Effective Date..... **11/15/2023**
Next Review Date.....**11/15/2024**
Coverage Policy Number **IP0312**

Nintedanib

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for nintedanib (**Ofev**®).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Nintedanib (Ofev) is considered medically necessary when ONE of the following is met:

1. **Idiopathic Pulmonary Fibrosis.** Individual meets **ALL** of the following criteria:
    A. Age 18 years or older
    B. Forced vital capacity is at least 40% of the predicted value
    C. Diagnosis of idiopathic pulmonary fibrosis is confirmed by **ONE** of the following:
        i. Findings on high-resolution computed tomography indicate usual interstitial pneumonia (for example, subpleural and basal predominant distribution and honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis)

ii. Surgical lung biopsy demonstrates usual interstitial pneumonia
iii. The combination of high-resolution computed tomography and biopsy pattern are both indicative of "probable" usual interstitial pneumonia

D. Exclusion of other potential causes of interstitial lung disease (for example, medication use, environmental exposures at home/work)
E. Medication is prescribed by, or in consultation with, a pulmonologist
F. Refer to Non-covered Product Criteria in table below for Individual and Family Plans:

Individual and Family Plan Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Ofev (nintedanib)	Documentation of **ONE** of the following: 1. Failure, contraindication or intolerance to pirfenidone (Esbriet) tablet or capsule [may require prior authorization] 2. Individual is currently using nintedanib (Ofev)

2. **Interstitial Lung Diseases, Chronic Fibrosing with a Progressive Phenotype.** Individual meets **ALL** of the following criteria:
   A. Age 18 years or older
   B. Forced vital capacity is at least 40% of the predicted value
   C. Documentation the individual has fibrosing lung disease on high-resolution computed tomography
   D. Individual has clinical signs of progression
   Examples of clinical signs of progression include a forced vital capacity decline at least 10% as compared to previous pulmonary function studies or forced vital capacity decline at least 5% to less than 10% with worsening symptoms and/or worsening imaging
   E. Medication is prescribed by, or in consultation with, a pulmonologist

3. **Interstitial Lung Disease Associated with Systemic Sclerosis.** Individual meets **ALL** of the following criteria:
   A. Age 18 years or older
   B. Forced vital capacity is at least 40% of the predicted value
   C. Diagnosis is confirmed by high-resolution computed tomography
   D. Medication is prescribed by or in consultation with a pulmonologist or a rheumatologist

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Nintedanib (Ofev) is considered medically necessary for continued use when **BOTH** of the following are met:
1. Pre-treatment clinical condition met the initial criteria
2. There is documentation of beneficial response (for example: a reduction in the anticipated decline in forced vital capacity; six-minute walk distance; and/or a reduction in the number or severity of disease-related exacerbations)

Authorization Duration

Initial and reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

Ofev is Being Used Concomitantly with Pirfenidone (Esbriet®). Esbriet is another medication indicated for IPF. The effectiveness and safety of concomitant use of Ofev with Esbriet has not been established. The 2015 ATS/ERS/JRS/ALAT clinical practice guideline regarding the treatment of idiopathic pulmonary fibrosis (an update of the 2011 clinical practice guideline) does not recommend taking Ofev and Esbriet in combination.[16] A small exploratory study was done in which individuals with IPF receiving Ofev added on to Esbriet.[18] Further research is needed to determine the utility of this combination regimen.

Background

OVERVIEW
Ofev, a kinase inhibitor, is indicated for the following uses:[1]

- **Idiopathic pulmonary fibrosis** (IPF), treatment.
- **Interstitial lung diseases, chronic fibrosing with a progressive phenotype**, treatment.
- **Interstitial lung disease associated with systemic sclerosis**, to slow the rate of decline in pulmonary function.

The safety and effectiveness of Ofev in pediatric patients have not been established.[1]

Disease Overview
IPF is a form of chronic interstitial lung pneumonia associated with histologic pattern of usual interstitial pneumonia (UIP).[2] The condition is specific for patients that have clinical features and the histologic pattern of UIP or a classical high-resolution computed tomography (HRCT) scan for IPF. In this lung condition there is cellular proliferation, interstitial inflammation, fibrosis, or the combination of these findings, within the alveolar wall that is not due to infection or cancer.[3] IPF is rather rare and the prevalence in the US ranges from 10 to 60 cases per 100,000. However, in one study, the prevalence was 494 cases per 100,000 in 2011 in adults > 65 years of age, which is higher than previous information. The disease mainly impacts older adults.[2] Symptoms include a progressive dry cough and exertional dyspnea. Patients experience a high disease burden with hospital admissions. The clinical course varies among patients but the mean survival after symptom onset is usually 3 to 5 years. The cause is unknown but environmental and occupational hazards may play a role, as well as a history of smoking. Medical therapy is only modestly effective and mainly shows the rate of disease progression. Agents FDA-approved for IPF are Ofev and Esbriet® (pirfenidone capsules and film-coated tablets). Lung transplantation is a therapeutic option.

Interstitial lung disease is a common manifestation of systemic sclerosis and is a leading cause of death.[4-6] Among patients who have systemic sclerosis, up to one-half of patients may have interstitial lung disease.[7] The estimate prevalence and annual incidence of systemic sclerosis-associated interstitial lung disease is 1.7 to 4.2 and 0.1 to 0.4 per 100,000 individuals, respectively.[7] However, it is notable that systemic sclerosis is a connective disease that it not limited to the lungs but impacts the skin, blood vessels, heart, kidneys, gastrointestinal tract, and musculoskeletal system. The condition displays great heterogeneity and can be challenging to treat.[4] When the disease affects the internal organs, significant morbidity and mortality may result. Mycophenolate, cyclophosphamide, and azathioprine are immunosuppressants that are utilized in the treatment of interstitial lung disease associated with systemic sclerosis. Corticosteroids are also used. Besides Ofev, Actemra® (tocilizumab subcutaneous injection) is also indicated for use in patients with systemic sclerosis-associated interstitial lung disease.

Clinical Efficacy

Idiopathic Pulmonary Fibrosis (IPF)

The clinical efficacy of Ofev if patients with IPF was established in one Phase II study and two Phase III studies that were identical in design (n = 1,231).[1,8,9] The trials were randomized, double-blind, placebo-controlled studies comparing treatment with Ofev 150 mg twice daily with placebo for 52 weeks. In the two Phase III studies, patients were ≥ 40 years of age and had a forced vital capacity (FVC) ≥ 50% of the predicted value. The diagnosis was confirmed by HRCT and, if available, surgical lung biopsy specimens were assessed. For all three studies, a statistically significant reduction in the annual rate of decline of FVC was observed in patients receiving Ofev compared with patients receiving placebo. Also, data shows that the proportion of patients that demonstrated categorical declines in lung function was lower for patients given Ofev compared with placebo. Acute IPF exacerbations were also reduced.[1,8,9] Some information suggests that patients who have FVC < 50% of predicted may also have some benefits from therapy.[10-13]

Interstitial Lung Diseases, Chronic Fibrosing with a Progressive Phenotype

The efficacy of Ofev was assessed in patients ≥ 18 years of age with chronic fibrosis interstitial lung diseases with a progressive phenotype in a Phase III, double-blind, placebo-controlled trial (INBUILD) [n = 663].[1,14,15] Patients received Ofev 150 mg BID or placebo for at least 52 weeks and the main endpoint was the annual rate in decline in FVC over 52 weeks. Patients who had a clinical diagnosis of chronic fibrosing interstitial lung disease were involved in the trial if they had relevant fibrosis (greater than 10% fibrotic features) and had clinical signs of progression (e.g., FVC decline ≥ 10%, recent FVC decline ≥ 5% but < 10% with worsening symptoms or imaging, or worsening symptoms and worsening imaging). Patients were required to have an FVC ≥ 45% of predicted and a diffusing capacity of the lung for carbon monoxide of at least 30% and < 80% of predicted.

Interstitial Lung Disease Associated with Systemic Sclerosis

The efficacy of Ofev was established in SENSCIS, a randomized, double-blind, placebo-controlled Phase III trial in patients ≥ 18 years of age with systemic sclerosis-related interstitial lung disease (n = 576).[1,5] Patients were randomized to Ofev or placebo for at least 52 weeks and up to 100 weeks. Patients had ≥ 10% fibrosis on a chest HRCT scan conducted within the previous 12 months and had an FVC ≥ 40% of predicted. The primary efficacy endpoint was the annual rate of decline in FVC over 52 weeks. The annual rate of decline of FVC over 52 weeks was significantly reduced by 41 mL in patients receiving Ofev vs. placebo (-52 mL for Ofev vs. -93 mL with placebo).

Guidelines

In 2015, the clinical practice guideline from the American Thoracic Society (ATS), European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) on the treatment of IPF were updated.[16] Regarding Ofev, the guideline suggests use of this medication (conditional recommendation, moderate confidence in estimates of effect). The guideline notes that the data with Ofev focuses on patients with IPF who have mild to moderate impairment in pulmonary function tests. It is not known if the benefits would differ among patients with more severe impairment in pulmonary function testing or in patients who have other comorbidities.[16] Updated recommendations by this group in 2022 support use of Ofev in patients with IPF.[17] Regarding the treatment of progressive pulmonary fibrosis, Ofev is a suggested treatment in patients who have failed standard management for fibrotic interstitial lung disease (e.g., immunosuppressive treatment) other than IPF.

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