OFEV® (nintedanib) capsule, for oral use

Initial U.S. Approval: 2014

See full prescribing information for OFEV.

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Revised: 1/2018
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 not to 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 elevations 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 sign 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 (2.2.3)).

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 postmarketing 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 elevations of liver enzymes ALT, AST, ALKP, and GGT and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. The majority (84%) 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 elevation 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 of mild to moderate intensity and occurred within the first three 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 3% 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 anti-diarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues (see Dosage and Administration (2.2.3)). 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 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 postmarketing 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 postmarketing 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:

- 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%), 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 7% 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 13% of placebo-treated patients. The most frequent adverse reaction 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>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>12%</td>
<td>3%</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 system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

† Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
‡ Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase increased, alanine aminotransferase abnormal.
aqueous aminopeptidase abnormal, and gamma-glutamyltransferase abnormal.

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

Combination with Pirfenidone
Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 165 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone.

Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (≥3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3/6%) compared to nintedanib alone (n=0) (see Warnings and Precautions (5.2, 5.3)).

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. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury (see Warnings and Precautions (5.2)), non-serious and serious bleeding events, some of which were fatal (see Warnings and Precautions (5.6)), pancreatitis, thrombocytopenia, rash, pruritus.

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)). Concomitant administration of oral doses of a P-gp and CYP3A4 inhibitor, lecience, 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)).

Concomitant administration of 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 Antianginals
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)).

7.3 Pirfenidone
In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent (see Clinical Pharmacology (12.3)). Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action (see Clinical Pharmacology (12.3)), 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
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., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternum (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female/male ratio of approximately 71%/29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased postnatal viability of rat pups during the first 4 postnatal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 38 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 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. 

Infertile
plasma with a blood to plasma ratio of 0.87.

The distribution which was larger than total body volume ($V_{\text{t}}$).

After food intake, nintedanib exposure increased by approximately 20% compared to administration as a soft gelatin capsule under fed conditions. The absolute bioavailability of a 100 mg dose was 4.7%. Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration.

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.

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 2 and 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 and 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/rectal excretion (greater than 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 (2.2)). 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 discontinuation for management of adverse reactions in these patients (see Dosage and Administration (2.2)). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended (see Warnings and Precautions (5.3)).

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/1.73 m²) 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 as the ethanesulfonic acid (esylate), with the chemical name 1H-benzo[5,6,7]carbazol-2,3-dihydro-3-[4-(methyl[4-methyl-1-piperazinyl]acetyl)amino]phenylmethylene]-2-oxo-methyl ester, (3Z)-ethanesulfonate (1:1).

Its structural formula is:

Nintedanib esylate is a bright yellow powder with an empirical formula of $C_{31}H_{31}N_{5}O_{4} \cdot C_{2}H_{9}O_{3}$ 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: microcrystalline cellulose, 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 mechanism 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 Pharmacokinetics
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.
Patients were also excluded if they received other investigational therapy, azathioprine, or planned lung transplantation during the studies were excluded (being listed for lung transplant was acceptable for bronchodilator FEV1/FVC ratio). However, the hemoglobin was 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre- or postbronchodilator FEV1/FVC ratio less than 0.7) or, in the opinion of the investigator, likely to receive a lung transplant within 6 months were not included.

Patients were required to have a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for less than 5 years. 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 an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone. Similar nintedanib trough plasma concentrations were observed when comparing patients receiving nintedanib alone with patients receiving nintedanib with add-on pirfenidone.

Concomitant treatment with nintedanib and pirfenidone was also investigated in a separate trial, which was an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (treated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. Similar nintedanib trough plasma concentration were observed when comparing patients receiving nintedanib alone with patients receiving nintedanib with add-on pirfenidone. Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH less than 3. Nintedanib and its major metabolites were negligibly bound to human plasma proteins.

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 OATP-1B1, 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.

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 mouse lymphoma cell forward mutation assay, the mouse lymphoma cell reverse mutation assay, and the in vitro micronucleus assay. In in vitro studies, nintedanib was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or BCRP. In vitro studies also showed that nintedanib was not a substrate of OCT-1; these findings are considered to be of low clinical relevance.

13. NONCLINICAL TOXICOLOGY

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

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 less than 5 years. Diagnoses were established based on pathologic and, if applicable, histopathologic confirmation. Patients were required to be greater than or equal to 40 years of age with an FVC greater than or equal to 50% of predicted and a carbon monoxide diffusing capacity (DLCO) corrected for hemoglobin greater than 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre-bronchodilator FEV1/FVC ratio less than 0.7) were, 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 greater than 5.5 times ULN of ALT, AST, or bilirubin, patients with a known risk for predisposition to bleeding, patients receiving a full course 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, or planned lung transplantation during the studies were excluded (being listed for lung transplant was acceptable for bronchodilator FEV1/FVC ratio). However, the hemoglobin was 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre- or postbronchodilator FEV1/FVC ratio less than 0.7) or, in the opinion of the investigator, likely to receive a lung transplant within 6 months were not included.

Based on a population PK analysis of data from 933 patients with IPF, exposure to nintedanib was not influenced by sex (C max: 60 to 90 mL/min; n=399) or moderate (C max: 30 to 60 mL/min; n=116) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited.

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 OATP-1B1, 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. Co-administration with the P-gp and CYP3A4 inhibitors, 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 59.3% based on AUC and to 60.3% based on C max upon co-administration with rifampicin compared to administration of nintedanib alone.

Effect of pirfenidone co-administration on nintedanib AUC and C max was evaluated in a multiple-dose drug-drug interaction study. Pirfenidone did not have an effect on the exposure of nintedanib.

In vitro studies, nintedanib is a weak inhibitor of CYP1A1, UGT 1A7, UGT 1A9, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biliary excretion 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% enteric cleavage.

The contribution of renal clearance to the total clearance was low (0.63% of dose). The overall recovery was considered complete (above 90%) within 4 days after dosing.

Effect of nintedanib co-administration on pirfenidone AUC and C max was evaluated in a multiple-dose drug-drug interaction study. In a dedicated drug-drug interaction study with the P-gp and CYP3A4 inhibitors, 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 59.3% based on AUC and to 60.3% based on C max upon co-administration with rifampicin compared to administration of nintedanib alone.

In in vitro studies, nintedanib was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or BCRP. In vitro studies also showed that nintedanib was not a substrate of OCT-1; these findings are considered to be of low clinical relevance.
cyclophosphamide, or cyclosporine A within 8 weeks of entry into this trial, or n-acetyl cysteine and prednisone (greater than 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 (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

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<th>Study</th>
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<th>Placebo</th>
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</table>

*Randomized set in Study 1; treated set in Studies 2 and 3

*Estimated based on a random coefficient regression model

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

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

---

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

---

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

**Time to First Acute IPF Exacerbation**

Acute IPF exacerbation was defined as unexplained worsening or development of dyspnea within 30 days, new diffuse pulmonary infiltrates on chest x-ray, and/or new high-resolution CT parenchymal abnormalities with no pneumothorax or pleural effusion, and exclusion of alternative causes. Acute IPF exacerbation was adjudicated in Studies 2 and 3. In Studies 1 (investigator-reported) and 3 (adjudicated), the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving OFEV compared 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
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 60NDC: 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 60NDC: 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 Function Tests and Drug-Induced Liver Injury
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, loss of appetite) [see Warnings and Precautions (5.2)].

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 providers may recommend hydration, anti-diarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuation 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 (5.3) and Adverse Reactions (6.1)].

Embryo-Fetal Toxicity
Counsel patients on pregnancy prevention and planning. 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, 8.3)].

Amelanotic 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 (5.5)].

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

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)].

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

Smokers
Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using 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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Ridgefield, CT 06877 USA
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IT69961282018

Patient Information
OFEV® (OHI-lev) (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.
- 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, 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 arm, 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.
- Heart failure. Tell your doctor right away if you have symptoms of a heart problem. These symptoms may include chest pain or pressure, pain in your arm, back, neck or jaw, or shortness of breath.
- Nervous system problems. OFEV may increase your chances of having nervous system problems. Tell your doctor if you have numbness or weakness on 1 side of your body, trouble talking, headache, or dizziness.
- Seizures. If you have a history of seizures, tell your doctor right away if you have symptoms of a seizure. These symptoms may include stiff muscles, shaking, loss of consciousness, or convulsions.
- Diarrhea. Call your doctor right away if you have severe diarrhea. Do not drink milk or take medicine to treat diarrhea.
- Liver problems.
- See “What is the most important information I should know about OFEV?”
- 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.

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 68°F to 77°F (20°C to 25°C).
- Keep OFEV dry and protect from high heat.

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 (TTY) 1-800-459-9906, or scan the code below to go to www.ofev.com.

What is the most important information I should know about 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, 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.
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  - Seizures. If you have a history of seizures, tell your doctor right away if you have symptoms of a seizure. These symptoms may include stiff muscles, shaking, loss of consciousness, or convulsions.
  - Diarrhea. Call your doctor right away if you have severe diarrhea. Do not drink milk or take medicine to treat diarrhea.
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- 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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IT859561262018

This Patient Information has been approved by the U.S. Food and Drug Administration. 11/28/2018

Revised: November 2018

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

**Product Information**

**Product Type:** HUMAN PRESCRIPTION DRUG  
**Item Code (Source):** NDC:0597-0145-01

**Route of Administration:** ORAL

**Active Ingredient/Active Moiety**

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### OFEV

**Product Information**

**Product Type:** HUMAN PRESCRIPTION DRUG  
**Item Code (Source):** NDC:0597-0143-01

**Route of Administration:** ORAL

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Revised: 11/2018
Boehringer Ingelheim Pharmaceuticals, Inc.