

Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider nintedanib (Ofev[®])[‡] or pirfenidone (Esbriet[®], branded Pirfenidone 534 mg tablets, generics)[‡] for the treatment of their respective Food and Drug Administration (FDA) approved indications to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for nintedanib (Ofev) or pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets, generics) will be considered when all of the following criteria are met for the requested drug and the requested indication:

- For pirfenidone (Esbriet, generics) or nintedanib (Ofev) requests in idiopathic pulmonary fibrosis:
 - Nintedanib (Ofev) and pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets, generics) are NOT used as combination therapy; AND
 - Patient has a confirmed diagnosis of idiopathic pulmonary fibrosis by:
 - Exclusion of other known causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective tissue disease, drug toxicity); AND
 - ❖ The presence of usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy; OR
 - ❖ A combination of HRCT and surgical lung biopsy pattern that is indicative of a diagnosis of IPF in patients subjected to surgical lung biopsy; AND

Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

- If the request is for brand pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets), patient has tried and failed (e.g., intolerance or inadequate response) GENERIC pirfenidone unless there is clinical evidence or patient history that suggests GENERIC pirfenidone will be ineffective or cause an adverse reaction to the patient; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- If the request is for branded Pirfenidone 534 mg tablets, documentation of clinical evidence or patient history is provided suggesting that the use of generic pirfenidone will be ineffective or cause an adverse reaction to the patient; OR
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- For nintedanib (Ofev) requests in Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD):
 - Patient has a diagnosis of Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD) as confirmed by chest high resolution computed tomography (HRCT) WITHOUT contrast; AND
 - Patient's HRCT indicates at least 10% fibrosis; AND
*(Note: This specific patient selection criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
 - Patient is experiencing a decline in pulmonary function; AND
 - Patient has Forced Vital Capacity (FVC) greater than or equal to 40% of the predicted value; AND
*(Note: This specific patient selection criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met.)*
 - Patient has tried and failed (e.g., intolerance or inadequate response) mycophenolate mofetil after at least 6 months of therapy unless there is clinical evidence or patient history that suggests the use of mycophenolate mofetil will be ineffective or cause an adverse reaction to the patient; AND
*(Note that this specific patient selection criterion is an additional company requirement and will be denied as not medically necessary** if not met.)*
 - Patient will not use the requested drug in combination with tocilizumab (Actemra®)‡ for the treatment of SSc-ILD; OR



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

- For nintedanib (Ofev) requests in Chronic Fibrosing Interstitial Lung Disease with a Progressive Phenotype:
 - Patient has a diagnosis of Chronic Fibrosing Interstitial Lung Disease with a Progressive Phenotype; AND
 - Fibrotic interstitial lung disease is confirmed by the presence of pulmonary fibrosis on high-resolution computed tomography (HRCT) involving at least 10 percent of the lungs OR a lung biopsy confirming the presence of fibrotic interstitial lung disease; AND
 - Patient's Forced Vital Capacity (FVC) is greater than or equal to 45% of the predicted value; AND
*(Note: This specific patient selection criterion is an additional company requirement, based on clinical trials, and will be denied as not medically necessary** if not met.)*
 - Patient meets one of the following:
 - Patient had a FVC decline of greater than or equal to 10% in the previous 24 months; OR
 - Patient had a FVC decline greater than or equal to 5% but less than 10% with worsening symptoms or imaging in the previous 24 months; OR
 - Patient had worsening symptoms AND worsening imaging in the previous 24 months; OR
*(Note: This specific patient selection criterion is an additional company requirement, based on clinical trials, and will be denied as not medically necessary** if not met.)*
- For ALL renewal requests:
 - Patient had an initial authorization; AND
 - Patient is benefitting from the requested medication as supported by provider documentation; AND
 - If the request is for brand pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets), patient has tried and failed (e.g., intolerance or inadequate response) GENERIC pirfenidone unless there is clinical evidence or patient history that suggests GENERIC pirfenidone will be ineffective or cause an adverse reaction to the patient; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
 - If the request is for branded Pirfenidone 534 mg tablets, documentation of clinical evidence or patient history is provided suggesting that the use of generic pirfenidone will be ineffective or cause an adverse reaction to the patient.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of nintedanib (Ofev) when any of the following are NOT met for the treatment of SSc-ILD to be **not medically necessary**:**

- Patient's HRCT indicates at least 10% fibrosis
- Patient has FVC greater than or equal to 40% of the predicted value
- Patient has tried and failed (e.g., intolerance or inadequate response) mycophenolate mofetil after at least 6 months of therapy

Based on review of available data, the Company considers the use of nintedanib (Ofev) when the following are NOT met for the treatment of Chronic Fibrosing Interstitial Lung Disease with a Progressive Phenotype to be **not medically necessary**:**

- Patient's FVC is greater than or equal to 45% of the predicted value
- Patient meets one of the following:
 - Patient had a FVC decline of greater than or equal to 10% in the previous 24 months; OR
 - Patient had a FVC decline greater than or equal to 5% but less than 10% with worsening symptoms or imaging in the previous 24 months; OR
 - Patient had worsening symptoms AND worsening imaging in the previous 24 months.

Based on review of available data, the Company considers the use of brand pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets) for the treatment of idiopathic pulmonary fibrosis when the patient has not tried and failed GENERIC pirfenidone to be **not medically necessary**.**

Based on review of available data, the Company considers the use of branded Pirfenidone 534 mg tablets when there is no clinical evidence or patient history that suggests the use of generic pirfenidone will be ineffective or cause an adverse reaction to the patient to be **not medically necessary**.**

Based on review of available data, the Company considers the use of nintedanib (Ofev) or pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets, generics) for continuation of therapy when the patient is NOT benefitting from the requested medication to be **not medically necessary**.**



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of nintedanib (Ofev) or pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets, generics) when patient selection criteria are NOT met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinase and non-receptor tyrosine kinases. It is believed that it mainly works by vascular endothelial growth factor (VEGFR) inhibition. Nintedanib is dosed at 150 mg twice daily. There is also consideration for dose reductions as the drug is also supplied in a 100 mg capsule dosage form. Pirfenidone's mechanism of action is unknown, however it does belong to the chemical class of pyridone drugs. Pirfenidone (Esbriet, branded pirfenidone 534 mg tablets, and its generic) is available in several different dosage forms, which include 267 mg capsules, 267 mg tablets, and 801 mg tablets. Branded Pirfenidone 534 mg tablets were originally approved as brand Esbriet tablets but was discontinued in 2019 for reasons other than safety and efficacy and is only available as an authorized generic product. Pirfenidone is dosed at 801 mg three times a day. Dose modifications are also recommended for this drug. The availability of the generic product gives a more economical, yet equally efficacious, option for treatment compared to the brand product.

Idiopathic Pulmonary Fibrosis

There are currently only two drugs that are FDA approved for the treatment of interstitial pulmonary fibrosis, nintedanib (Ofev) and pirfenidone (Esbriet, branded Pirfenidone 534 mg tablets, generics). Idiopathic pulmonary fibrosis is a rare, chronic, fatal disease characterized by a progressive and irreversible loss of lung function (decline in forced vital capacity [FVC]). Idiopathic pulmonary fibrosis usually occurs in middle aged to elderly adults and is more common in males. Survival rates are poor in patients with interstitial pulmonary fibrosis.

Systemic Sclerosis Associated Interstitial Lung Disease

Ofev and Actemra are currently the only FDA approved medications to slow the rate of decline in pulmonary function in patients with systemic sclerosis associated interstitial lung disease. Scleroderma, or systemic sclerosis, is an autoimmune condition affecting the skin and other organs in the body. The main finding in scleroderma is thickening of the skin and other inflammation and scarring of many body parts. There are two major subsets of systemic sclerosis: diffuse cutaneous systemic sclerosis and limited cutaneous systemic sclerosis. As the nomenclature insinuates, the diffuse variety has extensive skin involvement. Patients with this subset are more likely to develop interstitial lung disease. Interstitial lung disease is a frequent complication of systemic sclerosis.



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

Early interstitial lung disease is typically asymptomatic, however it is progressive and has a poor prognosis. Diagnosis involves use of HRCT without the use of contrast so as to avoid pseudo-ground-glass opacities or so-called hurricane artifacts. Treatment of this condition often includes use of an immunosuppressant, such as mycophenolate mofetil or cyclophosphamide. The Scleroderma Lung Study II compared mycophenolate mofetil with cyclophosphamide and found no difference in lung function, however there was better tolerance to mycophenolate mofetil.

Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype

Ofev is currently the only FDA approved medication for the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype. Interstitial lung disease is discussed above, however it should be noted that this approval is specifically for the progressive phenotype of interstitial lung disease.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Both Esbriet and Ofev were approved in October of 2014 for the treatment of IPF. These two agents are the first drugs that are FDA approved for this indication. In September of 2019, Ofev was approved to slow the rate of decline in pulmonary function in patients with systemic sclerosis associated interstitial lung disease. In March of 2020, Ofev was approved for the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype. In May of 2022, Esbriet 267 mg and 801 mg tablets became available as generic products. Esbriet 534 mg film coated tablets were initially approved in January of 2017 and were withdrawn from the market in 2019. In August of 2022, branded Pirfenidone 534 mg tablets became available. Generic pirfenidone capsules became available in January of 2023.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Interstitial Pulmonary Fibrosis (IPF)

The clinical efficacy of Ofev was established in 3 pivotal trials (Studies 1, 2, and 3). These were randomized, double-blind, placebo-controlled studies comparing treatment with Ofev 150 mg twice daily to placebo for 52 weeks. Studies 2 and 3 were identical in design. Study 1 was very similar in design. Patients were randomized in a 3:2 ratio (1:1 for Study 1) to either Ofev 150 mg or placebo twice daily for 52 weeks. Study 1 also included other treatment arms (50 mg daily, 50 mg twice daily, and 100 mg twice daily) that are not further discussed. The primary endpoint was the annual rate of decline in FVC. Time to first acute IPF exacerbation was a key secondary endpoint in Studies



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

2 and 3 and a secondary endpoint in Study 1. Change from baseline in FVC percent predicted and survival were additional secondary endpoints in all studies. A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving Ofev compared to patients receiving placebo based on the random coefficient regression model, adjusted for gender, height, and age. The rate of decline for Ofev in the 3 studies ranged from -60 mL to -115 mL vs. a rate of decline ranging from -191mL to -240 mL in the placebo group. The treatment effect on FVC was consistent in all 3 studies.

The efficacy of Esbriet was evaluated in patients with IPF in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3). Study 1 was a 52 week trial comparing Esbriet 2403 mg/day vs. placebo in patients with IPF. Studies 2 and 3 were nearly identical, however Study 2 had an intermediate dose treatment arm. The study drug was administered three times daily. The primary endpoint was the change in percent predicted FVC from baseline to study end. The first two studies showed a statistically significant change in the percent FVC from baseline. The third study showed no statistically significant difference for the change in percent FVC from baseline.

Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD)

The clinical efficacy of Ofev has been studied in patients with SSc-ILD in a randomized, double-blind, placebo-controlled phase 3 trial (Study 4). A total of 580 patients were randomized in a 1:1 ratio to receive either Ofev 150 mg twice daily or matching placebo for at least 52 weeks, of which 576 patients were treated. Individual patients remained on blinded trial treatment for up to 100 weeks. The primary endpoint was the annual rate of decline in FVC over 52 weeks. The absolute change from baseline in the modified Rodnan skin score (mRSS) at week 52 was a key secondary endpoint. Mortality over the whole trial was an additional secondary endpoint. Patients were diagnosed with SSc-ILD based upon the 2013 American College of Rheumatology / European League Against Rheumatism classification criteria for SSc with onset of disease (first non-Raynaud symptom) of less than 7 years and greater than or equal to 10% fibrosis on a chest high resolution computed tomography (HRCT) scan conducted within the previous 12 months. Patients were required to have an FVC greater than or equal to 40% of predicted and a carbon monoxide diffusing capacity (DLCO) 30-89% of predicted. At baseline, 49% of patients were on stable therapy with mycophenolate. The annual rate of decline in FVC was -52 mL in the Ofev group vs. -93 mL in the placebo group. No benefit in Modified Rodnan Skin Score or survival were observed in patients receiving Ofev.

Chronic Fibrosing Interstitial Lung Diseases (ILDs) with a Progressive Phenotype

The clinical efficacy of Ofev was 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 Ofev 150 mg twice daily or matching placebo for at least 52 weeks. The primary endpoint was the annual rate of decline in FVC over 52 weeks.



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

Patients with a clinical diagnosis of a chronic fibrosing ILD were selected if they had relevant fibrosis (greater than 10% fibrotic features) on HRCT and presented with clinical signs of progression (defined as FVC decline $\geq 10\%$, FVC decline $\geq 5\%$ and $<10\%$ with worsening symptoms or imaging, or worsening symptoms and worsening imaging all in the 24 months prior to screening). Patients were required to have an FVC greater than or equal to 45% of predicted. There was a statistically significant reduction in the annual rate of decline in FVC over 52 weeks in patients receiving Ofev compared to patients receiving placebo. The annual rate of decline in FVC over 52 weeks was significantly reduced by 107 mL in patients receiving Ofev compared to patients receiving placebo.

References

1. Ofev [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, Connecticut. Updated October 2020.
2. Esbriet [package insert]. Intermune, Inc. Brisbane, California. Updated February 2022.
3. Ofev. Express Scripts Drug Evaluation. Updated October 2014.
4. Esbriet Express Scripts Drug Evaluation. Updated October 2014.
5. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med, Vol.183, No. 6, (2011), pp 788-824.
6. UpToDate. High resolution computed tomography of the lungs. Updated August 2019.
7. UpToDate. Treatment and prognosis of interstitial lung disease in systemic sclerosis (scleroderma). Updated October 2019.
8. Pirfenidone [package insert]. Laurus Labs Limited. Visakhapatnam, India. Updated April 2022.

Policy History

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

01/08/2015 Medical Policy Committee review

01/21/2015 Medical Policy Implementation Committee approval. New policy.

01/07/2016 Medical Policy Committee review

01/22/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/05/2017 Medical Policy Committee review

01/18/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/04/2018 Medical Policy Committee review

01/17/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

01/10/2019 Medical Policy Committee review

01/23/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/03/2020 Medical Policy Committee review

01/08/2020 Medical Policy Implementation Committee approval. Included the newest FDA approved indication, systemic sclerosis associated interstitial lung disease. Update applicable sections of the policy. Updated title to include interstitial lung disease.

01/07/2021 Medical Policy Committee review

01/13/2021 Medical Policy Implementation Committee approval. Added a new FDA approved indication, chronic fibrosing interstitial lung disease with a progressive phenotype. Updated applicable sections of the policy.

01/06/2022 Medical Policy Committee review

01/12/2022 Medical Policy Implementation Committee approval. Added a new criterion under SSc-ILD to prevent combination use of Actemra (newly approved for SSc-ILD) and Ofev.

09/01/2022 Medical Policy Committee review

09/14/2022 Medical Policy Implementation Committee approval. Generic pirfenidone added to policy with criterion requiring trial of generic prior to brand.

12/01/2022 Medical Policy Committee review

12/14/2022 Medical Policy Implementation Committee approval. Added branded Pirfenidone 534 mg to the policy with criteria. Updated relevant background information.

11/02/2023 Medical Policy Committee review

11/08/2023 Medical Policy Implementation Committee approval. Updated background information to reflect availability of generic pirfenidone capsules.

11/07/2024 Medical Policy Committee review

11/13/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or



Pharmacotherapy for Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

Policy # 00467

Original Effective Date: 01/21/2015

Current Effective Date: 12/09/2024

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

