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

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**INDICATIONS AND USAGE**

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

**Dosage and Administration**

Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food.

**Indications and Usage**


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

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**INDICATIONS AND USAGE**

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

**Dosage and Administration**

Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food.

**Contraindications**

- Hepatic impairment: OFEV is not recommended for use in patients with moderate or severe hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the recommended dosage is 150 mg twice daily approximately 12 hours apart taken with food. Consider treatment interruption, or discontinuation for management of adverse reactions in these patients.
- Gastrointestinal perforation: Only use OFEV in patients with known risk of gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation in the presence of known benefit outweighs the potential risk.
- Arterial thromboembolic events: Use caution when treating patients at higher cardiovascular risk including known coronary artery disease.
- Pregnancy: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception.
- Lactation: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Geriatric Use: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Females and Males of Reproductive Potential: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Pediatric Use: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Hypersensitivity: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.

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**ADVERSE REACTIONS**

Common adverse reactions include:

- Diarrhea
- Nausea
- Vomiting
- Hypertension
- Weight decrease
- Dyspnea
- Headache

**Postmarketing Experience**

- Diarrhea
- Nausea
- Vomiting
- Hypertension
- Weight decrease
- Dyspnea
- Headache

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**DRUG INTERACTIONS**

Concomitant use of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for adverse effects.

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**USE IN SPECIFIC POPULATIONS**

- Alcohol: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Renal impairment: The safety and efficacy of OFEV have not been studied in patients with severe renal impairment and end-stage renal disease.
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Pregnancy: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception.
- Geriatric Use: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Hypersensitivity: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.
- Sex: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV.

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**Drug Interactions**

Concomitant use of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for adverse effects.
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 and a pregnancy test prior to initiating treatment with OFEV [see Warnings and Precautions (5.2, 5.4)].

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.

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.

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 (5.2, 5.3, 5.5, 5.7) and Adverse Reactions (6.1)].

Dose modifications or interruptions may be necessary for liver enzyme elevations. Conduct liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Discontinue OFEV in patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevation greater than 5 times the upper limit of normal. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of 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 reinitiated 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 (5.2) and Adverse Reactions (6.1)].

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Impairment
Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV [see Dosage and Administration (2.2)].

5.2 Elevated Liver Enzymes and Drug-Induced Liver Injury
Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the post-marketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. In clinical trials, administration of OFEV was associated with elevation of liver enzymes ALT, AST, ALKP, GGT, and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes [see Clinical Pharmacology (12.3)].

Conduct liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications or interruption may be necessary for liver enzyme elevations [see Dosage and Administration (2.1, 2.3)].

5.3 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 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 less than 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 antimicrobial 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 persist 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.

5.4 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 the 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 [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].

5.5 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.

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. In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed.

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

5.7 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. In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs.

Discontinue therapy with OFEV in patients who develop signs or symptoms of acute myocardial ischemia. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

6. ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Elevated Liver Enzymes and Drug-Induced Liver Injury [see Warnings and Precautions (5.2)]
- Gastrointestinal Disorders [see Warnings and Precautions (5.3)]
- Embryo-Fetal Toxicity [see Warnings and Precautions (5.4)]
- Arterial Thromboembolic Events [see Warnings and Precautions (5.5)]
- Risk of Bleeding [see Warnings and Precautions (5.6)]
- Gastrointestinal Perforation [see Warnings and Precautions (5.7)]

6.1 Clinical Trial 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 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. 0.0%), and myocardial infarction (0.3% vs. 0.2%).

In the pre-defined 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 3% 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 reaction with an incidence of greater than or equal to 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

<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&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal tenderness.

<sup>b</sup> Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminases increased, blood alkaline phosphatase increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
the recommended dosage of OFEV is 100 mg twice daily.

Increased exposure to nintedanib was performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased (see Clinical Pharmacology (12.3)). In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily (see Dosage and Administration (2.3)).

Non-serious and serious bleeding events, some of which were fatal, have been observed in the postmarketing period (see Warnings and Precautions (5.6)).

DRUG INTERACTIONS

P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers
Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4 [see Clinical Pharmacology (12.3)]. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, lomitapide, 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)).

Anti-oxidants
Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anti-oxidant therapy closely for bleeding and adjust anti-oxidant treatment as necessary (see Warnings and Precautions (5.6)).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings from animal studies and its mechanism of action (see Clinical Pharmacology (12.3)), OFEV 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 (see Data). 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. Vascular anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebrae), 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 caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times the 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).

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).

Data
Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites.

Females and Males of Reproductive Potential

Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential (see Use in Specific Populations (8.1), Clinical Pharmacology (12.1), and Nonclinical Toxicology (13.1)). Counsel patients on pregnancy prevention and planning.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV (see Dosage and Administration (2.3), Warnings and Precautions (5.4) and Use in Specific Populations (8.1)).

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 (see Nonclinical Toxicology (13.1)).

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

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 subjects cannot be ruled out.

Hepatic Impairment
Nintedanib is predominantly eliminated via biliary/renal excretion (greater than 98%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased (see Clinical Pharmacology (12.3)). In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily (see Dosage and Administration (2.3)).
Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients [see Dosage and Administration (2.3)]. 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 (2.2)]. 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 (less than 30 mL/min CrCl) and end-stage renal disease.

8.8 Smokers
Smoking was associated with decreased exposure to OFEV [see Clinical Pharmacology (2.2)], 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 institute general supportive measures as appropriate.

11. DESCRIPTION
OFEV capsules contain nintedanib, a kinase inhibitor [see Mechanism of Action (12.1)]. Nintedanib is presented in the ethanolamine salt (esylate), with the chemical name: 6H-Benz[b]indole–2,3-dicarboxylic acid, 2,3-dihydro-1H–[4–(4-methyl–1-piperazinyl)acetyl]amino–phenyl–acetyl–l–alanine–phenyl–methylene–2–oxo–methyl ester, (Z), ethanesulfonate (1:1). Its structural formula is:

Nintedanib esylate is a bright yellow powder with an empirical formula of C₃₃H₃₁N₅O₈·H₂O·C₂H₃O₂S 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%).

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: 2.62 to 6.80) 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 tmax fasted: 2.00 hours; fed: 3.39 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 (Vss, 1054 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 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 [14C]nintedanib was via fecal 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 (0.85% of dose). The overall
All 3 studies. See Table 2 for individual study results.

The treatment effect on FVC was consistent in patients receiving OFEV compared to patients receiving placebo based on the random coefficient percent predicted of 80%.

Caucasian (60%) or Asian (30%) and male (79%). Patients had a mean age of 67 years and a mean FVC of 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre-bronchodilator FEV1/FVC less than 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 Study 1).

Bronchodilator FEV1/FVC less than or equal to 50% of predicted and a carbon monoxide diffusing capacity (DLCO, corrected for hemoglobin) 30% to 79% of predicted. Patients with a recent history of myocardial infarction or stroke were excluded from the studies.

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.

The clinical efficacy of OFEV has been studied in 1231 patients with IPF in one phase 2 (Study 1) and two phase 3 studies. Study 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).

Comparison vs placebo

Number of analyzed patients

Rate of decline over 52 weeks

95% CI

Study 1

Study 2

Study 3

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

Comparison vs placebo

Difference

AUC basis at an oral dose of 20 mg/kg/day). Nintedanib had no effects on male fertility in rats at exposures approximately equal to the MRHD (on an AUC basis). Conversely, females with resorptions only was observed at exposures approximately equal to the MRHD (on an AUC basis).

In vitro, nintedanib was shown not to be an inhibitor of OCT-1, OCT-2, and OCT-3. 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.

In vitro studies, nintedanib was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2. Co-administration of rifampicin and ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on Cmax, 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 Cmax upon coadministration with rifampicin compared to administration of nintedanib alone.

Based on a multiple-dose study in Japanese IPF pattern, exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on Cmax upon coadministration with rifampicin compared to administration of nintedanib alone.

Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH less than 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 vitro studies, nintedanib was shown not to be a substrate of OCT-1 to OCT-3; these findings are considered to be of low clinical relevance.
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

- **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.

*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).

*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

130 mg: brown, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and “130”. 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 tight container. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

17.1 Liver Enzymes and Drug-Induced Liver Injury

Advising patients that they will need laboratory liver function testing periodically. Advise patients to immediately report any symptom 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, itching, loss of appetite) [see Warnings and Precautions (5.2)].

17.2 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, anti-diarrheal 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 sign of diarrhea or for any other or potential diarrhea, nausea, or vomiting [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)].

17.3 Endo-Peptic Toxicity

Counsel patients on preventing drug-induced liver injury. Advise females of reproductive potential of the potential risk to a fetus and 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. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV [see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)].

17.4 Arterial Thromboembolic Events

Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and encourage to seek immediate medical care for these conditions [see Warnings and Precautions (5.5)].

17.5 Risk of Bleeding

Bleeding events have been reported. Advise patients to report unusual bleeding [see Warnings and Precautions (5.6)].

17.6 Gastrointestinal Perforation

Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see Warnings and Precautions (5.7)].

17.7 Lactation

Advise patients that breastfeeding is not recommended while taking OFEV [see Use in Specific Populations (8.2)].

17.8 Smokers

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

17.9 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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IT6996HA092018

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

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 have a pregnancy test before starting treatment with 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 should not breastfeed while taking OFEV.

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.
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:

- 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, feeling tired, or loss of appetite. 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 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.

- Leak in your stomach or intestinal wall (perforation). OFEV may increase your chances of having a leak 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 or pharmacist or 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 (TTY) 1-800-459-9906, or scan the code below to go to www.ofev.com.

What are the ingredients in OFEV?

Active ingredient: nintedanib.


Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA

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

Revised: January 2018

OFEV 150 mg Label
NDC: 0597-0145-60
OFEV 150 mg Carton
NDC: 0597-0145-60
# OFEV nintedanib capsule

## Product Information

**Product Type: HUMAN PRESCRIPTION DRUG**

**Item Code (Source):** NDC:0597-0145

**Route of Administration:** ORAL

### Active Ingredient/Active Moiety

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**Product Information**

**OFEV nintedanib capsule**

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**Labeler** - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

**Registrant** - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

**Establishment**

- **Boehringer Ingelheim Pharma GmbH and Co. KG**
  - Address: 510175944
  - Business Operations: ANALYSIS(0597-0143, 0597-0145) , API MANUFACTURE(0597-0143, 0597-0145) , PACK(0597-0143, 0597-0145) , LABEL(0597-0143, 0597-0145) 

- **West-Ward Columbus Inc.**
  - Address: 058839929
  - Business Operations: ANALYSIS(0597-0143, 0597-0145) , LABEL(0597-0145, 0597-0143) 

- **Catalent Germany Eberbach GmbH**
  - Address: 318612223
  - Business Operations: ANALYSIS(0597-0143, 0597-0145) , MANUFACTURE(0597-0143, 0597-0145) 

- **Sixarp, LLC**
  - Address: 016329513
  - Business Operations: LABEL(0597-0145, 0597-0143) , PACK(0597-0143, 0597-0145) 

Revised: 1/2018