**Medication Policy Manual**

**Topic:** Esbriet®, pirfenidone  
**Policy No:** dru368

**Date of Origin:** November 13, 2014  
**Committee Approval Date:** November 11, 2016  
**Next Review Date:** November 2017

**Effective Date:** December 1, 2016

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Pirfenidone (Esbriet) is an oral medication used to treat idiopathic pulmonary fibrosis (IPF), a progressive interstitial lung disease. The exact mechanism of action is unknown; however, pirfenidone (Esbriet) has anti-inflammatory and anti-fibrotic activity.
Policy/Criteria

I. Most contracts require prior authorization approval of pirfenidone (Esbriet) prior to coverage. Pirfenidone (Esbriet) may be considered medically necessary when criteria A, B, C and D below are met.

A. There is a diagnosis of idiopathic pulmonary fibrosis (IPF) confirmed by the presence of usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT) and/or surgical lung biopsy.

AND

B. The baseline percent predicted forced vital capacity (FVC) is between 50-90%.

AND

C. The baseline percent predicted diffusing capacity of the lung for carbon monoxide (DLCO) is between 30-90%.

AND

D. There is clinical documentation that the patient is a nonsmoker or has been abstinent from smoking for at least six weeks.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers pirfenidone (Esbriet) to be a self-administered medication.

B. When prior authorization is approved, pirfenidone (Esbriet) may be authorized in quantities of up to 270 capsules per month.

C. Authorization shall be reviewed at least every six months to confirm that current medical necessity criteria are met and that the medication is effective defined as improvement or maintenance (< 10% decline in percent predicted FVC or < 200 mL decrease in FVC) of disease, and there is clinical documentation that the member has remained tobacco-free.

III. Pirfenidone (Esbriet) is considered investigational when given in combination with nintedanib (Ofev).

IV. Pirfenidone (Esbriet) is considered investigational when used for all other conditions, including but not limited to:

A. Diabetic nephropathy

B. Glomerulosclerosis

C. Hypertrophic cardiomyopathy

D. Neurofibromatosis

E. Other forms of interstitial lung disease (e.g. systemic sclerosis-related interstitial lung disease)
Position Statement

- Pirfenidone (Esbriet) is an oral pyridone for the treatment of idiopathic pulmonary fibrosis (IPF). The exact mechanism is unknown; however, pirfenidone (Esbriet) has antiinflammatory and anti-fibrotic activity.

- To date, no therapy has shown conclusive benefit in the treatment of IPF. Historically, corticosteroids and immunosuppressants (such as azathioprine, cyclophosphamide) were used, despite the lack of evidence to support their use. Current therapies are supportive, with oxygen therapy, pulmonary rehabilitation, and lung transplantation. [1]

- Pirfenidone (Esbriet) may add value to the treatment of IPF, as current treatment options have never been proven to consistently affect surrogate endpoints, such as lung function or disease progression. However, similar to current therapies, the value of pirfenidone (Esbriet) (Esbriet) on health outcomes, such as mortality, is uncertain. Mortality is the most important outcome for this rapidly progressive, fatal condition. [1]

- The use of forced vital capacity (FVC) as an efficacy measure has been both supported and discouraged in the available literature. [2] FVC is used as a surrogate marker of disease severity and progression. Diffusing capacity of the lung for carbon monoxide (DLCO) is considered a standard predictor of survival. [3]

- Establishing an accurate diagnosis of IPF is very important since misdiagnosis can lead to inappropriate therapy. In general, the diagnosis of IPF can be made with a high degree of confidence in patients with a compatible clinical presentation, typical HRCT findings, and no evidence of another contributing process. [4,5]

- Pirfenidone (Esbriet) has only been studied in subjects with mild-to-moderate IPF (percent predicted FVC between 50-90% and a percent predicted DLCO between 30-90%). The safety and efficacy in patients with more severe disease is unknown. Pirfenidone (Esbriet) has not been studied in combination with nintedanib (Ofev); therefore, concomitant therapy with nintedanib (Ofev) is considered investigational.

- Pirfenidone (Esbriet) has also been studied in a variety of investigational indications [6]; however, safety and effectiveness in larger, phase 3 trials have not been established.

- The recommended dosing is 801 mg (3 capsules) orally three times daily after the initial 14-day dose titration.

Tolerability of pirfenidone (Esbriet) in clinical practice is uncertain. Gastrointestinal-related events, such as nausea, vomiting, and diarrhea, led to dose reductions or interruptions in 18.5% of pirfenidone (Esbriet)-treated subjects in clinical trials.
**Clinical Efficacy**

- The evidence of efficacy for pirfenidone (Esbriet) is based on three published, randomized, double-blind, placebo-controlled, multicenter trials in patients with confirmed IPF. Two concurrent 72-week trials (n = 779) and one supporting 52-week trial (n = 555) evaluated the change in percent predicted FVC from baseline to study end, measured at 52 or 72 weeks. [7-9]
  * There was a statistically significant reduction in the decline of percent predicted FVC in the pirfenidone (Esbriet) arm as compared to placebo in one of the 72-week trials. The other 72-week trial failed to reach the primary endpoint.
  * However, the FDA noted statistically significant findings at the 12-and 48-week time points. Subsequently, the 52-week trial was conducted to confirm a statistically significant reduction in the decline of percent predicted FVC with pirfenidone (Esbriet).
  * Based on the inconsistent benefit seen at 72 weeks, the durability of the treatment effect is uncertain.
  * Mortality was evaluated as an exploratory analysis to support the primary endpoint. No individual trial was adequately designed to detect a change in mortality, the most meaningful health outcome for IPF. Therefore, the overall clinical significance of the primary endpoint findings, change in percent predicted FVC, is uncertain.

- Pirfenidone (Esbriet) is being evaluated in phase 1 and phase 2 trials for a variety of indications including, but not limited to, diabetic nephropathy, glomerulosclerosis, neurofibromatosis, hypertrophic cardiomyopathy, and other forms of interstitial lung disease. Larger, well-controlled phase 3 studies are needed to evaluate the safety and effectiveness of pirfenidone (Esbriet) in these indications. [6]

- The American thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guideline has been updated since the approval of nintedanib (Ofev). The joint guideline provides a strong recommendation against most therapies (e.g. anticoagulation, selective endothelin receptor antagonists, imatinib, and combination prednisone, azathioprine, and N-acetylcysteine); however, both nintedanib (Ofev) and pirfenidone (Esbriet) are given conditional recommendations for use. [3]

**Safety** [7]

- Pirfenidone (Esbriet) is associated with nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, and weight decrease.

- Significant concerns with pirfenidone (Esbriet) include a risk of photosensitivity, gastrointestinal disorders, and elevated liver function tests.

- Gastrointestinal-related events, such as nausea, vomiting, and diarrhea, led to dose reductions or interruptions in 18.5% of pirfenidone-treated subjects in clinical trials.

- Serious postmarketing adverse events include agranulocytosis and angioedema.
Dosing [7]

- Liver function tests should be conducted prior to initiating treatment with pirfenidone (Esbriet) due to the risk of elevated liver enzymes.
- The recommended daily maintenance dosage of pirfenidone (Esbriet) is 801 mg (three 237 mg capsules) three times daily with food for a total of 2,403 mg/day. Doses above 2,403 mg/day (9 capsules per day) are not recommended for any patient.
- Upon initiation of treatment, titration to the full dosage of nine capsules per day should be completed over a 14-day period as follows:

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<tr>
<th>Treatment Days</th>
<th>Dosage</th>
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<tr>
<td>Days 1 through 7</td>
<td>1 capsule three times a day with food</td>
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<tr>
<td>Days 8 through 14</td>
<td>2 capsules three times a day with food</td>
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<tr>
<td>Days 15 onward</td>
<td>3 capsules three times a day with food</td>
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- Patients who miss 14 or more days of pirfenidone (Esbriet) should re-initiate treatment by undergoing the initial 2-week titration up to the full maintenance dosage.
- Dosage adjustments or interruptions may be considered if patients experience significant adverse reactions, including elevated liver enzymes.
- Dosage modifications due to drug interactions with strong CYP1A2 inhibitors (e.g. fluvoxamine, enoxacin) and moderate CYP1A2 inhibitors (e.g. ciprofloxacin) are recommended.

Cross References

Ofev®, nintedanib, Medication Policy Manual, Policy No. dru369

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References


Revision History

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<th>Revision Summary</th>
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<tr>
<td>11/11/2016</td>
<td>No criteria changes with this annual update.</td>
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