GUIDELINES FOR USE

1. Was nintedanib prescribed by or in consultation with a pulmonologist?
   
   If yes, continue to #2.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

2. Does the patient have a diagnosis of idiopathic pulmonary fibrosis (IPF)?
   
   If yes, continue to #3.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

3. Does the patient have other known causes of interstitial lung disease (e.g., connective tissue disease, drug toxicity, asbestos or beryllium exposure, hypersensitivity pneumonitis, systemic sclerosis, rheumatoid arthritis, radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV) infection, viral hepatitis, or cancer)?
   
   If yes, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.
   If no, continue to #4.

4. Does the patient have a usual interstitial pneumonia (UIP) pattern as evidenced by high-resolution computed tomography (HRCT) alone or via a combination of surgical lung biopsy and HRCT?
   
   If yes, continue to #5.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

5. Does the patient have a predicted forced vital capacity (FVC) of at least 50%?
   
   If yes, continue to #6.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

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GUIDELINES FOR USE (CONTINUED)

6. Has the patient obtained liver function tests?

If yes, approve for 12 months by HICL with a quantity limit of #2 capsules per day. If no, do not approve.

DENIAL TEXT: See the denial text at the end of the guideline.

DENIAL TEXT: Our guideline for NINTEDANIB requires a diagnosis of idiopathic pulmonary fibrosis (IPF). IPF is defined by the American Thoracic Society with the following criteria: a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g., connective tissue disease, drug toxicity, asbestos or beryllium exposure, hypersensitivity pneumonitis, systemic sclerosis, rheumatoid arthritis, radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV) infection, viral hepatitis, or cancer) AND b) The presence of usual interstitial pneumonia (UIP) pattern as evidenced by high-resolution computed tomography (HRCT) alone or via a combination of surgical lung biopsy and HRCT. In addition, our guideline requires:

- treatment is prescribed by or in consultation with a pulmonologist
- patient must obtain liver function tests prior to the start of nintedanib
- patient has a predicted forced vital capacity (FVC) of at least 50%

RATIONALE
Promote appropriate utilization of Ofev based on FDA approved indication and dosage.

Ofev (NINTEDANIB) is one of the first drugs to be approved by the FDA to treat idiopathic pulmonary fibrosis (IPF). Esbriet (pirfenidone), the other agent for the treatment of IPF, was also approved on the same day. These two drugs were granted Breakthrough Therapy Designation as well as 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. IPF is a chronic, progressive disorder of the lower respiratory tract in which lung tissue becomes scarred or fibrotic over time. As a result, patients with IPF experience shortness of breath, cough, and difficulty participating in everyday physical activities.

The American Thoracic Society guidelines state the diagnosis of IPF requires:

a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
b) The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy
c) Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

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RATIONALE (CONTINUED)
There is no cure for IPF; many people live only about 3 to 5 years, with the most common cause of death related to IPF being respiratory failure. 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.

Treatment options for IPF have been extremely limited, mainly consisting of supportive care (e.g., oxygen therapy, pulmonary rehabilitation) and lung transplantation. Systemic glucocorticoid monotherapy, combination therapy with azathioprine, prednisone, and N-acetylcysteine, and monotherapy with N-acetylcysteine have been tried, but were unsuccessful in demonstrating efficacy and may in fact cause potential harm. Many other pharmacological treatments (e.g.; sildenafil, endothelin receptor antagonist, TNFs and chemotherapeutic agents) have been studied in IPF but were found to be ineffective or have inconclusive evidence to routinely support their use in IPF. The approval of Ofev provides a new treatment option that may slow disease progression for patients with IPF. Ofev is a kinase inhibitor that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Ofev has been shown to inhibit platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR) which are associated with IPF pathogenesis.

Liver function tests (ALT, AST, and bilirubin) should be conducted prior to initiation of treatment and monthly for 3 months, and every 3 months thereafter and as clinically indicated. In clinical trials, Ofev was associated with elevations of liver enzymes that were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. Ofev also associated with increases in bilirubin.

Ofev is classified as a pregnancy category D and can cause fetal harm when administered to pregnant women. Women of childbearing age should avoid becoming pregnant during treatment with Ofev and should be advised to use adequate contraception during and at least 3 months after the last dose of Ofev.

Other warnings and precautions include gastrointestinal distress, gastrointestinal perforation, arterial thromboembolic events and increased risk of bleeding.

Most common adverse reactions (≥5%) of Ofev treated patients and more commonly than placebo are: diarrhea (62% vs. 18%), nausea (24% vs. 7%), abdominal pain (15% vs. 6%), vomiting (12% vs. 3%), liver enzyme elevation (14% vs. 3%), decreased appetite (11% vs. 5%), headache (8% vs. 5%), weight decreased (10% vs. 3%), and hypertension (5% vs. 4%).

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DOSAGE
The recommended dosage of Ofev is 150 mg twice daily administered approximately 12 hours apart. Do not exceed the recommended maximum daily dosage of 300 mg. If a dose of Ofev is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose.

Ofev capsules should be taken with food and swallowed whole with liquid. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known.

Dose reduction (100mg twice daily) or temporary interruption maybe necessary for management of adverse events until the specific adverse reaction resolves to levels that allow continuation of therapy. If a patient cannot tolerate 100 mg twice daily treatment with Ofev should be discontinued. In patients with aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce Ofev to 100 mg twice daily. Discontinue Ofev for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

FDA APPROVED INDICATION
Ofev is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

REFERENCES