Clinical Policy: Nintedanib (Ofev)

Reference Number: ERX.SPA.172
Effective Date: 01.11.17
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Nintedanib (Ofev®) is a kinase inhibitor.

FDA Approved Indication(s)
Ofev is indicated:
- For the treatment of idiopathic pulmonary fibrosis (IPF);
- For the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype;
- To slow the rate of decline in pulmonary function in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Ofev is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Idiopathic Pulmonary Fibrosis (must meet all)**:**
1. Diagnosis of IPF;
2. Prescribed by or in consultation with a pulmonologist;
3. Age ≥ 18 years;
4. Member meets (a and b):
   a. Pulmonary fibrosis on high resolution computed tomography (HRCT) with one of the following (i or ii):
      i. Usual interstitial pneumonia (UIP) pattern;
      ii. Probable or indeterminate UIP pattern, and surgical lung biopsy or cellular analysis of bronchoalveolar lavage fluid confirms the diagnosis of IPF
   b. Known causes of pulmonary fibrosis have been ruled out *(see Appendix D);*
5. Baseline forced vital capacity (FVC) ≥ 50% of predicted;
6. Baseline carbon monoxide diffusing capacity (DLCO) ≥ 30% of predicted;
7. Ofev is not prescribed concurrently with Esbriet®;
8. Member is not an active smoker as evidenced by recent (within the last 30 days) negative nicotine metabolite (i.e., cotinine) test;
9. Dose does not exceed 300 mg (2 capsules) per day.

Approval duration: 6 months

B. Chronic Fibrosing Interstitial Lung Disease (must meet all)**:**
1. Diagnosis of one of the following chronic fibrosing ILD subtypes (a-g):
   a. Chronic fibrosing hypersensitivity pneumonitis;
   b. Autoimmune ILD (e.g., rheumatoid arthritis-related ILD);
   c. Mixed connective tissue disease-associated ILD;
   d. Idiopathic non-specific interstitial pneumonia;

e. Unclassifiable idiopathic interstitial pneumonia;
f. Environmental/occupational exposure-related ILD;
g. Sarcoidosis;
2. Prescribed by or in consultation with a pulmonologist;
3. Age ≥ 18 years;
4. For new starts only: member meets both of the following within the past 24 months (a and b):
   a. Pulmonary fibrosis affecting > 10% of lung volume on HRCT;
   b. Documentation of one of the following (i or ii):
      i. A relative decline in the FVC of ≥ 10% of the predicted value;
      ii. A relative decline in the FVC of 5% to < 10% of the predicted value plus either worsening of respiratory symptoms or an increased extent of fibrosis on HRCT;
5. Baseline FVC ≥ 45% of predicted;
6. Baseline DLCO ≥ 30% of predicted;
7. Ofev is not prescribed concurrently with Esbriet;
8. Member is not an active smoker as evidenced by recent (within the last 30 days) negative nicotine metabolite (i.e., cotinine) test;
9. Dose does not exceed 300 mg (2 capsules) per day.

Approval duration: 6 months

C. Systemic Sclerosis Associated Interstitial Lung Disease (must meet all)**:**
1. Diagnosis of SSc-ILD;
2. Prescribed by or in consultation with a pulmonologist or rheumatologist;
3. Age ≥ 18 years;
4. Member meets (a and b):
   a. Pulmonary fibrosis affecting ≥ 10% of lung volume on HRCT;
   b. Additional signs of SSc are identified *(see Appendix E);*
5. Failure of a ≥ 3 consecutive month trial of cyclophosphamide or mycophenolate mofetil, at up to maximally indicated doses, unless both are contraindicated or clinically significant adverse effects are experienced;
6. Baseline FVC ≥ 40% of predicted;
7. Baseline DLCO ≥ 30% of predicted;
8. Ofev is not prescribed concurrently with Esbriet;
9. Member is not an active smoker as evidenced by recent (within the last 30 days) negative nicotine metabolite (i.e., cotinine) test;
10. Dose does not exceed 300 mg (2 capsules) per day.

Approval duration: 6 months

D. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Ofev is not prescribed concurrently with Esbriet;
4. If request is for a dose increase, new dose does not exceed 300 mg (2 capsules) per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACR: American College of Rheumatology
ATS: American Thoractic Society
CTD: connective tissue disease
DLCO: carbon monoxide diffusing capacity
FDA: Food and Drug Administration
FVC: forced vital capacity
IPF: idiopathic pulmonary fibrosis
ILD: interstitial lung disease
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
SSc-ILD: systemic sclerosis associated interstitial lung disease
UIP: usual interstitial pneumonia

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cyclophosphamide (Cytoxan®, Neosar®)	**SSc-ILD*** PO: 1 – 2 mg/kg/day IV: 600 mg/m^2/month	PO: 2 mg/kg/day IV: 600 mg/m^2/month
mycophenolate mofetil (CellCept®)	**SSc-ILD*** PO: 1 – 3 g/day	3 g/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: American Thoracic Society (ATS) 2018 IPF Guidelines

- ATS diagnostic criteria for IPF are built around pulmonary fibrosis findings on HRCT and exclusion of known causes of ILD (e.g., domestic and occupational environmental exposures, CTD, drug toxicity).
- UIP is the hallmark radiologic pattern of IPF. Honeycombing is a distinguishing feature of UIP and must be present for a definite HRCT diagnosis of UIP to be made.
- In patients with a probable or indeterminate UIP pattern, surgical lung biopsy or cellular analysis of bronchoalveolar lavage fluid is recommended to confirm the diagnosis of IPF

Appendix E: American College of Rheumatology (ACR) 2013 SSc Classification Criteria

While the majority of patients with SSc experience skin thickening and variable involvement of internal organs, there is no one confirmatory test for SSc. Similar to the IPF guidelines above, ACR lists HRCT as a diagnostic method for determining pulmonary fibrosis in SSc-ILD. The other diagnostic parameters below are drawn from ACR's scoring system purposed for clinical trials. While informative, ACR cautions that the scoring system parameters are not all inclusive of the myriad of SSc manifestations that may occur across musculoskeletal, cardiovascular, renal, neuromuscular and genitourinary systems.

<u>Examples of SSc skin/internal organ manifestations and associated laboratory tests:</u>

- Skin thickening of the fingers
- Fingertip lesions
- Telangiectasia
- Abnormal nailfold capillaries
- Raynaud's phenomenon

- SSc-ILD
- Pulmonary arterial hypertension
- SSc-related autoantibodies
  - Anticentromere
  - Anti–topoisomerase I [anti–Scl-70]
  - Anti–RNA polymerase III

Appendix F: General Information

- Smoking was associated with decreased exposure to Ofev, which may alter the efficacy profile of Ofev.
- The Ofev pivotal studies included only patients with mild to moderate lung impairment per FVC and DLCO.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
IPF, SSc-ILD, chronic fibrosing ILD with a progressive phenotype	150 mg PO BID approximately 12 hours apart (100 mg BID for patients with mild hepatic impairment or management of adverse reactions)	300 mg/day

VI. Product Availability

Capsules: 100 mg, 150 mg

VII. References

1. Ofev Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2020. Available at: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Ofev/ofev.pdf. Accessed June 24, 2021.
2. Raghu G, Remy-Jardin M, Myers JL. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. American Thoracic Society. Am J Respir Crit Care Med. Stepember 1, 2018; 198(5):e44-e68.
3. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism Collaborative Initiative. Ann Rheum Dis. 2013; 72:1747-1755.
4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718-27.
5. Richeldi L, Varone F, Bergna M, et al. Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev 2018;27:180074.
6. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: Treatment of idiopathic pulmonary fibrosis: An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. July 15, 2015; 192(2): e3–e19.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q17 Annual Review Converted to new template. Added age restriction as safety and efficacy have not been established in pediatric patients per PI.	09.27.17	11.17
3Q 2018 annual review: removed requirement for high-resolution computed tomography or surgical lung biopsy findings confirming diagnosis; references reviewed and updated.	05.10.18	08.18
3Q 2019 annual review: no significant changes; references reviewed and updated.	05.21.19	08.19
Criteria added for new FDA indication: SSc-ILD; diagnostic criteria added for IPF; references reviewed and updated.	10.22.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2020 annual review: criteria added for new FDA indication: chronic fibrosing ILD with a progressive phenotype; references reviewed and updated.	04.21.20	08.20
3Q 2021 annual review: for IPF, added requirements for HRCT UIP pattern and surgical biopsy/bronchoalveolar lavage per ATS guidelines; for SSc-ILD, added rheumatologist prescriber option per specialist feedback, clarified the fibrosis should affect at least 10% of lung volume on HRCT per pivotal trial inclusion criteria, and added redirection to cyclophosphamide or mycophenolate mofetil; for all indications, added baseline FVC/DLCO requirements per pivotal trial inclusion criteria, requirement against concurrent use with Esbriet, and requirement that member is not an active smoker; references reviewed and updated.	06.24.21	08.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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