

Ofev	Updated Prescribing Information
100 mg, 150 mg	December 2017

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# **OFEV**

## **NINTEDANIB**

### **SOFT CAPSULES**

### **100 MG, 150 MG**

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

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

### **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

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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. 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* (5.2) 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.

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

Cases of drug-induced liver injury have been observed with OFEV treatment [see *Adverse Reactions* (6.2)]. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption. 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)]. Patients with a low body weight (<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 treatment with OFEV, then as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. If serious liver injury with clinical symptoms

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and/or hyperbilirubinemia or jaundice occurs during treatment with OFEV, promptly interrupt therapy [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 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.

### 5.4 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 a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to treatment with OFEV [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

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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.

### **5.6 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 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 (5.2)*]
- 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 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.

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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%), 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  $\geq 5\%$  and more frequent in the OFEV than placebo treatment group are listed in Table 1.

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**Table 1 Adverse Reactions Occurring in  $\geq 5\%$  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
<b>Gastrointestinal disorders</b>		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain <sup>a</sup>	15%	6%
Vomiting	12%	3%
<b>Hepatobiliary disorders</b>		
Liver enzyme elevation <sup>b</sup>	14%	3%
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	11%	5%
<b>Nervous systemic disorders</b>		
Headache	8%	5%
<b>Investigations</b>		
Weight decreased	10%	3%
<b>Vascular disorders</b>		
Hypertension <sup>c</sup>	5%	4%

<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, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

<sup>c</sup> 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%).

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OFEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Drug-induced liver injury [see *Warnings and Precautions* (5.2)]
- Pancreatitis
- Thrombocytopenia

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

### Reporting of suspected adverse reactions

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form ([@moh.health.gov.il](http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedi)) or by email ([adr@MOH.HEALTH.GOV.IL](mailto:adr@MOH.HEALTH.GOV.IL)).

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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 (5.6)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], 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. 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 sternbrae

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(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).

## 8.2 Lactation

### Risk Summary

There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats [see Data].

Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV.

### Data

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

## 8.3 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 (2.1)*, *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)*].

## 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



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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%). 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 (2.2)*].

Monitor for adverse reactions and consider treatment interruption or 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 (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

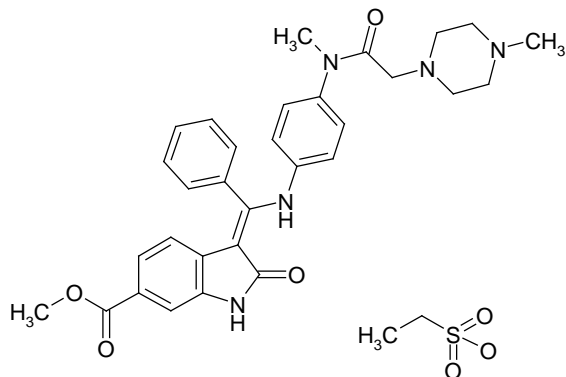
In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology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

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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: 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.

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## Specific Populations

### *Age, Body Weight, and Sex*

Based on population PK analysis, age and body weight were correlated with nintedanib exposure. However, the 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.

### *Hepatic Impairment*

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

### *Smokers*

In the population PK analysis, the exposure of nintedanib was 21% lower in current smokers compared 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.

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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.

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.

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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  $\geq 40$  years of age with an FVC  $\geq 50\%$  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<sub>1</sub>/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.

**Table 2 Annual Rate of Decline in FVC (mL) in Studies 1, 2, and 3<sup>a</sup>**

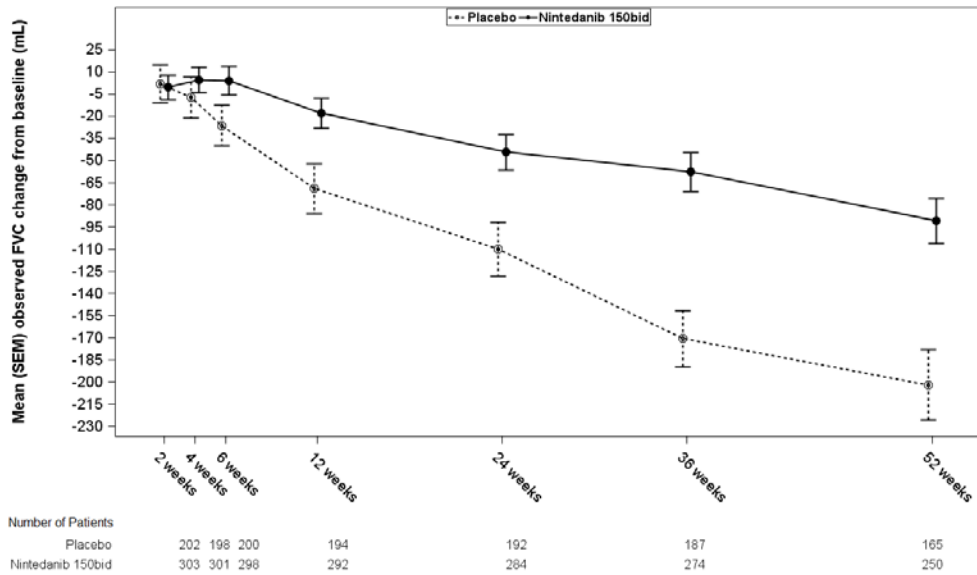
	Study 1		Study 2		Study 3	
	OFEV 150 mg twice daily	Placebo	OFEV 150 mg twice daily	Placebo	OFEV 150 mg twice daily	Placebo
Number of analyzed patients	84	83	309	204	329	219
Rate <sup>a</sup> of decline over 52 weeks	-60	-191	-115	-240	-114	-207
Comparison vs placebo Difference <sup>b</sup>	131		125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

<sup>a</sup>Randomized set in Study 1; treated set in Studies 2 and 3

<sup>b</sup>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**

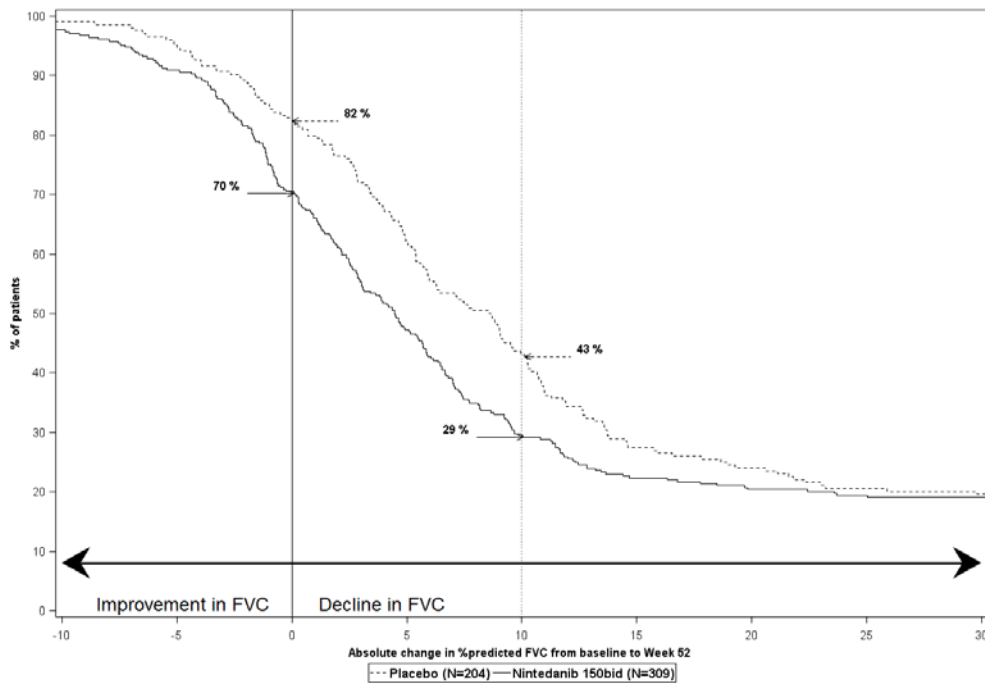


bid = twice daily

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  $\geq 0\%$  decline or  $\geq 10\%$  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).

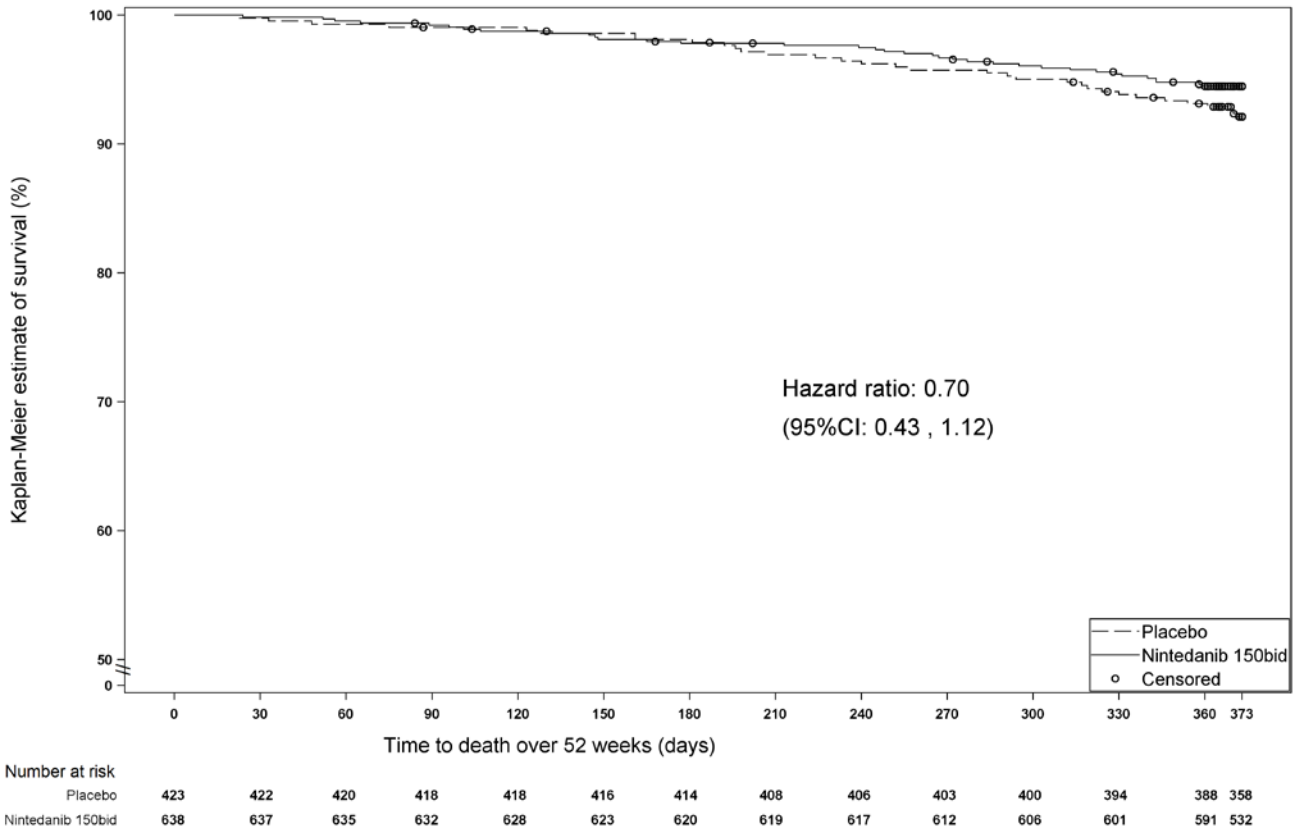
### Survival

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 aluminium blisters containing 10 capsules each, pack-size available as follows: 60 capsules.

100 mg: peach, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "100". They are packaged in aluminium blisters containing 10 capsules each, pack-size available as follows: 30 or 60 capsules.

Not all pack sizes may be marketed.

### Storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

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**19 MANUFACTURER**

Boehringer Ingelheim Pharma GmbH & Co. KG  
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Germany

**18 MARKETING AUTHORISATION HOLDER**

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P.O. Box 4124  
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**19 MARKETING AUTHORISATION NUMBER(S)**

Ofev 100 mg            154 74 34335 00  
Ofev 150 mg            154 75 34339 00

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