PROGRESS AGAINST PROGRESSION

OF PULMONARY FIBROSIS[1-4]

3 INDICATIONS[1]

1 PROVEN THERAPY[1]

OFEV (nintedanib) is a tyrosine kinase inhibitor with a proven mechanism of action[1]

OFEV®
(nintedanib)
capsules 150mg

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).

IMPORTANT SAFETY INFORMATION

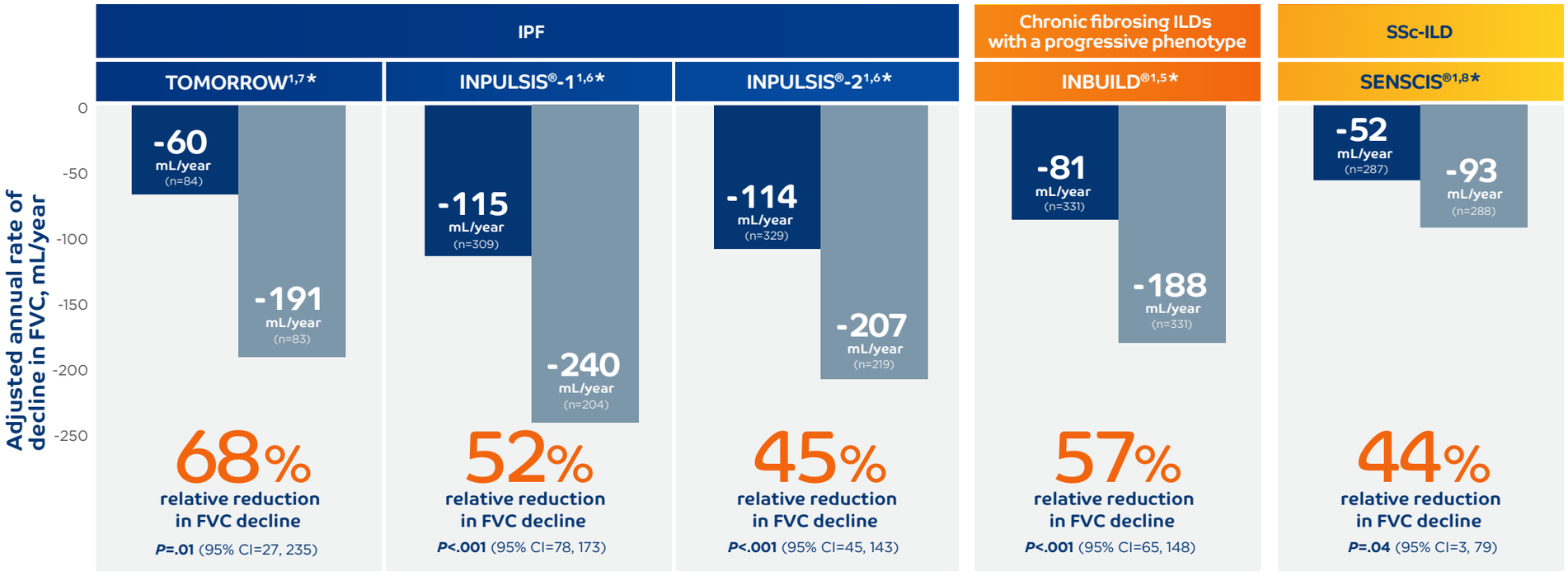
WARNINGS AND PRECAUTIONS

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.

With consistent results across 5 clinical trials, OFEV is advancing the management of fibrosing ILDs[1-4]

THE RELATIVE TREATMENT EFFECT OF OFEV (nintedanib) VS PLACEBO ON FVC DECLINE WAS CONSISTENT ACROSS TRIALS[1,5-8]



- **TOMORROW, INPULSIS®-1, and INPULSIS®-2** are landmark trials in IPF, the prototypical chronic progressive fibrosing ILD[1,4,9†]

- **INBUILD®** is the first-of-its-kind clinical trial in ILD in which patients were grouped based on clinical behavior[3‡]

- **SENSCIS®** is the largest phase 3 trial in SSc-ILD, one of the most common autoimmune ILDs[2,10§]

OFEV Placebo

CI, confidence interval; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; mRSS, modified Rodnan skin score; SSc-ILD, systemic sclerosis-associated ILD.

*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.[1]

†OFEV was studied in 1231 patients with IPF across 3 randomized, double-blind, placebo-controlled studies—one phase 2 (TOMORROW) and 2 phase 3 studies (INPULSIS®-1 and INPULSIS®-2). The primary endpoint was the annual rate of decline in FVC at 52 weeks (measured in mL/year). Time to first acute IPF exacerbation was a secondary endpoint.[1]

‡INBUILD® was a randomized, double-blind, placebo-controlled phase 3 trial evaluating OFEV in 663 patients with a range of chronic fibrosing ILDs with a progressive phenotype enrolled. The primary endpoint was the annual rate of decline in FVC at 52 weeks (measured in mL/year). Other endpoints included time to first acute ILD exacerbation and time to death.[1]

§SENSCIS® was a randomized, double-blind, placebo-controlled phase 3 trial evaluating OFEV in 580 patients with SSc-ILD. The primary endpoint was the annual rate of decline in FVC at 52 weeks (measured in mL/year). Absolute change from baseline in mRSS at Week 52 was a key secondary endpoint.[1]

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.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)
Elevated Liver Enzymes and Drug-Induced Liver Injury (cont'd)

- 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

OFEV has a proven safety profile across 5 clinical trials[1,5]

ADVERSE REACTIONS REPORTED IN ≥5% OF OFEV (nintedanib)-TREATED PATIENTS VS PLACEBO*

TOMORROW, INPULSIS®-1, and -2[1]

	OFEV (n=723)	Placebo (n=508)
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain	15%	6%
Vomiting	12%	3%
Liver enzyme elevation	14%	3%
Decreased appetite	11%	5%
Headache	8%	5%
Weight decreased	10%	3%
Hypertension	5%	4%

- In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs 0.6%)[1]
- Alopecia was also reported in more patients treated with OFEV than placebo (0.8% vs 0.4%)[1]

INBUILD®[1,5,11]

	OFEV (n=332)	Placebo (n=331)
Diarrhea	67%	24%
Nausea	29%	9%
Liver enzyme elevation	23%	6%
Abdominal pain	18%	5%
Vomiting	18%	5%
Decreased appetite	15%	5%
Nasopharyngitis	13%	12%
Weight decreased	12%	3%
Headache	11%	7%
Fatigue	10%	6%
Upper respiratory tract infection	7%	6%
Urinary tract infection	6%	4%
Back pain	6%	5%

*Only adverse reactions that were more common in OFEV were listed.[1]
†The incidence of infections and infestations was similar in the OFEV and placebo groups across trials (TOMORROW, INPULSIS®-1, and INPULSIS®-2: 56% vs 55%, respectively; INBUILD®: 53% vs 56%, respectively; and SENSCIS®: 63% vs 64%, respectively).[11]

SENSCIS®[1]

	OFEV (n=288)	Placebo (n=288)
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain	18%	11%
Liver enzyme elevation	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension	5%	2%

- In addition, alopecia was reported in patients treated with OFEV, more than placebo (1.4% vs 1.0%)[1]

✔ **NO NEW SAFETY CONCERNS** identified in INBUILD® compared with pivotal IPF trials[1,5]

✔ **THE MOST COMMON ADVERSE REACTIONS WERE GASTROINTESTINAL** in nature and generally of mild to moderate intensity[1]

✔ **NO OVERALL INCREASED RISK OF INFECTION** compared with placebo[11†]

The long-term safety of OFEV is evaluated in open-label extension trials[11-14]

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.

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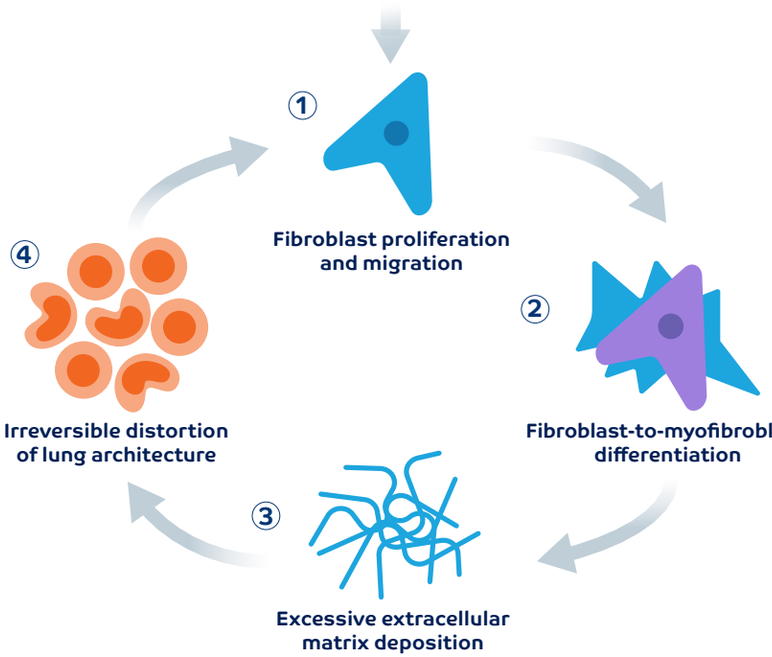
OFEV® (nintedanib) capsules 150mg

While ILDs differ, common pathogenic pathways to pulmonary fibrosis are shared[15-17]

REGARDLESS OF THE INITIAL CAUSE, THE FIBROTIC RESPONSE CAN BECOME SELF-SUSTAINING[16,17]

Chronic tissue injury or inflammation INITIATES THE FIBROTIC RESPONSE



1. Fibroblasts migrate from different sources to the site of injury at the alveolar epithelium and proliferate.[16]
2. Activated fibroblasts transition to myofibroblasts, which release extracellular matrix.[16]
3. Invading fibroblasts and myofibroblasts evade apoptosis, while continuing to release extracellular matrix, leading to excessive deposition.[16,18,19]
4. The cycle of abnormal repair leads to the irreversible distortion of lung architecture and increased lung tissue stiffness, which results in impaired gas exchange and pulmonary function.

   Increased lung tissue stiffness further activates fibroblasts in a feed-forward loop.[16,18]

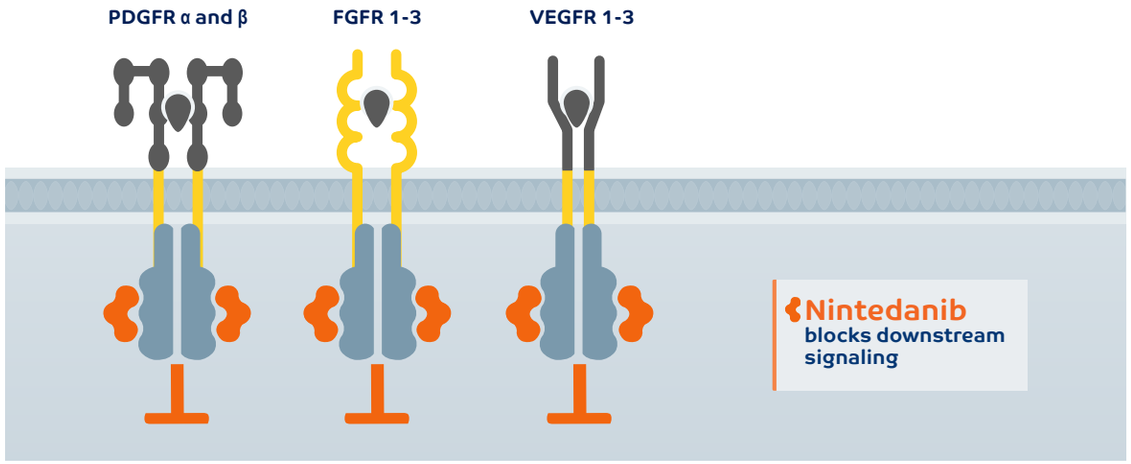
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)
Gastrointestinal Disorders

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.

Nintedanib is a multi-targeted tyrosine kinase inhibitor that inhibits pathways involved in the pathogenesis of ILDs[1,20,21]

NINTEDANIB BINDS INTRACELLULARLY TO KEY RECEPTORS TO BLOCK DOWNSTREAM SIGNALING CASCADES[1,21]



Nintedanib has been shown to inhibit[1,21]:

- Fibroblast proliferation
- Migration
- Fibroblast-to-myofibroblast transformation

FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

Nintedanib has a proven mechanism of action[1]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)
Gastrointestinal Disorders (cont'd)

Diarrhea (cont'd)

- 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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OFEV can benefit patients with fibrosing ILDs from different etiologies[1,5]

1st indication	2nd indication	3rd indication
OFEV (nintedanib) was first approved for the treatment of IPF—the prototypical chronic progressive fibrosing ILD[1,9]	OFEV is the only FDA-approved therapy to slow the rate of decline in pulmonary function in patients with SSc-ILD[1,2]	OFEV is the only FDA-approved therapy for the treatment of chronic fibrosing ILDs with a progressive phenotype[1,3]
2014	2019	2020

FDA, Food and Drug Administration.

OFEV can be used in patients who have an ILD that is progressive in nature and fibrosing in type[1,22]

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.

OFEV delivers a comprehensive body of evidence along with worldwide clinical experience[1,23,24]

5
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS[1]

~2500
PATIENTS STUDIED[1]

5+ YEARS
TREATING THE MOST COMMON ILD: IPF[1,22]

APPROVED IN OVER
75 COUNTRIES[23]

80,000+
PATIENT-YEARS OF WORLDWIDE CLINICAL EXPERIENCE IN IPF[24]

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.

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.

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

References: 1. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2020. **2.** Distler O et al. *Clin Exp Rheumatol*. 2017;35(suppl106):S75-S81. **3.** Flaherty KR et al. *BMJ Open Respir Res*. 2017;4(1):e000212. **4.** Boehringer Ingelheim Press Release. Available at: https://www.boehringer-ingelheim.us/press-release/fda-grants-ofev-breakthrough-therapy-designation-chronic-fibrosing-ilds-progressive. Updated October 10, 2019. Accessed May 6, 2020. **5.** Flaherty KR et al. *N Engl J Med*. 2019;381(18):1718-1727. **6.** Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med*. 2014;370(22):2071-2082. **7.** Richeldi L et al. *N Engl J Med*. 2011;365(12):1079-1087. **8.** Distler O et al. *N Engl J Med*. 2019;380(26):2518-2528. **9.** Cottin V et al. *Eur Respir Rev*. 2019;28(151). doi:10.1183/16000617.0100-2018. **10.** Koo SM, Uh ST. *Korean J Intern Med*. 2017;32(4):600-610. **11.** Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **12.** Crestani B et al. *Lancet Respir Med*. 2019;7(1):60-68. **13.** Food and Drug Administration. Arthritis Advisory Committee briefing materials. https://www.fda.gov/media/129233/download. Updated June 24, 2019. Accessed May 18, 2020. **14.** National Institute of Health. https://clinicaltrials.gov/ct2/show/NCT03820726. Updated April 24, 2020. Accessed May 6, 2020.
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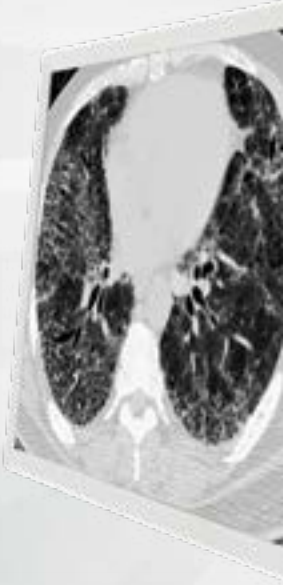
OFEV®
(nintedanib)
capsules 150mg

FACE FIBROSING ILDs HEAD ON



✔ 3 indications[1]

- For the treatment of IPF
- For the treatment of chronic fibrosing ILDs with a progressive phenotype
- To slow the rate of decline in pulmonary function in patients with SSc-ILD

✔ Proven mechanism of action[1]

- Multi-targeted tyrosine kinase inhibitor
- Inhibits key pathways involved in ILD pathogenesis

✔ Demonstrated reduction in lung function decline across 3 indications[1]

✔ Robust clinical experience[1,24]

- 5 randomized, double-blind, placebo-controlled trials[1]
- ~2500 patients studied[1]
- 80,000+ patient-years of worldwide clinical experience in IPF[24]

IMPORTANT SAFETY INFORMATION

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.

CL-OF-100031 03.2020

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