09-J2000-24

Original Effective Date: 12/15/14

Reviewed: 12/12/18

Revised: 01/15/19

Subject: Pirfenidone (Esbriet®)

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Idiopathic pulmonary fibrosis is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis.

The American Thoracic Society published guidelines for the diagnosis and management of IPF in 2011, with an update to treatment recommendations in 2015. According to those guidelines, the diagnosis of IPF requires exclusion of other known causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity), the presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy, and specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

Pirfenidone (Esbriet®) was approved by the U.S. Food and Drug Administration (FDA) in October 2014 as a breakthrough therapy for the treatment of idiopathic pulmonary fibrosis (IPF). Prior to FDA approval, pirfenidone was designated as an orphan drug for this same indication.

The CAPACITY trial reported on two independent study protocols: study 004 included 435 patients randomized to one of three treatment groups (high-dose pirfenidone [2,403 mg/d], low-dose pirfenidone [1,197 mg/d], and placebo), whereas study 006 had 344 patients randomized to only two treatment groups (high-dose pirfenidone [2,403 mg/d] and placebo). Patients were eligible if they were diagnosed with IPF and had a FVC greater than or equal to 50%. The results of the low-dose pirfenidone group were intermediate to the higher dose, and to avoid heterogeneity of intervention, we chose to focus on the results of the high-dose pirfenidone group versus those of the placebo group across both studies. In study

004, pirfenidone showed a reduction in decline of FVC during the 72-week treatment period. Study 006 did not show a benefit in the same outcome during the same period. Importantly, patients from both studies who were assigned to receive high-dose pirfenidone reported increased rates of nausea, dyspepsia, vomiting, anorexia, photosensitivity, and rash compared with placebo.

The ASCEND trial (A Randomized, Double-Blind, Placebo Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis) randomized 555 patients with IPF to either high-dose pirfenidone (2,403 mg/d) or placebo (38). As opposed to the CAPACITY trials, the ASCEND trial had stricter patient selection criteria, such as a FEV1/FVC ratio below 0.8 (FVC required to be greater than 50%). Of 1,562 screened patients, 1,007 were excluded because of these predefined exclusion criteria. Pirfenidone significantly reduced the proportion of patients who had a more than 10% decline in their FVC during the 52-week follow-up period (47% reduction in pirfenidone group vs placebo). Pirfenidone treatment increased 6-minute-walk distance and progression-free survival when compared with placebo. Mortality or dyspnea scores did not differ. Consistent with previous studies, patients randomized to pirfenidone reported more treatment-related adverse effects.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of pirfenidone (Esbriet®) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with idiopathic pulmonary fibrosis (IPF) confirmed by **ONE** of the following:
    a. Presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) – imaging documentation must be provided
    b. Surgical lung biopsy – lung biopsy documentation must be provided
2. Member's interstitial lung disease has not resulted from known causes (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
3. Member's forced vital capacity (FVC) is equal to or greater than 50% of the predicted FVC – documentation of assessment within the most recent 6 months must be provided
4. Member does not have severe (Child Pugh C) hepatic impairment (see Table 1)
5. Pirfenidone is prescribed by a pulmonologist
6. Use is not in combination with with nintedanib (Ofev)
7. Dose does not exceed 801 mg three times daily – dosage will be achieved using the fewest number of capsules or tablets per day

Duration of approval: 6 months

Continuation of pirfenidone (Esbriet®) **meets the definition of medical necessity** for members meeting the following criteria:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of IPF, **OR** the member has previously met all indication-specific initiation criteria
2. Member is receiving clinical benefit from treatment with pirfenidone – documentation from the medical must be provided
3. Use is not in combination with nintedanib (Ofev)
4. Dose does not exceed 801 mg three daily – dosage will be achieved using the fewest number of capsules or tablets per day

Duration of approval: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 801 mg (three capsules) three times daily, with food
- Upon initiation of treatment, titrate to the full dosage of 2403 mg/day over a 14-day period

Dose Adjustments

- Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions

Drug Availability

- Capsules: 267 mg
- Tablets: 267 mg, 801 mg

PRECAUTIONS:

Boxed Warning

None

Contraindications

None

Precautions/Warnings

- Elevated liver enzymes
- Gastrointestinal disorders, including perforation

- Photosensitivity

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

J84.112	Idiopathic pulmonary fibrosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

Table 1. Child-Pugh Classification of Severity of Liver Disease

Using the table below, a total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease):

Parameter	Points Assigned		
	1	2	3

Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	</=2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time • Seconds over control • INR	1-3 <1.8	4-6 1.8-2.3	>6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/12/18.

GUIDELINE UPDATE INFORMATION:

12/15/14	New Medical Coverage Guideline.
12/15/15	Review and revision to guideline, consisting of updating position statement, decription, references.
04/15/16	Revision of guideline; consisting of updating position statement.

12/15/16	Review and revision to guideline, consisting of updating position statement, coding, references.
07/15/17	Revision to position statement and dosage/administration; added new FDA approved dosage form (tablets).
12/15/17	Review and revision to guideline; consisting of updating dosage and references.
01/15/19	Review and revision to guideline; consisting of updating references.