
I. Pancreatic Cancer
J. Used in combination with other medications within this policy
K. Multiple Sclerosis
L. Chronic Lung Allograft Dysfunction
M. Radiation-induced Lung Injury
N. Diabetic nephropathy
O. Glomerulosclerosis
P. Cardiac Failure

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. The member is not continuing therapy based off established therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for continuation through this health plan; **AND**
III. Provider attests that member has exhibited improvement or stability of disease symptoms (e.g., increase in forced vital capacity (%FVC), carbon monoxide diffusing capacity (DLCO), or six-minute walking distance (6MWD) from baseline); **AND**
IV. Nintedanib (Ofev) and prifenidone (Esbriet) will not be used in combination with each other; **AND**
V. Provider attests that member is currently abstaining from any form of smoking; **AND**
VI. A diagnosis of one of the following:
- **Idiopathic pulmonary fibrosis (IPF); AND**
    1. The request is for nintedanib (Ofev); **OR**
    2. The request is for generic pirfenidone tablets; **OR**
        a. The request is for generic pirfenidone capsules, and treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
        b. The request is for brand Esbriet; **AND**
            i. Treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **AND**

ii. Treatment with generic pirfenidone capsules has been ineffective, not tolerated, or contraindicated; **OR**

- **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
  i. Request is for nintedanib (Ofev); **OR**
- **Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND**
  i. Request is for nintedanib (Ofev)

Supporting Evidence

I. Nintedanib (Ofev) inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). It binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling 13 cascades.

II. Idiopathic pulmonary fibrosis (IPF) is an idiopathic chronic fibrosing interstitial pneumonia with a histopathologic or radiographic pattern of usual interstitial pneumonia (UIP).

III. High resolution computed tomography (HRCT) should be obtained in all patients suspected of having IPF. When the results of the HRCT cannot allow the clinician to make a confident diagnosis of IPF, surgical lung biopsy may be warranted. However, the decision requires assessment of the benefits of having a definitive diagnosis relative to the risks of the surgical procedure.

IV. For the treatment of IPF, nintedanib (Ofev) was studied in 1,066 patients with IPF in two Phase 3 trials (INPULSIS-1 and INPULSIS-2). These were randomized, double-blind, placebo-controlled studies comparing treatment with nintedanib (Ofev) 150 mg twice daily to placebo for 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL):
  i. INPULSIS-1: -114.7 mL per year in the nintedanib (Ofev) group and -239.9 mL per year in the placebo group over week 52 (absolute difference of 125.2 mL, 95% CI: 77.7, 172.8; $p<0.001$)
  ii. INPULSIS-2: -113.6 mL per year in the nintedanib (Ofev) group and -207.3 mL per year in the placebo group over week 52 (absolute difference of 93.7 mL, 95% CI: 44.8, 142.7; $p<0.001$)
- The secondary lung function outcomes:

	INPULSIS-1			INPULSIS-2		
End Points	**Nintedanib (N=307)**	**Placebo (N=204)**	**95% CI; *P* value**	**Nintedanib (N=327)**	**Placebo (N-217)**	**95% CI; *P* value**
Adjusted absolute mean change from baseline in FVC (mL)	-95.1	-205.0	109.9 (71.3, 148.6; *P*<0.001)	-95.3	-205.0	109.8 (70.9, 148.6; *P*<0.001)
Adjusted absolute mean change from	-2.8%	-6.0%	3.2% (2.1, 4.3; *P*<0.001)	-3.1%	-6.2%	3.1% (1.9, 4.3; *P*<0.001)

baseline in FVC (% predicted)						
FVC response at week 52 (%): FVC decline ≤ 5%	52.8%	38.2%	1.85% (1.28, 2.66; *p*=0.001)	53.2%	39.3%	1.79% (1.23, 2.55; *p*=0.001)
FVC response at week 52 (%): FVC decline ≤ 10%	70.6%	56.9%	1.91% (1.32, 2.79; *P*<0.001)	69.6%	63.9%	1.29% (0.89, 1.86; *p*=0.18)

V. The presence of SSc-ILD is defined by the identification of fibrotic features on HRCT scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.

VI. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).

VII. For systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib (Ofev) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial (N=576) (SENSCIS trial). Patients received either nintedanib (Ofev) 150 mg twice daily (N=228) or placebo (N=288) for at least 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL): -52.4 mL per year in the nintedanib (Ofev) group and -93.3 mL per year in the placebo group over week 52 (absolute difference of 40.9 mL, 95% CI: 2.9, 79.0; *p*=0.04).

VIII. Safety and efficacy of nintedanib (Ofev) have not been established in pediatric patients.

IX. The safety and efficacy of pirfenidone (Esbriet) was studied in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients (40 to 80 years of age) with idiopathic pulmonary fibrosis (IPF) and a %FVC of at least 50%.

A. Study One: 52-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=278) versus placebo (n=277). The primary efficacy outcome for the change in %FVC at week 52 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.

B. Study Two: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=174) or pirfenidone (Esbriet) 1197 mg/day (n=87) to placebo (n=174). The primary efficacy outcome for the change in %FVC at week 72 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.

C. Study Three: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=171) to placebo (n=173). In this study, there was no statistically significant difference at week 72 for the change in %FVC from baseline when compared to placebo.

X. The exact etiology of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

XI. According to the American Thoracic Society guidelines, the diagnosis of IPF requires:
   A. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
   B. The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.
   C. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

XII. The clinical efficacy of nitendanib (Ofev) has been studied in patients with chronic fibrosing ILDs with a progressive phenotype in a randomized, double-blind, placebo-controlled phase 3 trial (Study 5). A total of 663 patients were randomized in a 1:1 ratio to receive either nitendanib (Ofev) 150 mg twice daily or matching placebo for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern.
   A. The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. There was a statistically significant reduction by 107 mL in patients receiving OFEV compared to patients receiving placebo.

XIII. High-resolution computed tomography (HRCT) of the chest is mandatory in order to assess if ILD is present and, if so, to begin the differential diagnosis.

XIV. Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in FVC and gas exchange (DLCO), worsening of symptoms and exercise capacity (6MWD), and deterioration in health-related quality of life.
   A. There is no standardized definition of PF-ILD that clinicians and researchers have agreed upon. Several criteria have been used to define progression in patients with IPF, with most of these based on an absolute or relative decline in FVC and diffusing capacity of the lung for DLCO of greater than or equal to 5–10% or greater than or equal to 10–15%, a decline in 6MWD > 50 m, or worsening dyspnea and quality of life scores. FVC is a reliable, valid, and responsive measure of clinical status in patients, and a decline of 2-6%, although small, represents a clinically important difference. FVC is used as a surrogate marker of disease severity and progression. DLCO is considered a standard predictor of survival. The distance walked in the 6MWT is used in a variety of pulmonary diseases and is predictive of mortality.

Investigational or Not Medically Necessary Uses

I. There is currently no evidence to suggest safety and/or efficacy with nitendanib (Ofev) or pirfenidone (Esbriet), when used for the treatment of bronchiolitis obliterans syndrome (BOS), lymphangioleiomyomatosis (LAM), non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), esophagogastric cancer, thyroid cancer, breast cancer, ovarian cancer, or pancreatic cancer. Further there is no evidence to support the use of nitendanib (Ofev) in combination with pirfenidone (Esbriet).

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added step for branded Esbriet through both generic tablets and capsules prior to brand use; added step through generic tablets prior to use of generic capsules	01/2023
Added generic pirfenidone 534mg tablets to QL table	08/2022
Added new generic pirfenidone, requiring trial of generic pirfenidone prior to brand Esbriet	06/2022
• Added nintedanib (Ofev) to the Moda Split Fill program • Added criteria for nintedanib (Ofev) new indication Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype [request is for nintedanib (Ofev) and member has greater than 10% fibrotic features confirmed by a high resolution computed tomographic (HRCT) scan and clinical signs of progression (eg. decline in %FVC with worsening of respiratory symptoms, or increasing extent of fibrotic changes on chest imaging)]. • Added criteria for baseline assessment [eg. forced vital capacity (%FVC) or carbon monoxide diffusing capacity (DLCO) or six minute walking distance (6MWD)]	06/2020
Criteria updated to new policy format. Specific changes include: Updated idiopathic pulmonary fibrosis (IPF) initial evaluation. Combined policies with pirfenidone (Esbriet) for the indication of idiopathic pulmonary fibrosis (IPF). Added new indication of systemic sclerosis-associated interstitial lung disease (SSc-ILD), SSc-	12/2019

ILD initial evaluation, investigational use, and renewal evaluation. Added new supporting evidences and references.	
Policy created	10/2014