nintedanib (Ofev®); prifenidone (Esbriet®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO138

Description

Nintedanib (Ofev) is an orally administered tyrosine kinase inhibitor while 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: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
nintedanib (Ofev)	100 mg capsules	Idiopathic pulmonary fibrosis (IPF) Systemic sclerosis-associated interstitial lung disease (SSc-ILD)	60 capsules/30 days
	150 mg capsules		60 capsules/30 days
pirfenidone (Esbriet)	267 mg capsules or tablets	Idiopathic Pulmonary Fibrosis (IPF)	63 capsules or tablets/14 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 <u>any form of smoking</u>; **AND**
   E. 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; **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

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 %FVC 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. If for the diagnosis of **Systemic sclerosis-associated interstitial lung disease (SSc-ILD):**
   A. 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 does not allow the clinician to make a confident

diagnosis of IPF, surgical lung biopsy may be indicated. 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 baseline in FVC (% predicted)	-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)
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 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 percent forced vital capacity (%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.

Investigational or Not Medically Necessary Uses

I. There is currently no evidence to suggest safety and/or efficacy with nitendanib (Ofev), 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, pancreatic cancer, and used in combination with pirfenidone (Esbriet).

References

1. Ofev [package insert].Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2019.
2. Raghu G, Remy-jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68. doi: 10.1164/rccm.201807-1255ST.
3. Richeldi L, Du bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-82. doi: 10.1056/NEJMoa1402584.
4. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med*. 2019;380(26):2518-2528. doi: 10.1056/NEJMoa1903076.
5. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). *Respir Res*. 2019;20(1):13. doi: 10.1186/s12931-019-0980-7.
6. Esbriet [Prescribing Information]. South San Francisco, CA: Genentech, Inc. July 2019.

Policy Implementation/Update:

Date Created	October 2014
Date Effective	November 2014

Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	**Date**
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-ILD initial evaluation, investigational use, and renewal evaluation. Added new supporting evidences and references.	12/2019