INDICATION AND USAGE
OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).
Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
Executive summary

Idiopathic pulmonary fibrosis (IPF) is a rare and serious lung disease with an unknown etiology. According to the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT), IPF is defined as a specific form of chronic fibrosing interstitial pneumonia of unknown cause, occurring in older adults, and limited to the lungs.

**IPF is a rare disease* with up to 132,000 people in the United States having IPF.**

For healthcare professionals, diagnosing IPF can be a challenge. In fact, the average time from IPF symptom onset to IPF diagnosis is approximately 1 to 2 years. IPF manifests in an unexplained manner and patients are often misdiagnosed with other conditions, such as bronchitis, asthma, chronic obstructive pulmonary disease (COPD), emphysema, or heart disease. The accuracy of an IPF diagnosis increases with multidisciplinary discussion between IPF experts, including pulmonologists, radiologists, and pathologists.

*Rare Diseases Act of 2002: defines orphan diseases as rare diseases and disorders that affect small populations—typically populations smaller than 200,000 individuals in the United States."
IPF overview

INCI DENCE AND PREVALENCE

IPF is considered a rare disease,* affecting up to 132,000 people in the United States.1-5† The prevalence of IPF is estimated as 14‡ to 43§ out of 100,000 persons, and the incidence of IPF is estimated as 7‡ to 16§ per 100,000 persons.4

There are between 14,000‡ and 34,000§ new cases of IPF diagnosed each year, and both the prevalence and incidence of IPF increase with age.4 The median age when IPF is diagnosed is 66 years, and the disease affects more men than women.4,10,11 According to a recent study, 7 out of 10 patients were covered by Medicare.12

Both prevalence and incidence of IPF increase with age4

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*Rare Diseases Act of 2002: defines orphan diseases as rare diseases and disorders that affect small populations—typically populations smaller than 200,000 individuals in the United States.3
†Estimated based on broad prevalence definition in Raghu et al and 2010 US census data.4,5
‡ Narrow definition: patients meeting broad definition who also had evidence of a prior diagnostic test (including surgical lung biopsy, transbronchial lung biopsy, or computed tomography of the thorax).4
§ Broad definition: patients with an ICD-9 code (516.3) for idiopathic fibrosing alveolitis and no subsequent diagnoses of other interstitial lung diseases.4

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Adapted from Raghu G et al.4

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Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
IPF overview (cont’d)

PATHOPHYSIOLOGY

Researchers are looking to clarify the underlying pathophysiology of IPF to help them better inform IPF diagnosis and treatment decisions.\textsuperscript{13,14} There is a theory that IPF is initially formed by repetitive injuries to the alveolar epithelium.\textsuperscript{13} These injuries initiate fibroblast migration and proliferation.\textsuperscript{13,14} The continuous disruption of the alveolar epithelial cell layer or basement membrane causes an imbalance in proteases and antiproteases, resulting in increased angiogenesis and myofibroblast foci formation leading to fibrosis.\textsuperscript{13}

Current hypothesis of the pathogenesis of IPF\textsuperscript{12}

![Diagram of IPF pathogenesis]

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
FDA-APPROVED TREATMENT OPTIONS

There are FDA-approved treatment options, including OFEV (nintedanib), available for patients with IPF. The use of OFEV to treat patients with IPF is recommended in the 2015 ATS/ERS/JRS/ALAT Clinical Practice Guideline.

Recommendation

This recommendation for OFEV use in IPF patients is conditional with a moderate confidence in effect estimates. Interpretation of this conditional recommendation for patients and clinicians

• The majority of patients would want OFEV treatment, but many would not

• Clinicians should recognize that different choices will be appropriate for individual patients and each patient must be helped to arrive at a management decision consistent with his or her values and preferences

Justifications and Considerations

In making this recommendation, the 2015 guideline places a high value on the potential benefit of OFEV on patient-important outcomes, such as disease progression, as measured by:

• The rate of forced vital capacity (FVC) decline

• Mortality

A lower value is placed on:

• Potentially significant adverse effects

• Expected treatment cost

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
Considerations include:\n
- No significant effect on overall mortality was seen with OFEV
- The concerns based on current costs may limit feasibility and use
- Adverse effects were commonly reported with OFEV, specifically diarrhea, and patients must be informed of these risks when making treatment decisions
- Available evidence focuses only on patients with IPF with mild to moderate impairment (FVC ≥50%) in pulmonary function tests and it is unknown if benefits would differ in more severe patients

Conclusions

When treating patients with IPF, clinicians are advised to:\n
- Individualize therapy decisions with their patients as suggested by this conditional recommendation
- Exercise caution in comparing the relative net benefits of interventions
- Avoid inferring that guideline recommendations of similar strength, ie, grade, will achieve the same net benefit or harm
- Consider significant variations in inclusion criteria, the confidence in effect estimates, and cost to be important factors

OTHER TREATMENT OPTIONS

The 2011 ATS/ERS/JRS/ALAT guidelines provide limited recommendations for treating IPF, including beginning pulmonary rehabilitation in the majority of patients, initiating long-term oxygen therapy in patients with clinically significant resting hypoxemia, and considering and evaluating patients for lung transplantation in a timely manner.²
IPF overview (cont’d)

For patients with IPF who meet eligibility requirements, lung transplantation has been a possible treatment option. In fact, patients with IPF represent approximately one-third of all lung transplants performed and the median survival after lung transplant in patients with IPF is approximately 4 years.


*The guideline development panel reviewed the evidence and formulated grades for recommendations using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.
References

INDICATION AND USAGE
OFEV 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
• OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
• Conduct liver function tests prior to treatment, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Monitor for adverse reactions and consider dosage modifications, interruption, or discontinuation as necessary for liver enzyme elevations.

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 <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 anti-diarrheal 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.

Please see additional Important Safety Information on page 11 and click here for full Prescribing Information, including Patient Information.
EXECUTIVE SUMMARY

PRODUCT DESCRIPTION

CLINICAL PHARMACOLOGY

CLINICAL EFFICACY

SAFETY PROFILE

IPF OVERVIEW

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont’d)

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.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus in 0% placebo patients. Use caution when treating patients who have had recent abdominal surgery. 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 ≥5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.

• The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. 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.

Please click here for full Prescribing Information, including Patient Information.
**INDICATION AND USAGE**

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

**DESCRIPTION**

OFEV capsules contain nintedanib, a kinase inhibitor. Nintedanib is presented as the ethanesulfonate salt (esylate), with the chemical name 1H-Indole-6-carboxylic acid, 2,3-dihydro-3-[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino]phenylmethylene]-2-oxo-,methyl ester, (3Z)-, ethanesulfonate (1:1). Its structural formula is shown to the right.

Nintedanib esylate is a bright yellow powder with an empirical formula of C₃₁H₄₃N₅O₄·C₂H₆O₃S and a molecular weight of 649.76 g/mol.

OFEV capsules for oral administration are available in 2 dose strengths containing 100 mg or 150 mg of nintedanib (equivalent to 120.40 mg or 180.60 mg nintedanib ethanesulfonate, respectively). The inactive ingredients of OFEV are the following: fill material: triglycerides, hard fat, and lecithin; capsule shell: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, and black ink.

**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 (PK) 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 dose 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.

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
DOSAGE AND ADMINISTRATION (cont’d)

Dosage Modification due to Adverse Reactions

In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV (nintedanib) 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. For aspartate 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. 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). Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

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

HOW SUPPLIED/STORAGE AND HANDLING

150 mg: brown, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and “150.” They are packaged in high-density polyethylene (HDPE) bottles with a child-resistant closure, available as follows:

| Bottles of 60 | NDC: 0597-0145-60 |

100 mg: peach, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and “100.” They are packaged in HDPE bottles with a child-resistant closure, available as follows:

| Bottles of 60 | NDC: 0597-0143-60 |

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from exposure to high humidity and avoid excessive heat. If repackaged, use USP tight container. Keep out of reach of children.
Clinical pharmacology

Mechanism of Action
Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and nonreceptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling that is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology. In addition, nintedanib inhibits the following nRTKs: Lck, Lyn, and Src kinases. The contribution of FLT3 and nRTK inhibition to IPF efficacy is unknown.

Pharmacodynamics
Cardiac Electrophysiology
In a study in patients with renal cell cancer, QT/QTc measurements were recorded and showed that a single oral dose of 200-mg nintedanib as well as multiple oral doses of 200-mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

Pharmacokinetics
The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and patients with cancer. The PK of nintedanib is linear. Dose proportionality was shown by an increase of nintedanib exposure with increasing doses (dose range 50 to 450 mg once daily and 150 to 300 mg twice daily). Accumulation upon multiple administrations in patients with IPF was 1.76-fold for area under the curve (AUC). Steady-state plasma concentrations were achieved within 1 week of dosing. Nintedanib trough concentrations remained stable for more than 1 year. The interindividual variability in the PK of nintedanib was moderate to high (coefficient of variation of standard PK parameters in the range of 30% to 70%), intraindividual variability low to moderate (coefficients of variation below 40%).

Absorption
Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as a soft gelatin capsule under fed conditions. The absolute bioavailability of a 100-mg dose was 4.7% (90% confidence interval [CI]=3.62, 6.08) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

After food intake, nintedanib exposure increased by approximately 20% compared with administration under fasted conditions (90% CI=95.3% to 152.5%), and absorption was delayed (median T_{max} fasted: 2.00 hours; fed: 3.98 hours), irrespective of the food type.
Clinical pharmacology (cont’d)

Pharmacokinetics (cont’d)

Distribution
Nintedanib follows biphasic disposition kinetics. After intravenous infusion, a high volume of distribution, which was larger than total body volume (Vss: 1050 L), was observed. The in vitro protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8%. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87.

Elimination
The effective half-life of nintedanib in patients with IPF was 9.5 hours (gCV 31.9%). Total plasma clearance (CL) after intravenous infusion was high (CL: 1390 mL/min; gCV 28.8%). Urinary excretion of unchanged drug within 48 hours was about 0.05% of the dose after oral and about 1.4% of the dose after intravenous administration; the renal clearance was 20 mL/min.

Metabolism
The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by glucuronosyltransferase (UGT) enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biotransformation of nintedanib consisted of cytochrome P (CYP) pathways, with CYP3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human absorption, distribution, metabolism, and elimination study. In vitro, CYP-dependent metabolism accounted for about 5% compared with about 25% ester cleavage.

Excretion
The major route of elimination of drug-related radioactivity after oral administration of [14C] nintedanib was via fecal/biliary excretion (93.4% of dose), and the majority of OFEV (nintedanib) was excreted as BIBF 1202. The contribution of renal excretion to the total clearance was low (0.65% of dose). The overall recovery was considered complete (above 90%) within 4 days after dosing.

Specific Populations
Age, Body Weight, and Sex
Based on population PK analysis, age and body weight were correlated with nintedanib exposure. However, their effects on exposure are not sufficient to warrant a dose adjustment. There was no influence of sex on the exposure of nintedanib.

Renal Impairment
Based on a population PK analysis of data from 933 patients with IPF, exposure to nintedanib was not influenced by mild (creatinine clearance [CrCl]: 60 mL/min to 90 mL/min; n=399) or moderate (CrCl: 30 mL/min to 60 mL/min; n=116) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited.
Clinical pharmacology (cont’d)

Pharmacokinetics (cont’d)

Hepatic Impairment

A dedicated single-dose phase I pharmacokinetics study of OFEV (nintedanib) compared 8 subjects with mild hepatic impairment (Child Pugh A) and 8 subjects with moderate hepatic impairment (Child Pugh B) to 17 subjects with normal hepatic function. In subjects with mild hepatic impairment, the mean exposure to nintedanib was 2.4-fold higher based on $C_{\text{max}}$ (90% CI 1.6 to 3.6) and 2.2-fold higher based on $\text{AUC}_{0-\text{inf}}$ (90% CI 1.4 to 3.5). In subjects with moderate hepatic impairment, exposure was 6.9-fold higher based on $C_{\text{max}}$ (90% CI 4.4 to 11.0) and 7.6-fold higher based on $\text{AUC}_{0-\text{inf}}$ (90% CI 5.1 to 11.3). Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Smokers

In the population PK analysis, the exposure of nintedanib was 21% lower in current smokers compared with ex- and never-smokers. The effect is not sufficient to warrant a dose adjustment.

Drug Interaction Studies

Potential for Nintedanib to Affect Other Drugs

Effect of nintedanib coadministration on pirfenidone AUC and maximum plasma concentration ($C_{\text{max}}$) was evaluated in a multiple-dose study. Nintedanib did not have an effect on the exposure of pirfenidone.

In in vitro studies, nintedanib was shown not to be an inhibitor of organic anion-transporting polypeptide (OATP)-1B1, OATP-1B3, OATP-2B1, organic cation transporter (OCT)-2, or multidrug resistance-associated protein 2 (MRP-2). In vitro studies also showed that nintedanib has weak inhibitory potential on OCT-1, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp); these findings are considered to be of low clinical relevance. Nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in vitro.

Potential for Other Drugs to Affect Nintedanib

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with the P-gp and CYP3A4 inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on $C_{\text{max}}$ in a dedicated drug-drug interaction study. In a drug-drug interaction study with the P-gp and CYP3A4 inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on $C_{\text{max}}$ upon coadministration with rifampicin compared with administration of nintedanib alone.

Based on a multiple-dose study in Japanese patients with IPF, exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on $C_{\text{max}}$ upon coadministration with pirfenidone compared with administration of nintedanib alone.

Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH <3. However, in the clinical trials, coadministration with proton pump inhibitors or histamine H2 antagonists did not influence the exposure (trough concentrations) of nintedanib.

In in vitro studies, nintedanib was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, MRP-2, or BCRP. In vitro studies also showed that nintedanib was a substrate of OCT-1; these findings are considered to be of low clinical relevance.
Clinical efficacy

CLINICAL STUDIES DESCRIPTION

The clinical efficacy of OFEV (nintedanib) has been studied in 1231 patients with IPF in one phase 2 (Study 1) and two phase 3 studies (Studies 2 and 3). These were randomized, double-blind, placebo-controlled studies comparing treatment with OFEV 150 mg twice daily to placebo for 52 weeks.

Studies 2 and 3 were identical in design. Study 1 was very similar in design. Patients were randomized in a 3:2 ratio (1:1 for Study 1) to either OFEV 150 mg or placebo twice daily for 52 weeks. Study 1 also included other treatment arms (50 mg daily, 50 mg twice daily, and 100 mg twice daily) that are not further discussed. The primary endpoint was the annual rate of decline in forced vital capacity (FVC). Time to first acute IPF exacerbation was a key secondary endpoint in Studies 2 and 3 and a secondary endpoint in Study 1. Change from baseline in FVC percent predicted and survival were additional secondary endpoints in all studies.

Patients were required to have a diagnosis of IPF (American Thoracic Society [ATS], European Respiratory Society [ERS], Japanese Respiratory Society [JRS], and Latin American Thoracic Association [ALAT] criteria) for <5 years. Diagnoses were centrally adjudicated based on radiologic and, if applicable, histopathologic confirmation. Patients were required to be ≥40 years of age with an FVC ≥50% of predicted and a carbon monoxide diffusing capacity (DL\textsubscript{CO}, corrected for hemoglobin) 30% to 79% of predicted. Patients with relevant airway obstruction (ie, prebronchodilator forced expiratory volume in 1 second [FEV\textsubscript{1}]/FVC <0.7) or, in the opinion of the investigator, likely to receive a lung transplant during the studies were excluded (being listed for lung transplant was acceptable for inclusion). Patients with >1.5 times ULN of ALT, AST, or bilirubin; patients with a known risk or predisposition to bleeding; patients receiving a full dose of anticoagulation treatment; and patients with a recent history of myocardial infarction or stroke were excluded from the studies. Patients were also excluded if they received other investigational therapy, azathioprine, cyclophosphamide, or cyclosporine A within 8 weeks of entry into this trial, or n-acetyl cysteine and prednisone (>15 mg/day or equivalent) within 2 weeks. The majority of patients were Caucasian (60%) or Asian (30%) and male (79%). Patients had a mean age of 67 years and a mean FVC percent predicted of 80%.

Annual Rate of Decline in FVC

A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving OFEV compared with patients receiving placebo based on the random coefficient regression model, adjusted for gender, height, and age. The treatment effect on FVC was consistent in all 3 studies. See Table 1 for individual study results.
Clinical efficacy (cont’d)

Table 1: Annual Rate of Decline in FVC (mL) in Studies 1, 2, and 3*

<table>
<thead>
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<th>Study</th>
<th>OFEV 150 mg twice daily</th>
<th>Placebo</th>
<th>OFEV 150 mg twice daily</th>
<th>Placebo</th>
<th>OFEV 150 mg twice daily</th>
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<td>309</td>
<td>204</td>
<td>329</td>
<td>219</td>
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<tr>
<td>Study 2</td>
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<td>-115</td>
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<tr>
<td>Study 3</td>
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<td>94</td>
<td>27 (235)</td>
<td>178 (173)</td>
<td>45 (143)</td>
</tr>
</tbody>
</table>

*Randomized set in Study 1; treated set in Studies 2 and 3.
†Estimated based on a random coefficient regression model.

Figure 1 displays the change from baseline over time in both treatment groups for Study 2. When the mean observed FVC change from baseline was plotted over time, the curves diverged at all timepoints through week 52. Similar plots were seen for Studies 1 and 3.

**Figure 1: Mean (SEM) Observed FVC Change From Baseline (mL) Over Time in Study 2**

![Figure 1: Mean (SEM) Observed FVC Change From Baseline (mL) Over Time in Study 2](image)

Number of patients:
- Placebo: 202, 198, 200, 194, 192, 187, 165
- OFEV 150 mg bid: 303, 301, 298, 292, 284, 274, 250

bid, twice daily.

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
Clinical efficacy (cont’d)

Change From Baseline in Forced Vital Capacity Percent Predicted

Figure 2 presents the cumulative distribution for all cut-offs for the change from baseline in FVC percent predicted at week 52 for Study 2. For all categorical declines in lung function, the proportion of patients declining was lower on OFEV (nintedanib) than on placebo. Study 3 showed similar results.

Figure 2: Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52 (Study 2).* The vertical lines indicate ≥0% decline or ≥10% decline.

*Missing data for change from baseline at week 52 in percent-predicted FVC (due to death, lost to follow-up or censoring before 52 weeks) was imputed using the worst decline from baseline at week 52 observed among all patients with available data, regardless of treatment.

Time to First Acute IPF Exacerbation

Acute IPF exacerbation was defined as unexplained worsening or development of dyspnea within 30 days, new diffuse pulmonary infiltrates on chest x-ray, and/or new high-resolution CT parenchymal abnormalities with no pneumothorax or pleural effusion, and exclusion of alternative causes. Acute IPF exacerbation was adjudicated in Studies 2 and 3. In Studies 1 (investigator-reported) and 3 (adjudicated), the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving OFEV compared with placebo (HR=0.16, 95% CI=0.04, 0.71) and (HR=0.20, 95% CI=0.07, 0.56), respectively. In Study 2 (adjudicated), there was no difference between the treatment groups (HR=0.55, 95% CI=0.20, 1.54).
Clinical efficacy (cont’d)

Survival Analysis
Survival was evaluated for OFEV (nintedanib) compared to placebo in Studies 2 and 3 as an exploratory analysis to support the primary endpoint (FVC). All-cause mortality was assessed over the study duration and available follow-up period, irrespective of cause of death and whether patients continued treatment. All-cause mortality did not show a statistically significant difference. (See figure below.)

Figure 3: Kaplan-Meier Estimates of All-Cause Mortality at Vital Status—End of Study: Studies 2 and 3

![Kaplan-Meier Estimates of All-Cause Mortality at Vital Status—End of Study: Studies 2 and 3](image)

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

**Hepatic Impairment**
Treatment with OFEV (nintedanib) 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 dose of OFEV.

**Elevated Liver Enzymes**
In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, alkaline phosphatase [ALKP], gamma-glutamyl transpeptidase [GGT]). Liver enzyme increases were reversible with dose modification or interruption and were not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations.

**Gastrointestinal Disorders**

**Diarrhea**
Diarrhea was the most frequent gastrointestinal event reported in 62% vs 18% of patients treated with OFEV and placebo, respectively. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared with 0 placebo-treated patients. Diarrhea led to discontinuation in 5% of the OFEV-treated patients compared with <1% of placebo-treated patients.

Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (eg, 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 despite symptomatic treatment, discontinue treatment with OFEV.

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
SAFETY PROFILE (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

Gastrointestinal Disorders (cont’d)

Nausea and Vomiting
Nausea was reported in 24% vs 7% and vomiting was reported in 12% vs 3% of patients treated with OFEV (nintedanib) and placebo, respectively. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of patients.

For nausea or vomiting that persists despite appropriate supportive care, including antiemetic therapy, dose reduction or treatment interruption may be required. 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 nausea or vomiting does not resolve, discontinue treatment with OFEV.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to treatment with OFEV.

Arterial Thromboembolic Events
Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared with 0.4% 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
Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo.

Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
WARNINGS AND PRECAUTIONS (cont’d)

Gastrointestinal Perforation

Based on the mechanism of action, OFEV (nintedanib) may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV compared with 0 cases in the placebo-treated patients.

Use caution when treating patients who have had recent abdominal surgery. 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.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OFEV was evaluated in over 1000 patients with IPF, with over 200 patients exposed to OFEV for more than 2 years in clinical trials.

OFEV was studied in 3 randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%).

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 patients treated with OFEV, more than placebo, were pneumonia (0.7% vs 0.6%), lung neoplasm malignant (0.3% vs 0%), and myocardial infarction (MI) (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-treated patients and 1.8% of placebo-treated patients.

Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%).

Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%).

The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 2.
WARNINGs AND PRECAUTIONs (cont’d)
Clinical Trials Experience (cont’d)

Table 2: Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OFEV, 150 mg (n=723)</th>
<th>Placebo (n=508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>62%</td>
<td>18%</td>
</tr>
<tr>
<td>Nausea</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver enzyme elevation†</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Nervous systemic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal tenderness.
†Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
‡Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV (nintedanib), more than placebo (1.1% vs 0.6%).

DRUG INTERACTIONS

P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (eg, 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 (eg, carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

Anticoagulants

Nintedanib is a VEGFR inhibitor, and 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

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%.

Data

Animal Data

In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female: male ratio of approximately 71:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased postnatal viability of rat pups during the first 4 postnatal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Lactation

Risk Summary

There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant, or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats [see Data]. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV.

Data

Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites.
**USE IN SPECIFIC POPULATIONS (cont’d)**

**Females and Males of Reproductive Potential**

Based on findings from animal studies and its mechanism of action, OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential. Counsel patients on pregnancy prevention and planning.

*Pregnancy Testing*

Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV.

*Contraception*

Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV.

*Infertility*

Based on animal data, OFEV may reduce fertility in females of reproductive potential.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the total number of subjects in phase 2 and phase 3 clinical studies of OFEV, 60.8% were ≥65 years old, while 16.3% were ≥75 years old. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were ≥65 and younger subjects; no overall differences in safety were observed between subjects who were ≥65 or ≥75 and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

**Hepatic Impairment**

Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended.

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.
USE IN SPECIFIC POPULATIONS (cont’d)

Renal Impairment

Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease.

Smokers

Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

OVERDOSAGE

In the trials, 1 patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A nonserious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in 2 patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

Reference

OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016.

Please see Important Safety Information on pages 10-11 and click here for full Prescribing Information, including Patient Information.