

Dear Healthcare Professional,

Please note that this resource, *Appeal Tips and Checklist*, includes general guidance related to appealing treatment decisions and fulfilling prior authorizations. Boehringer Ingelheim makes no guarantee that use of the information included in these forms will result in a positive outcome.

DOSAGE AND ADMINISTRATION

Testing Prior to OFEV Administration

Conduct liver function tests and a pregnancy test prior to initiating treatment with OFEV.

Recommended Dosage

The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart.

OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known.

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. Do not exceed the recommended maximum daily dosage of 300 mg.

In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily approximately 12 hours apart taken with food.

Dosage Modification due to Adverse Reactions

In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV.

Dose modifications or interruptions may be necessary for liver enzyme elevations. Conduct liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Discontinue OFEV in patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevations greater than 5 times the upper limit of normal. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced

dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily).

In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

INDICATION

OFEV (nintedanib) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Hepatic Impairment

- OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Elevated Liver Enzymes and Drug-Induced Liver Injury

- Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the post-marketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. The majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN.
- Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may result in increased liver enzymes.
- Conduct liver function tests prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Please see additional Important Safety Information on next page and [Prescribing Information](#) for OFEV®.



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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Gastrointestinal Disorders

Diarrhea

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and less than 1% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

Nausea and Vomiting

- Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Events were primarily of mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryofetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to starting OFEV.

Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding: OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. In the post-marketing period, non-serious and serious bleeding events, some of which were fatal, have been observed.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus in 0% placebo patients. In the post-marketing period, cases of gastrointestinal

perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Adverse reactions reported in greater than or equal to 5% of OFEV patients, and more than placebo, included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.
- The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

DRUG INTERACTIONS

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers:** Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.
- **Anticoagulants:** Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.
- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

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APPEAL TIPS AND CHECKLIST

Tips for Filing an Appeal of Treatment Denial

The following tips can be helpful for handling common denial issues. Each denial is different. Refer to the original denial documentation for specific requests for additional information.

IDENTIFY THE REASON FOR DENIAL

- Find out in writing why the authorization request has been denied. The reason should be in the denial letter from the patient's health plan or in the explanation of benefits letter. If you did not receive either of these, they can be obtained from the insurer

DETERMINE THE APPEAL GUIDELINES

- Contact the insurer to find out its deadline for appealing, the number of appeals permitted (some plans only allow one), and the mailing address or fax number to which the appeal should be sent. Some insurers have short appeal periods—you may need to respond promptly. Also, inquire whether the appeal should be submitted by the patient or the healthcare provider and proceed accordingly

CONTACT THE REVIEW DEPARTMENT

- Many denial letters include a telephone number for the review department that physicians can call for further clarification. If a reviewer agrees with your rationale and approves treatment for the patient during the call, the appeal process is completed

COMPOSE A WRITTEN APPEAL

- Most insurers require a written appeal from either the member or the healthcare provider. The insurer should tell you what is needed. A written appeal package includes an appeal letter and supporting documents

PROVIDE ADDITIONAL SUPPORTING DOCUMENTATION

- A patient's appeal package should include all relevant medical documentation—including clinical notes and related test results—to support your case for coverage. Any newly available information related to the patient's condition should be supplied as well

CHECK PATIENT'S INSURER

- Do you know the type of insurance your patient has? Is the treatment a covered benefit? Are there state laws that may impact the treatment decision? Ask your patient to check his or her benefit plan to help determine whether the requested treatment is excluded. If it is, provide a written explanation as to why the plan should make an exception for your patient. Depending on the state where your practice is located, seeking an independent external review may be an option

FOLLOW UP AS NEEDED

- Contact the patient's insurer if they have not responded within 30 to 60 days of receipt of the appeal package

MAINTAIN COMPLETE RECORDS

- Retain a duplicate copy of all documentation submitted with the patient's appeal and record all subsequent communications made to the patient's insurer. Include the date and the name of the person contacted

APPEAL TIPS AND CHECKLIST (cont'd)

Documents for Filing a Response to Treatment Denial: An Appeal Checklist

If an insurer denies coverage of a prescribed treatment for your patient, the following is a sample checklist of materials you may need for an appeal package. Note that each appeal may need different information depending on the insurer and/or patient. Carefully review each denial and the insurer's requirements to determine what to include in a patient's appeal package.

COMMONLY REQUIRED DOCUMENTS INCLUDE:

- Statement of medical necessity
- Patient authorization and notice of release of information
- Copy of the patient's health plan or prescription card (front and back)
- Denial information, including the patient's denial letter and/or explanation of benefits
- Letter of appeal
- Supporting documentation
 - OFEV® (nintedanib) FDA approval letter and prescribing information
 - OFEV capsules published clinical studies
 - Patient clinical/diagnostic records and related laboratory reports within last 6 months unless otherwise noted
 - HRCT and lung biopsy results indicating IPF, honeycombing, and/or usual interstitial pneumonia within the last 12 to 18 months
 - Radiology report (eg, tissue panel)
 - Pulmonary function tests (eg, FEV₁/FVC, DL_{CO}, TLC values)