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Last P&T Approval/Version: 10/25/2023
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Policy Number: C16582-A

Esbriet (pirfenidone)

PRODUCTS AFFECTED

Esbriet (pirfenidone), pirfenidone

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Idiopathic Pulmonary Fibrosis (IPF)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. IDIOPATHIC PULMONARY FIBROSIS:
1. Documented diagnosis of idiopathic pulmonary fibrosis (IPF) confirmed by the presence of usual interstitial pneumonia (UIP) via high-resolution computed tomography (HRCT) AND/OR Surgical lung biopsy OR transbronchial lung cryobiopsy (TBLC) [DOCUMENTATION

REQUIRED: *Submit chest HRCT study, pathology report if a surgical lung biopsy was performed, or TBLC result*]
AND

2. Prescriber attests that member does not have other known causes of interstitial lung disease.
   a) No significant environmental exposure known to cause pulmonary fibrosis (e.g., drugs, asbestos, beryllium, radiation, raising birds/livestock, and metal)
   AND
   b) 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) No diagnosis of any connective tissue disease known to cause interstitial lung disease (e.g., scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis)
   AND
3. Documented baseline Forced Vital Capacity (%FVC) ≥ 50% of expected value for the member [DOCUMENTATION REQUIRED]
   AND
4. Documented baseline diffusing capacity of the lungs for carbon monoxide (%DLCO) ≥ 30% of expected value for the member [DOCUMENTATION REQUIRED]
   AND
5. Prescriber attests to obtaining a liver function test at baseline confirming that member does NOT have ANY of the following (including ALT, AST, and bilirubin):
   a. Significant impaired liver function [ALT/AST more than 3 times the upper limit of normal (ULN)]
   b. Total bilirubin greater than the ULN
   c. Alkaline phosphatase greater than 3 times the ULN
   d. Severe hepatic impairment (Child- Pugh C)

   AND
6. Prescriber attests the member does not have end-stage renal disease requiring dialysis
   AND
7. Prescriber attests that member is a non-smoker OR has been counseled on actively working to quit smoking in order to not alter the efficacy profile of Esbriet (pirfenidone) per the FDA label
   AND
8. Prescriber attests that Esbriet (pirfenidone) will not be used concurrently with Ofev (nintedanib)

CONTINUATION OF THERAPY:

A. IDIOPATHIC PULMONARY FIBROSIS:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
2. Prescriber attests that liver function tests continue to be monitored per label (monthly for the first 6 months and every 3 months thereafter) or as clinically indicated
   AND
3. Documentation of stabilized or improved condition as indicated by one of the following [DOCUMENTATION REQUIRED]:
   a. < 10% decline in percent predicted FVC [NOTE: A >10% decline in FVC over a 12-month period indicates disease progression and continuation of treatment will not be authorized], OR
   b. < 15% decline in predicted DLCO during a 6-month period

   AND
4. Prescriber attests that member continues to be a non-smoker or is actively working to quit smoking in order to not alter the efficacy profile of Esbriet (pirfenidone) per the FDA

label
AND

5. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:
Initial authorization: 6 months**,** Continuation of therapy authorization: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified pulmonologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
801 mg 3 times daily with food (total dose: 2,403 mg/day)

Maximum Quantity Limits – 30 day supply per fill, fewest tablets/capsules to make dose
Strong CYP1A2 inhibitors (e.g., fluvoxamine): Reduce pirfenidone to 267 mg 3 times daily (total dose: 801 mg/day).
Moderate CYP1A2 inhibitors (e.g., ciprofloxacin): Reduce pirfenidone to 534 mg 3 times daily (total dose: 1,602 mg/day) when used concomitantly with ciprofloxacin 1,500 mg/day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Pulmonary Fibrosis Agents

FDA-APPROVED USES:
Indicated for the treatment of idiopathic pulmonary fibrosis (IPF)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Idiopathic pulmonary fibrosis (IPF) is a rare chronic, progressive, severely debilitating, and ultimately lethal lung disease estimated to affect up to 132,000 people in the United States,12 and characterized

predominantly by progressive fibrosis of the alveoli leading to loss of lung function over time. As tissues thicken and stiffen due to scarring, the lungs lose ability to efficiently transfer oxygen to the bloodstream, and as a result vital organs will be starved for oxygen. Typically, as a result, individuals with IPF experience shortness of breath, develop chronic cough and often find participation in everyday physical activities difficult.

According to the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT), idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic fibrosing interstitial pneumonia of unknown cause, occurring in older adults, and limited to the lungs.

The clinical symptoms of idiopathic pulmonary fibrosis are non-specific and can be shared with many pulmonary and cardiac diseases. The diagnosis requires the exclusion of exposure to substances known to cause pulmonary fibrosis, connective tissue diseases, and drug toxicity. A There is no cure for IPF. Historically, a diagnosis of IPF has been associated with a poor prognosis with many only living for 3-5 years post diagnosis with the most common cause of death related to IPF being respiratory failure.A,D,G,2,3 Male patients over the age of 50 tend to be the demographic most diagnosed with IPF.D,E The exact cause of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

Since a cure for IPF is not currently available, the treatment goal is to stabilize or reduce the rate of disease progression. The goals of treatment in IPF are essentially to reduce the symptoms, stop disease progression, prevent acute exacerbations, and prolong survival.

Limited treatment options have made determining an optimal intervention strategy challenging. There has been a high need for a treatment option that can effectively slow the progression of IPF. Treatment options have primarily consisted of supportive care (e.g., oxygen therapy, pulmonary rehabilitation) and lung transplantation. Treatment courses for pulmonary fibrosis are highly variable and difficult to predict. Each therapy strategy is individualized according to the patient's history and symptoms.

Non-pharmacologic treatment option is pulmonary rehabilitation. Pulmonary rehabilitation programs involve aerobic conditioning, strength and flexibility training, educational lectures, nutritional interventions, and psychosocial support. Pulmonary rehabilitation has recently been studied in patients with interstitial lung diseases (ILDs). Two controlled trials of pulmonary rehabilitation in IPF have demonstrated an improvement in walk distance and symptoms or quality of life. Other uncontrolled studies have found similar findings. The beneficial effects of pulmonary rehabilitation may be more pronounced in patients with worse baseline functional status. Pulmonary rehabilitation may not be reasonable in a minority.

Lung transplant is the only treatment for advanced IPF that results in a major functional improvement and an increase in the 1, 5 and 10-year survival of 74%, 45%, and 22%, respectively.4Due to the use of the Lung Allocation Score (LAS) IPF has now replaces COPD as the most common indication for lung transplantation in the United States.

Pharmacologic treatment options include corticosteroids, immunosuppressive/cytotoxic agents (e.g., azathioprine, cyclophosphamide), and antifibrotic agents (e.g., colchicine or d- penicillamine) alone or in combination; however, evidence-based guidelines for the diagnosis and management of idiopathic pulmonary fibrosis did not find sufficient evidence to support the use of any specific pharmacologic therapy for patients with idiopathic pulmonary fibrosis.

Esbriet (pirfenidone) and Ofev (nintedanib) are the first two FDA-approved medications indicated for use in idiopathic pulmonary fibrosis and had previously received “Fast Track” and “Breakthrough Therapy” designations by the FDA. These two agents were also granted Orphan Drug status since there are no

other drugs to date for the treatment of IPF, a disease that affects an estimated 100,000 people (mostly adults over the age of 40) in the United States. The exact mechanism of action Esbriet (pirfenidone) is unknown and Ofev (nintedanib) is a kinase inhibitor that blocks growth factor receptors implicated in IPF, including the vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR). Both medications were shown in clinical trials to help to slow disease progression.

Pirfenidone is an oral pyridone indicated for the treatment of IPF.a-d Precise mechanism by which pirfenidone may work in pulmonary fibrosis has not been established. Pirfenidone exerts both anti-fibrotic and anti-inflammatory properties, thus playing a key role in preventing the formation of certain factors involved in the fibrotic and inflammatory aspects of the disease. It inhibits transforming growth factor (TGF)-beta, a chemical mediator that controls many cell functions including proliferation and differentiation. It also inhibits the synthesis of TNF-alpha, a cytokine that is known to have an active role in inflammation. Clinical studies demonstrate a beneficial treatment effect for patients receiving Esbriet® versus patients in the placebo group by measuring Forced Vital Capacity (FVC). FVC provides a direct measure of lung volume, a decline in FVC is an indicator of disease progression.

GUIDELINES

The ATS/ERS consensus published in 2000 on idiopathic pulmonary fibrosis (IPF) set out, for the first time, the diagnostic criteria and recommendations for evaluating its course and treatment.* Since its publication, a number of studies have contributed to optimizing the diagnostic and therapeutic guidelines for IPF. As a result, an international consensus was published in 2011, in which the diagnostic criteria were redefined, and new therapeutic recommendations were established. A The evidence-based international recommendations were jointly sponsored by the European Respiratory Society (ERS), the American Thoracic Association (ATS), the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT).A

*American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646–664.

ARaghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011; 183:788-824.

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management (Raghu G, et al. 2011)

The guidelines have not been updated since the approval of nintedanib but are currently under review.

NOTE: The ATS/ERS/JRS/ALAT guideline committee gave a Weak No recommendation for pirfenidone, with high value placed on costs and side-effects and low value on the possible small reduction in pulmonary decline. It must be noted, however, that the majority of committee members (16 out of 31) abstained from voting on pirfenidone as most were involved in the CAPACITY trials. In addition, the guidelines were devised before full publication of the CAPACITY study data and without taking into consideration the positive findings of the Cochrane meta-analysis. The complete dataset available to date is likely to have an important impact on confidence in the treatment effect of pirfenidone in the future.

Current American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines define IPF as: A type of chronic progressive fibrosing interstitial pneumonia with no known cause Occurring primarily in older adults

Limited to the lungs

Associated with a radiological or histological pattern of usual interstitial pneumonia
ATS/ERS/JRS/ALAT Consensus Guidelines (2011)

Recommend: FVC and DLCO measurements be performed during routine monitoring of IPF and that such monitoring occur at 3 to 6-month intervals. More frequent repetition of FVC and DLCO should be performed in the presence of progressive dyspnea or other features of a more rapidly progressive course.

Indicate: A change in absolute forced vital capacity (FVC) of 10% [with or without a concomitant change in carbon monoxide diffusing capacity (DLCO)] or a change in absolute

DLCO of 15% (with or without a concomitant change in FVC) is a surrogate marker of mortality and is evidence of disease progression. Nintedanib has been shown to decrease (not stop) progression of IPF; the extent of disease progression at which nintedanib inefficacy can be assumed has not been established.

The American Thoracic Society guidelines state the diagnosis of IPF requires:
Diagnostic accuracy of IPF is improved through formal multidisciplinary interaction (Pulmonary, Radiology, and Pathology joint consultation/conferencing) and the Consensus Committee strongly recommended that approach in the evaluation of suspected IPF.
Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)

The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy
Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.
Chronic management of IPF should include long-term oxygen therapy, lung transplantation, and potentially pulmonary rehabilitation.
No pharmacological treatment is recommended; guidelines recommend against the use of many of the previously available medications.
Medications that have been previously used for maintenance treatment include corticosteroid monotherapy, colchicine, cyclosporine A, combination of corticosteroid and immune-modulator therapy, interferon gamma-1b, bosentan, etanercept, acetylcysteine monotherapy, acetylcysteine plus azathioprine plus prednisone, anticoagulation, and pirfenidone.

Treatment of pulmonary hypertension and asymptomatic gastroesophageal reflux is not recommended. Corticosteroids may be used during acute exacerbations of IPF. At the time the guidelines were published, nintedanib was not approved.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Esbriet (pirfenidone) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Esbriet (pirfenidone) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

Pirfenidone initial titration to the full dosage of 2403 mg per day should occur over 14 days, as follows:

a. Day 1 through day 7, 267 mg is taken three times daily
b. Days 8 through day 14, 534 mg is taken three times daily
c. Days 15 and onward, 801 mg is taken three times daily

A 14-day titration blister pack carton is available for Esbriet capsules. Additionally, pirfenidone should be taken

with food to help decrease nausea and dizziness.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Esbriet CAPS 267MG
Esbriet TABS 267MG, 801MG
Pirfenidone TABS 267MG, 534MG, 801MG

REFERENCES

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12. Raghu, G., Remy-Jardin, M., Myers, J., Richeldi, L., Ryerson, C., & Lederer, D. et al. (2018). Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity References	Q4 2023
REVISION- Notable revisions: Products Affected Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file