A dosing and management guide for your patients with IPF who receive OFEV

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

Please see Important Safety Information on the following pages and full Prescribing Information, including Patient Information.
Offer your patients dosing that is one capsule, twice daily

TESTING PRIOR TO OFEV (NINTEDANIB) ADMINISTRATION

Conduct liver function tests (ALT, AST, and bilirubin) and a pregnancy test prior to initiating treatment with OFEV

RECOMMENDED DOSING

Dosing simplicity with one capsule, twice daily can be integrated into a patient’s morning and evening routines. Each capsule should be taken approximately 12 hours apart

No up-titration upon initiation. 150 mg twice daily is the recommended dose. In those with mild hepatic impairment (Child Pugh A), 100 mg twice daily is recommended

Should be taken with food

Should be swallowed whole with liquid. It should not be chewed or crushed

Dose reduction or temporary interruption of treatment with OFEV allows for the management of adverse events while supporting continued clinical benefit. If patient does not tolerate dose reduction, discontinue treatment with OFEV

If a dose of OFEV is missed, treatment should resume at the next scheduled time and at the recommended dose. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg.

RECOMMENDED TESTING

- Conduct liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first 3 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
- Conduct a pregnancy test prior to initiating treatment with OFEV

OFEV IS AVAILABLE IN 2 DOSAGE STRENGTHS

150-MG CAPSULE

100-MG CAPSULE

REMIND PATIENTS THAT DOSE ADHERENCE IS IMPORTANT WHILE TAKING OFEV

- In addition to symptomatic treatment, the dose of OFEV can be reduced, interrupted, or discontinued to manage adverse reactions. Please see complete details regarding dosage modifications throughout this brochure
- The most common adverse reactions were gastrointestinal (GI) in nature—including diarrhea, nausea, and vomiting—and generally of mild or moderate intensity

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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.

Please see additional Important Safety Information on the following pages and full Prescribing Information, including Patient Information.
Help patients start and stay on OFEV treatment

CONSIDERATIONS FOR TESTING, DOSING, AND MANAGING ADVERSE EVENTS

**CONDUCT:** A pregnancy test prior to initiation of treatment with OFEV (nintedanib), and liver function tests (ALT, AST, and bilirubin) prior to treatment initiation, at regular intervals during the first 3 months of treatment, and periodically thereafter or as clinically indicated.

**DOSING:** One capsule, twice daily with food. The recommended dose is 150 mg twice daily. In patients with mild hepatic impairment (Child Pugh A), the recommended dose is 100 mg twice daily.

**DOSAGE MODIFICATIONS:** Adverse reactions should be treated at first sign of:

<table>
<thead>
<tr>
<th>GI ADVERSE EVENTS</th>
<th>ELEVATED LIVER ENZYMES</th>
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<tbody>
<tr>
<td>Symptomatic treatment, including adequate hydration, antidiarrheal medication, and antiemetic medication</td>
<td>For patients with ALT or AST greater than 3x to less than 5x ULN without signs of liver damage, reduce dose to 100 mg twice daily or interrupt treatment</td>
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<tr>
<td>If GI symptoms persist, consider dose reduction to 100 mg twice daily or treatment interruption</td>
<td>Discontinue OFEV in patients with either:</td>
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<td></td>
<td>• ALT or AST elevations greater than 5x ULN OR</td>
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<td></td>
<td>• ALT or AST elevations greater than 3x ULN with signs or symptoms of liver damage</td>
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<tr>
<td>Discontinue treatment if severe symptoms persist</td>
<td>When liver enzymes have returned to baseline values, resume treatment at the reduced dosage, which subsequently may be increased to the full dosage</td>
</tr>
<tr>
<td>Resume treatment, either at full or reduced dosage, which subsequently may be increased to the full dosage</td>
<td>In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption or discontinuation for management of adverse reactions.</td>
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<tr>
<td>Discontinue treatment if the 100-mg twice-daily dose is not tolerated</td>
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ULN, upper limit of normal.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONT’D)**

**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 the following pages and full Prescribing Information, including Patient Information.
Additional considerations for monitoring and managing liver enzymes

**Conduct liver function tests (ALT, AST, and bilirubin)**
- Liver function tests should be conducted prior to initiation of treatment with OFEV (nintedanib), at regular intervals during the first 3 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

**Educate patients on the signs of liver damage**
- Make sure patients know to notify you right away if they have any of the following signs of a liver problem
  - Jaundice (e.g., skin or whites of eyes turn yellow)
  - Dark or brown (tea-colored) urine
  - Right-side stomach pain
  - Bleeding or bruising more easily than normal
  - Fatigue
  - Loss of appetite

**Dose modification or interruption may be necessary for liver enzyme elevations**
- For ALT or AST greater than 3x to less than 5x ULN without signs of liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, 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)
- For ALT or AST greater than 5x ULN, discontinue OFEV

**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.

Please see additional Important Safety Information on the following pages and full Prescribing Information, including Patient Information.
Additional considerations for managing GI-related adverse reactions

**advise** your patients before initiating OFEV (nintedanib)

- Talk to patients about the possibility of experiencing GI adverse reactions while taking OFEV. Diarrhea, nausea, and vomiting were the most commonly reported GI events occurring in patients who received OFEV.
- Inform patients that laxatives, stool softeners, and other medicines or dietary supplements may cause or worsen diarrhea.
- Recommend that they notify you at the first signs of symptoms or for any severe or persistent diarrhea, nausea, or vomiting.

**initiate** symptomatic treatment at the first signs of symptoms

At onset, treat with:

- Adequate hydration for patients experiencing diarrhea, vomiting, or nausea.
- Antidiarrheal medication (eg, loperamide) for patients experiencing diarrhea.
- Antiemetic medication for patients experiencing nausea or vomiting.

**dose modification** may be required if GI side effects are persistent or severe despite symptomatic treatment

Dose reduction, treatment interruption, or discontinuation may be required:

- Dose reduction and/or temporary interruption may be required until the specific adverse reaction resolves to levels that allow continuation of therapy.
- OFEV 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, OFEV should be discontinued.
- If severe symptoms persist, OFEV should be discontinued.

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONT'D)**

**Gastrointestinal Disorders (cont’d)**

**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.

Please see additional Important Safety Information on the following pages and full Prescribing Information, including Patient Information.
OFEV (NINTEDANIB) DEMONSTRATED REPRODUCIBLE REDuctions IN THE ANNUAL RATE OF FVC DECLINE ACROSS 3 CLINICAL TRIALS

OFEV SIGNIFICANTLY REDUCED THE RISK OF FIRST ACUTE IPF EXACERBATION IN 2 OUT OF 3 CLINICAL TRIALS

INPULSIS®-1 (Study 2)
INPULSIS®-2 (Study 3)
TOMORROW (Study 1)

INPULSIS®-1 (adjudicated)
INPULSIS®-2 (adjudicated)
TOMORROW (investigator-reported)

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.

Please see additional Important Safety Information on the following pages and full Prescribing Information, including Patient Information.
Provide your patients with access to their own personal OFEV care team designed to help meet their needs

Call 1-866-OPENDOOR (673-6366) or text “START” to 84537*

OPEN DOORS® AND THE PERSONAL OFEV (NINTEDANIB) CARE TEAM ENCOURAGE AN INFORMED AND PROACTIVE APPROACH TO IPF MANAGEMENT. THE PERSONAL OFEV CARE TEAM INCLUDES:

Nurse Counselor
• Helps patients understand IPF
• Answers patient questions about treatment with OFEV
• Available 24/7

Social Resource Specialist
• Calls patients periodically to see how they’re doing
• Finds local support for patients and/or caregivers
• Helps to identify local social services, like meal delivery, in-home support, or rides to doctor appointments

Case Manager
• Helps patients explore financial assistance options
• Assists in identifying benefits eligibility
• Coordinates paperwork, such as prior authorizations

Valuable patient resources:

Welcome Kit
• Includes a patient brochure, patient journal, medicine list, caregiver’s guide, patient opt-in consent form, loperamide samples, and the full Prescribing Information. The kit is sent to the patient’s home with their first delivery of OFEV

Patient Website—OFEV.com
• Includes information about IPF, treatment with OFEV, finding support, and insurance coverage, as well as information for caregivers

*Standard data rates may apply.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)

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.

Please see additional Important Safety Information on the following pages and full Prescribing Information, including Patient Information.
Encourage your patients to meet with an OFEV Clinical Educator

Programs for your patients and their caregivers

• A range of topics are covered, including living with IPF, what to expect from treatment, and how to get medication
  — In-depth information on topics such as supplemental oxygen, pulmonary rehabilitation, caregiving, and supportive/palliative care are also available
• A variety of forums are offered, including in the office, at support groups, or remote video calling
• A series of follow-up educational sessions can be scheduled to answer any questions and reinforce information

Programs for your practice

• The continuum of care is covered, including information for an accurate and timely diagnosis of IPF as well as support and training on the use of OFEV (nintedanib) for appropriate patients with IPF
  — Additional information on supplemental oxygen, pulmonary rehabilitation, caregiving, and supportive/palliative care are also available
• Can provide information about establishing a support group or speak at one

Initiate a program by calling OPEN DOORS® at 1-866-OPENDOOR (673-6366) or by asking your local OFEV sales consultant or Clinical Educator

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)

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.

Please see additional Important Safety Information on the following page and full Prescribing Information, including Patient Information.
IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

• Adverse reactions reported in greater than or equal to 5% of OFEV (nintedanib) 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. 0.0%), 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.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information, including Patient Information.