Dosing and management guide for your patients taking OFEV

Dosing for OFEV (nintedanib) is one capsule, twice daily, across all indications[1]

INDICATIONS

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

OFEV is indicated for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Please see Important Safety Information on the following pages and full Prescribing Information, including Patient Information.

OFEV® (nintedanib) capsules 150mg

Offer your patients dosing that is one capsule, twice daily[1]

RECOMMENDED TESTING

- **Conduct liver function tests (ALT, AST, and bilirubin)** in all patients 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 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** in females of reproductive potential prior to initiating treatment with OFEV and during treatment as appropriate

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[1]

Should be taken with food and swallowed whole with liquid. It should not be chewed or crushed[1]

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[1]

Dose reduction or temporary interruption of treatment with OFEV allows for the management of adverse reactions while supporting continued clinical benefit. If a patient does not tolerate dose reduction, discontinue treatment with OFEV[1-3]

- 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[1]
- The dosage of OFEV can be reduced, interrupted, or discontinued to manage adverse reactions[1]
- **Please see complete details regarding dose modifications on the next page**

OFEV IS AVAILABLE IN 2 DOSAGE STRENGTHS[1]

150-MG CAPSULE

Not shown at actual size

100-MG CAPSULE

Not shown at actual size

The most common adverse reactions were gastrointestinal (GI) in nature and generally of mild or moderate intensity[1]

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.

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OFEV® (nintedanib) capsules 150mg

Dose reduction, temporary interruption, or discontinuation can be used to manage adverse reactions[1]

DOSAGE MODIFICATION FOR THE MANAGEMENT OF ADVERSE REACTIONS:

ADVERSE REACTIONS

Symptomatic treatment, if applicable. This can include adequate hydration, antidiarrheals, or antiemetics for GI-related adverse reactions

Consider **dose reduction** to 100 mg twice daily or **treatment interruption** until the specific adverse reaction resolves to levels that allow for continuation of therapy

Resume treatment at the full dosage or at the reduced dosage, which subsequently may be increased to the full dosage

Discontinue treatment if the 100-mg twice-daily dose is not tolerated

ELEVATED LIVER ENZYMES

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**

When liver enzymes have returned to baseline values, resume treatment at the reduced dosage, which subsequently may be increased to the full dosage

Discontinue OFEV (nintedanib) in patients with either:

- ALT or AST elevations greater than 3x ULN with signs or symptoms of liver injury

OR

- ALT or AST elevations greater than 5x ULN

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

Full dosage=150 mg, twice daily; reduced dosage=100 mg, twice daily.

Adverse reactions should be treated at onset of symptoms[1]

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 clinical trials and post-marketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the post-marketing period. 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.
- In IPF studies, the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN.
- In the chronic fibrosing ILDs with a progressive phenotype study, the majority (95%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (94%) of patients with bilirubin elevations had elevations less than 2 times ULN.
- In the SSc-ILD study, a maximum ALT and/or AST greater than or equal to 3 times ULN was observed in 4.9% of patients treated with OFEV.

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OFEV® (nintedanib) capsules 150mg

Additional considerations for monitoring and managing liver enzymes

Conduct liver function tests (ALT, AST, and bilirubin) in all patients[1]

- 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[1]

- Make sure patients know to notify you right away if they have any of the following signs of a liver problem
  - Jaundice (eg, 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[1]

- 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 3x ULN with signs or symptoms of liver injury and for ALT or AST elevations greater than 5x ULN, discontinue OFEV

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes and Drug-Induced Liver Injury (cont'd)

- Patients with low body weight (less than 65 kg), patients who are 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.

Gastrointestinal Disorders

Diarrhea

- Events were primarily mild to moderate in intensity and occurred within the first 3 months.
- In IPF studies, diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. 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.
- In the chronic fibrosing ILDs with a progressive phenotype study, diarrhea was reported in 67% versus 24% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 16% and discontinuation in 6% of OFEV patients, compared to less than 1% of placebo-treated patients, respectively.

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Additional considerations for managing GI-related adverse reactions

a **advise your patients before initiating OFEV (nintedanib)[1]**

- 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

i **initiate symptomatic treatment at the first signs of symptoms[1]**

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

d **dose modification may be required if GI adverse reactions are persistent or severe despite symptomatic treatment[1]**

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders (cont'd)

Diarrhea (cont'd)

- In the SSc-ILD study, diarrhea was the most frequent gastrointestinal event reported in 76% versus 32% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 22% and discontinuation in 7% of OFEV patients versus 1% and 0.3% 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 dose reduction or 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

- In IPF studies, nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- In the chronic fibrosing ILDs with a progressive phenotype study, nausea was reported in 29% versus 9% and vomiting was reported in 18% versus 5% of patients treated with OFEV and placebo, respectively. Nausea led to discontinuation of OFEV in less than 1% of patients, and vomiting led to discontinuation of OFEV in 1% of the patients.

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OFEV offers comprehensive support for patients taking OFEV and their caregivers

OPENDOORS®
Individualized care and support for patients like you®

The OPEN DOORS® Patient Support Program helps your patients on OFEV (nintedanib) take an informed and proactive approach to care through education, support, and access assistance.

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

CLINICAL EDUCATORS
Engage. Empower. Educate.™

Clinical Educators can provide individualized educational programs to patients and their caregivers to help them understand their disease and how to manage it.

OFEV® Mentors

OFEV Patient Mentors can help inspire and empower your patients with their personal stories and experiences.

OFEV® | MENTOR CONNECTIONS

OFEV Patient Mentors can share their personal stories over the phone one-on-one with patients. Patients can call **1-855-378-5073** to register.

Welcome Kit
- Includes valuable educational resources and is sent to the patient's home with their first delivery of OFEV

Patient Website—OFEV.com
- Includes information about living with their disease, treatment with OFEV, finding support, and insurance coverage

Ask your OFEV Sales Consultant for more information about resources available for patients

*Standard data rates may apply.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders (cont'd)

Nausea and Vomiting (cont'd)

- In the SSc-ILD study, nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- In most patients, events were primarily of mild to moderate intensity. 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.

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IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

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 highly effective contraception during treatment and at least 3 months after the last dose of OFEV. As the impact of nintedanib on the effectiveness of hormonal contraception is unknown, advise women using hormonal contraceptives to add a barrier method. Verify pregnancy status prior to starting OFEV and during treatment as appropriate.

Arterial Thromboembolic Events

- In IPF studies, arterial thromboembolic events were reported in 2.5% of OFEV and less than 1% of placebo patients, respectively. Myocardial infarction (MI) was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and in less than 1% of placebo patients.
- In the chronic fibrosing ILDs with a progressive phenotype study, arterial thromboembolic events and MI were reported in less than 1% of patients in both treatment arms.
- In the SSc-ILD study, arterial thromboembolic events were reported in 0.7% of patients in both the OFEV-treated and placebo-treated patients. There were 0 cases of MI in OFEV-treated patients compared to 0.7% of placebo-treated 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.
- In IPF studies, bleeding events were reported in 10% of OFEV versus 7% of placebo patients.
- In the chronic fibrosing ILDs with a progressive phenotype study, bleeding events were reported in 11% of OFEV versus 13% of placebo patients.
- In the SSc-ILD study, bleeding events were reported in 11% of OFEV versus 8% of placebo patients.
- In clinical trials, epistaxis was the most frequent bleeding event. There have been post-marketing reports of non-serious and serious bleeding events, some of which were fatal. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation

- OFEV may increase the risk of gastrointestinal perforation.
- In IPF studies, gastrointestinal perforation was reported in less than 1% of OFEV versus in 0% of placebo patients.
- In the chronic fibrosing ILDs with a progressive phenotype study, gastrointestinal perforation was not reported in any treatment arm.
- In the SSc-ILD study, no cases of gastrointestinal perforation were reported in either OFEV or placebo-treated 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, have a previous history of diverticular disease, or who are 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.

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IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- Most common adverse reactions reported (greater than or equal to 5%) are diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased and hypertension.
- In IPF studies, the most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and MI (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.
- In the chronic fibrosing ILDs with a progressive phenotype study, the most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of OFEV patients and in 5% of placebo patients. No pattern was identified in the adverse events leading to death.
- In the SSc-ILD study, the most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% vs. 1.7%) and pneumonia (2.8% vs. 0.3%). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm.

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

References: 1. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2020. **2.** Richeldi L et al. *N Engl J Med.* 2011;365(12):1079-1087. **3.** Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.

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