CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OFEV safely and effectively. See full prescribing information for OFEV.

OFEV® (nintedanib) capsules, for oral use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
OFEV is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food. (2.2)
- Consider temporary dose reduction to 100 mg, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 6)
- Prior to treatment, conduct liver function tests. (2.1, 5.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 150 mg and 100 mg (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with OFEV. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
- Gastrointestinal disorders: Diarrhea, nausea, and vomiting have occurred with OFEV. Treat patients at first signs with adequate hydration and antidiarrheal medicine (e.g., loperamide) or anti-emetics. Discontinue OFEV if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment. (5.2)
- Embryofetal toxicity: Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.3)
- Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. (5.4)
- Bleeding events have been reported. Use OFEV in patients with known bleeding risk only if anticipated benefit outweighs the potential risk. (5.5)
- Gastrointestinal perforation has been reported. Use OFEV with caution when treating patients with recent abdominal surgery. Discontinue 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. (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5%) are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Coadministration of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for tolerability of OFEV. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Nursing mothers: Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (8.3)
- Hepatic impairment: Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment. OFEV is not recommended for use in patients with moderate or severe hepatic impairment. (8.6, 12 3)
- Renal impairment: The safety and efficacy of OFEV have not been studied in patients with severe renal impairment and end-stage renal disease. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to OFEV Administration

Conduct liver function tests prior to initiating treatment with OFEV *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

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

OFEV capsules should be taken with food *[see Clinical Pharmacology (12.3)]* and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known.

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

2.3 Dosage Modification due to Adverse Reactions

In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.6) and Adverse Reactions (6.1)]*.

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) *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

3 DOSAGE FORMS AND STRENGTHS

150 mg capsules: brown, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "150".

100 mg capsules: peach, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "100".

4 CONTRAINDICATIONS

None

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5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). 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. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

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 *[see Dosage and Administration (2.1, 2.3)]*.

5.2 Gastrointestinal Disorders

Diarrhea

Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions (6.1)]*. 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 to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <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 (e.g., loperamide), and consider treatment interruption if diarrhea continues *[see Dosage and Administration (2.3)]*. 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.

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 *[see Adverse Reactions (6.1)]*. 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 the patients.

For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required *[see Dosage and Administration (2.3)]*. 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.

5.3 Embryofetal Toxicity

OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetocidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised

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to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV *[see Use in Specific Populations (8.1)]*.

5.4 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 to 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.

5.5 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.

5.6 Gastrointestinal Perforation

Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme and Bilirubin Elevations *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Disorders *[see Warnings and Precautions (5.2)]*
- Embryofetal Toxicity *[see Warnings and Precautions (5.3)]*
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*
- Risk of Bleeding *[see Warnings and Precautions (5.5)]*
- Gastrointestinal Perforation *[see Warnings and Precautions (5.6)]*

6.1 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 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials.

OFEV was studied in three 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

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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 (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 1.

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

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous systemic disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] 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.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

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

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7 DRUG INTERACTIONS

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

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4 *[see Clinical Pharmacology (12.3)]*. 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 (e.g., erythromycin) with OFEV may increase exposure to nintedanib *[see Clinical Pharmacology (12.3)]*. 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 *[see Dosage and Administration (2.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

7.2 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 *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [See Warnings and Precautions (5.3)]

OFEV can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV.

In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects 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 post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

8.3 Nursing Mothers

Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

8.6 Hepatic Impairment
Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%) *[see Clinical Pharmacology (12.3)]*. No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended *[see Warnings and Precautions (5.1)]*.

8.7 Renal Impairment
Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney *[see Clinical Pharmacology (12.3)]*. 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.

8.8 Smokers
Smoking was associated with decreased exposure to OFEV *[see Clinical Pharmacology (12.3)]*, 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.

10 OVERDOSAGE
In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two 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.

11 DESCRIPTION
OFEV capsules contain nintedanib, a kinase inhibitor *[see Mechanism of Action (12.1)]*. Nintedanib is presented as the ethanesulfonate salt (esylate), with the chemical name 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino]phenylmethylene]-2-oxo-,methyl ester, (3*Z*)-, ethanesulfonate (1:1).

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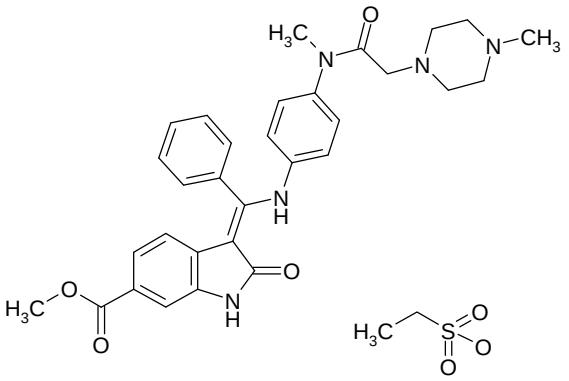
Its structural formula is:



Nintedanib esylate is a bright yellow powder with an empirical formula of $C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$ 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, lecithin. Capsule Shell: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor 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 which 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a study in renal cell cancer patients, 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.

12.3 Pharmacokinetics

The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients. 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 AUC. Steady-state plasma concentrations were achieved within one week of dosing. Nintedanib trough concentrations remained stable for more than one year. The inter-individual variability in the PK of nintedanib was moderate to high (coefficient of variation of standard PK parameters in the range of 30% to 70%), intra-individual variability low to moderate (coefficients of variation below 40%).

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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% CI: 3.62 to 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 to 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.

Distribution
Nintedanib follows bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution which was larger than total body volume (V_{ss}: 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 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 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 CYP pathways, with CYP 3A4 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 to about 25% ester cleavage.

Excretion
The major route of elimination of drug-related radioactivity after oral administration of [^{14}C] nintedanib was via fecal/biliary excretion (93.4% of dose), and the majority of OFEV 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 (CrCl: 60 to 90 mL/min; n=399) or moderate (CrCl: 30 to 60 mL/min; n=116) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited.

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Hepatic Impairment
No dedicated PK study was conducted in patients with hepatic impairment. As nintedanib is eliminated primarily by biliary/fecal excretion (>90%), hepatic impairment is likely to increase plasma nintedanib concentrations. Clinical studies excluded patients with AST or ALT greater than 1.5 times ULN. Patients with total bilirubin greater than 1.5 times ULN were also excluded. Therefore, monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment.

Smokers
In the population PK analysis, the exposure of nintedanib was 21% lower in current smokers compared to 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 C_{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 OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2. *In vitro* studies also showed that nintedanib has weak inhibitory potential on OCT-1, BCRP, and 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_{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_{max} upon coadministration with rifampicin compared to administration of nintedanib alone.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year oral carcinogenicity studies of nintedanib in rats and mice have not revealed any evidence of carcinogenic potential. Nintedanib was dosed up to 10 and 30 mg/kg/day in rats and mice, respectively. These doses were less than and approximately 4 times the MRHD on a plasma drug AUC basis.

Nintedanib was negative for genotoxicity in the *in vitro* bacterial reverse mutation assay, the mouse lymphoma cell forward mutation assay, and the *in vivo* rat micronucleus assay.

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In rats, nintedanib reduced female fertility at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day). Effects included increases in resorption and post-implantation loss, and a decrease in gestation index. Changes in the number and size of corpora lutea in the ovaries were observed in chronic toxicity studies in rats and mice. An increase in the number of females with resorptions only was observed at exposures approximately equal to the MRHD (on an AUC basis at an oral dose of 20 mg/kg/day). Nintedanib had no effects on male fertility in rats at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day).

14 CLINICAL STUDIES

The clinical efficacy of OFEV has been studied in 1231 patients with IPF in one phase 2 (Study 1) and two phase 3 (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 (ATS/ERS/JRS/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 (DLCO, corrected for hemoglobin) 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre-bronchodilator FEV_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 to 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 2 for individual study results.

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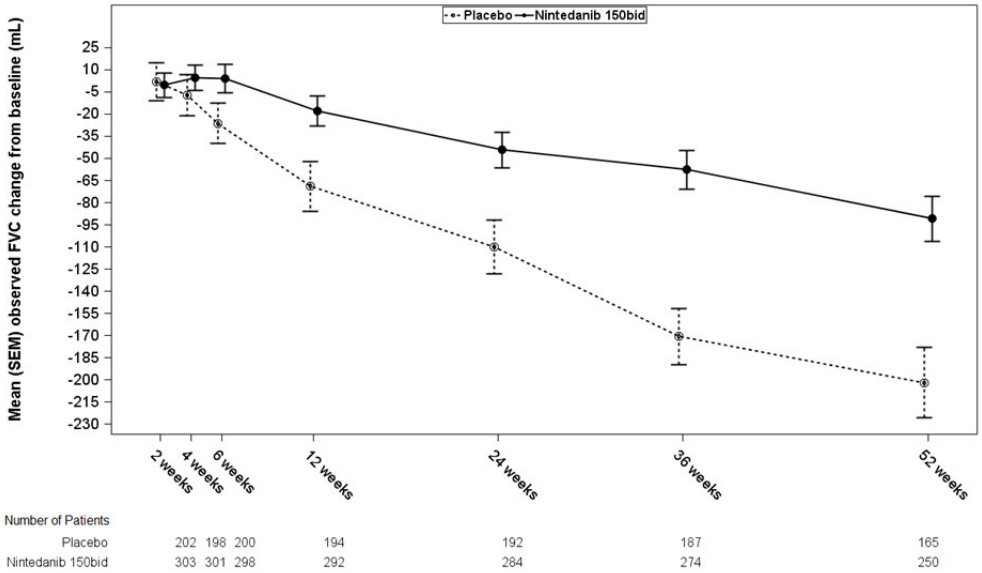
Table 2 Annual Rate of Decline in FVC (mL) in Studies 1, 2, and 3[a]

	Study 1		Study 2		Study 3	
	OFEV 150 mg twice daily	**Placebo**	**OFEV 150 mg twice daily**	**Placebo**	**OFEV 150 mg twice daily**	**Placebo**
Number of analyzed patients	84	83	309	204	329	219
Rate[a] of decline over 52 weeks	-60	-191	-115	-240	-114	-207
Comparison vs placebo Difference[b]	131		125		94	
95% CI	(27, 235)		(78, 173)		(45, 143)	

[a]Randomized set in Study 1; treated set in Studies 2 and 3
[b]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



bid = twice daily

Change from Baseline in Percent Predicted Forced Vital Capacity

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 than on placebo. Study 3 showed similar results.

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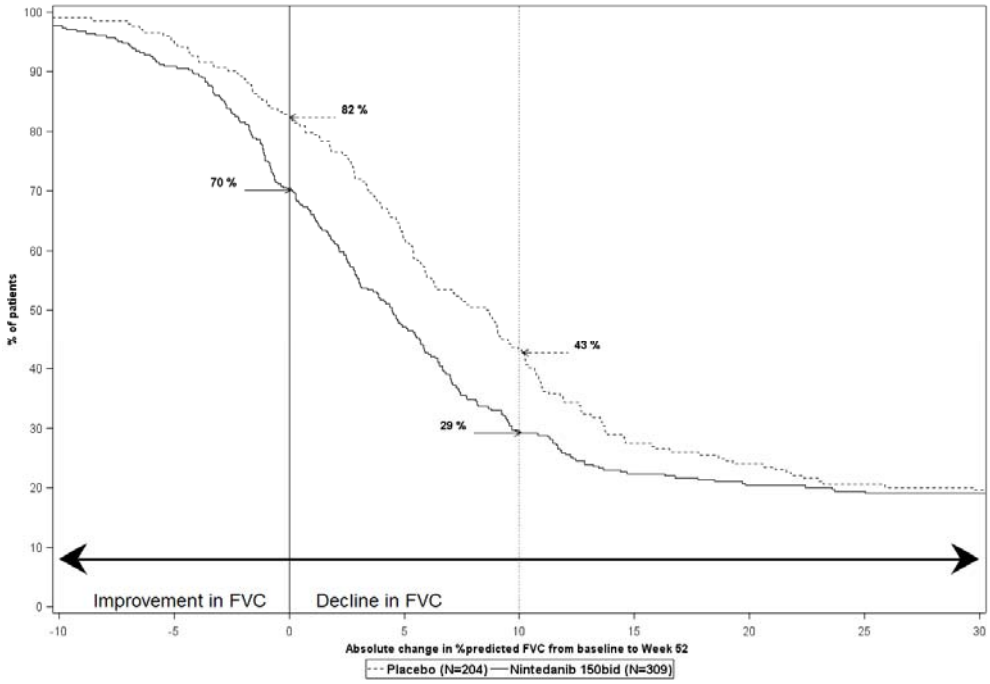
Figure 2 Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52 (Study 2).* The vertical lines indicate ≥0% decline or ≥10% decline.



*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.
bid = twice daily

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 to placebo (hazard ratio [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).

Survival

Survival was evaluated for OFEV 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 3).

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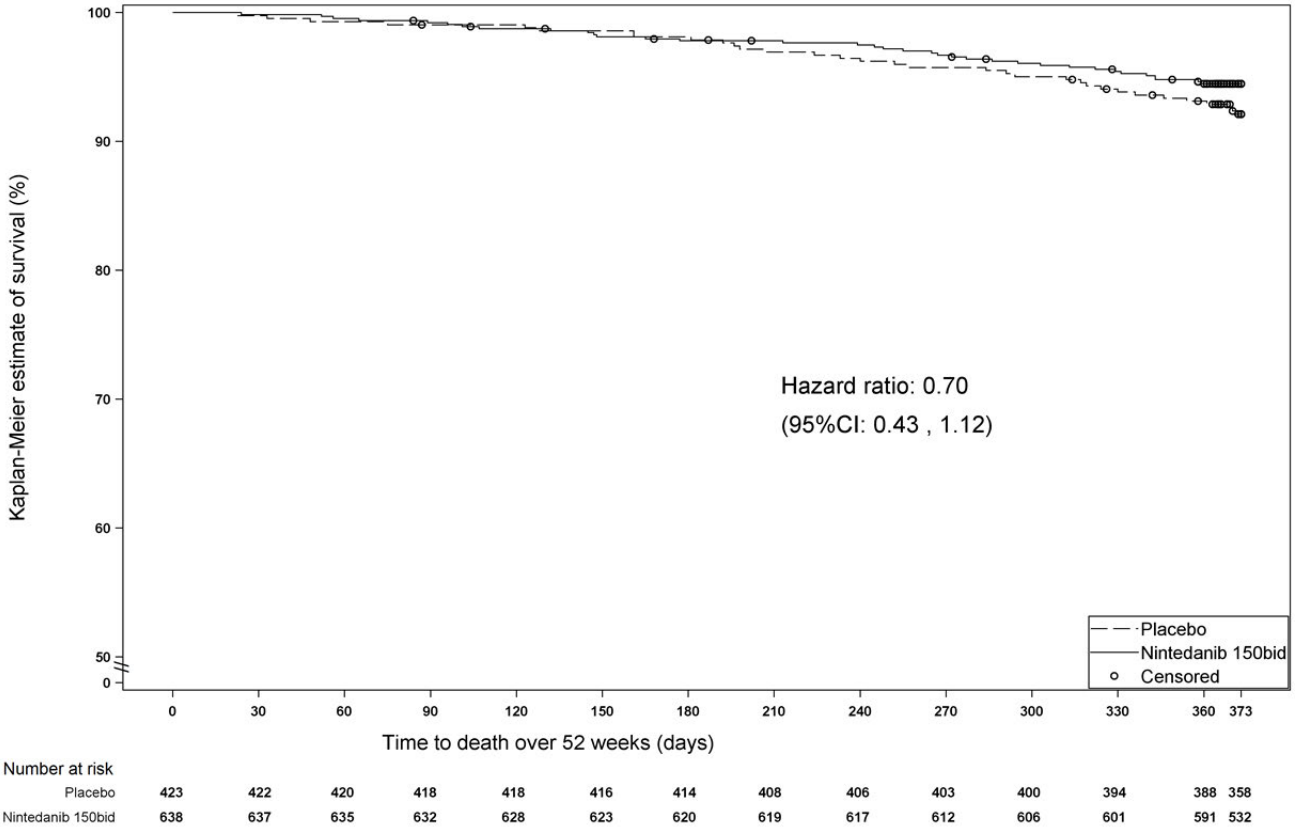
Figure 3 Kaplan-Meier Estimates of All-Cause Mortality at Vital Status – End of Study: Studies 2 and 3



bid = twice daily

16 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 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° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]**.** Protect from exposure to high humidity and avoid excessive heat. If repackaged, use USP tight container. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme and Bilirubin Elevations
Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions (5.1)]*.

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Gastrointestinal Disorders
Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV. Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Pregnancy
Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Arterial Thromboembolic Events
Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions *[see Warnings and Precautions (5.4)]*.

Risk of Bleeding
Bleeding events have been reported. Advise patients to report unusual bleeding *[see Warnings and Precautions (5.5)]*.

Gastrointestinal Perforation
Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation *[see Warnings and Precautions (5.6)]*.

Nursing Mothers
Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing *[see Use in Specific Populations (8.3)]*.

Smokers
Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV *[see Clinical Pharmacology (12.3)]*.

Administration
Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose *[see Dosage and Administration (2)]*.

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10009642/02

Reference ID: 3643917

Patient Information
OFEV® (OH-fev)
(nintedanib)
capsules

Read this Patient Information before you start taking OFEV and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about OFEV?

OFEV can cause birth defects or death to an unborn baby. Women should not become pregnant while taking OFEV. Women who are able to become pregnant should use birth control during treatment and for at least 3 months after treatment. If you become pregnant while taking OFEV, tell your doctor right away.

What is OFEV?

- OFEV is a prescription medicine used to treat people with a lung disease called idiopathic pulmonary fibrosis (IPF).
- It is not known if OFEV is safe and effective in children.

What should I tell my doctor before taking OFEV?

Before you take OFEV, tell your doctor if you:

- have liver problems
- have heart problems
- have a history of blood clots
- have a bleeding problem or a family history of a bleeding problem
- have had recent surgery in your stomach (abdominal) area
- are a smoker
- have any other medical conditions
- are pregnant or plan to become pregnant. OFEV can harm your unborn baby. OFEV can cause birth defects or death to an unborn baby. See **"What is the most important information I should know about OFEV?"**
- are breastfeeding or plan to breastfeed. It is not known if OFEV passes into your breast milk. You and your doctor should decide if you will take OFEV or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements such as St. John's wort. Keep a list of the medicines you take and show it to your doctor and pharmacist when you get a new medicine.

How should I take OFEV?

- Take OFEV exactly as your doctor tells you to take it.
- Your doctor will tell you how much OFEV to take and when to take it.
- Take OFEV with food. Swallow the OFEV capsules whole with a liquid.
- **Do not** chew or crush OFEV capsules.
- If you miss a dose of OFEV, take your next dose at your regular time. **Do not** take the missed dose.
- **Do not** take more than 300 mg of OFEV in 1 day.
- If you take too much OFEV, call your doctor or go to the nearest hospital emergency room right away.
- Your doctor should do certain blood tests before you start taking OFEV.

What are the possible side effects of OFEV?

OFEV may cause serious side effects, including:

- **See "What is the most important information I should know about OFEV?"**
- **liver problems.** Call your doctor right away if you have unexplained symptoms such as yellowing of your skin or the white part of your eyes (jaundice), dark or brown (tea colored) urine, pain on the upper right side of your stomach area (abdomen), bleeding or bruising more easily than normal, or feeling tired.

  Your doctor will do blood tests regularly to check how well your liver function is working during your treatment with OFEV.
- **diarrhea, nausea, and vomiting.** While you are taking OFEV, your doctor may recommend that you drink fluids or take medicine to treat these side effects. Tell your doctor if you have diarrhea, nausea, or

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vomiting or if these symptoms do not go away or become worse. Tell your doctor if you are taking over-the-counter laxatives, stool softeners, and other medicines or dietary supplements that can cause diarrhea.

- **heart attack.** Tell your doctor right away if you have symptoms of a heart problem. These symptoms may include chest pain or pressure, pain in your arms, back, neck or jaw, or shortness of breath.
- **stroke.** Tell your doctor right away if you have symptoms of a stroke. These symptoms may include numbness or weakness on 1 side of your body, trouble talking, headache, or dizziness.
- **bleeding problems.** OFEV may increase your chances of having bleeding problems. Tell your doctor if you have unusual bleeding, bruising, or wounds that do not heal. Tell your doctor if you are taking a blood thinner, including prescription blood thinners and over-the-counter aspirin.
- **tear in your stomach or intestinal wall (perforation).** OFEV may increase your chances of having a tear in your stomach or intestinal wall. Tell your doctor if you have pain or swelling in your stomach area.

The most common side effects of OFEV are diarrhea, nausea, stomach pain, vomiting, liver problems, decreased appetite, headache, and weight loss.

These are not all the possible side effects of OFEV. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OFEV?

- Store OFEV at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep OFEV dry and protect from high heat.
- Safely throw away any OFEV that is out of date or no longer needed.

Keep OFEV and all medicines out of reach of children.

General information about the safe and effective use of OFEV.

- Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OFEV for any condition for which it was not prescribed. Do not give OFEV to other people, even if they have the same symptoms you have. It may harm them. This Patient Information leaflet summarizes the most important information about OFEV. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about OFEV that is written for health professionals.
- For more information, go to www.ofev.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TYY) 1-800-459-9906, or scan the code below to go to www.ofev.com.

What are the ingredients in OFEV?

Active ingredient: nintedanib.

Inactive ingredients: Fill Material: triglycerides, hard fat, lecithin. Capsule Shell: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, black ink.

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Issued: October 2014

IT5950BJ142014, 10009642/02

This Patient Information has been approved by the U.S. Food and Drug Administration.

Reference ID: 3643917

Each capsule contains 180.60 mg nintedanib ethanesulfonate equivalent to 150 mg nintedanib.

Dosage: See package insert for dosage information.

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP controlled room temperature].

Protect from exposure to high humidity and avoid excessive heat.

Dispense in a tight container as defined in the USP.

Keep out of reach of children.

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NDC 0597-0145-60

Ofev®

(nintedanib)

Capsules

150 mg

℞ only

60 capsules

Boehringer Ingelheim

Exp.

Lot

3 05970 14560 8

NDC 0597-**0145**-60

Ofev®
(nintedanib)
Capsules

150 mg

℞ **only**

60 capsules

Boehringer Ingelheim

Ofev®
(nintedanib)
Capsules
150 mg

Ofev®
(nintedanib)
Capsules

150 mg

Each capsule contains 180.60 mg nintedanib ethanesulfonate equivalent to 150 mg nintedanib.

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Keep out of reach of children.

3 05970 14560 8

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Lot Exp.

NDC 0597-**0145**-60

Ofev®
(nintedanib)
Capsules

150 mg

℞ **only**

60 capsules

Boehringer Ingelheim

Ofev®
(nintedanib)
Capsules
150 mg

Ofev®
(nintedanib)
Capsules

150 mg

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F.P.O.

304969-01

Each capsule contains 120.40 mg nintedanib ethanesulfonate equivalent to 100 mg nintedanib.
Dosage: See package insert.
Store at 25°C (77°F) (see insert).
Protect from exposure to high humidity and avoid excessive heat.
Dispense in a tight container as defined in the USP.

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L5946A

304963-01

NDC 0597-0143-60

Ofev®

(nintedanib)
Capsules

100 mg

℞ only

60 capsules

Boehringer Ingelheim

3 05970 14360 4

Lot

Exp.

NDC 0597-0143-60

Ofev®
(nintedanib)
Capsules

100 mg

℞ only

60 capsules

Boehringer Ingelheim

Ofev®
(nintedanib)
Capsules
100 mg

Ofev®
(nintedanib)
Capsules

100 mg

Each capsule contains 120.40 mg nintedanib ethanesulfonate equivalent to 100 mg nintedanib.

Dosage: See package insert for dosage information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Protect from exposure to high humidity and avoid excessive heat.

Dispense in a tight container as defined in the USP.

Keep out of reach of children.

3 05970 14360 4

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Ofev®
(nintedanib)
Capsules

100 mg

℞ only

60 capsules

Boehringer Ingelheim

Ofev®
(nintedanib)
Capsules
100 mg

Ofev®
(nintedanib)
Capsules

100 mg

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/s/

MARY H PARKS
10/15/2014