# PRODUCT MONOGRAPH

# PrOFEV®

Nintedanib Capsules

100 mg and 150 mg nintedanib (as nintedanib esilate)

Protein Kinase Inhibitor

Anti-fibrotic/Anti-inflammatory Agent

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**Table of Contents**

**OFEV®**

Nintedanib Capsules

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| oral | Capsule 100 mg, 150 mg | Capsule fill: Medium chain triglycerides, hard fat, soya lecithin (E322)<br>Capsule shell: Gelatin, glycerol 85 %, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), black ink (Opacode®)<br>Black ink: Shellac glaze, iron oxide black (E172), propylene glycol (E1520) |

### INDICATIONS AND CLINICAL USE

OFEV (nintedanib) is indicated for:

- the treatment of Idiopathic Pulmonary Fibrosis (IPF).

**Geriatrics (> *65* years of age):**
No dose adjustment is necessary in patients 65 years and older.

**Pediatrics (<18 years of age):**
The safety and efficacy of OFEV in pediatric patients have not been studied in clinical trials and therefore, OFEV should not be used in patients under 18 years of age.

### CONTRAINDICATIONS

- OFEV is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or any of the excipients (see DOSAGE FORMS, COMPOSITION AND PACKAGING section).
- OFEV is contraindicated during pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women section).

## WARNINGS AND PRECAUTIONS

### General

Treatment with OFEV should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.

OFEV should be taken with food to reduce the incidence of gastrointestinal effects.

Physicians should monitor patients as frequently as clinically indicated for adverse reactions and according to the instructions of "DOSAGE AND ADMINISTRATION" and "DRUG INTERACTIONS". For significant side effects, the treatment of symptoms and dose reduction or interruption of OFEV should be considered. Most adverse events with nintedanib were managed with supportive treatment, dose reduction and/or treatment interruption.

### Cardiovascular

Arterial thromboembolic events

Patients with a recent history of myocardial infarction or stroke were excluded from the clinical trials. Arterial thromboembolic events were reported in patients treated with OFEV: in 2.5% of patients in the OFEV group and 0.7% of patients in the placebo group.

While adverse events reflecting ischaemic heart disease were balanced between the OFEV and placebo groups, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%) in the clinical trials. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischemia.

### Endocrine and Metabolism

Weight loss has been reported in 9.7% versus 3.5% patients treated with OFEV and placebo, respectively. Physicians should monitor patients' weight, and when appropriate, encourage increased caloric intake if weight loss is considered to be of clinical significance.

### Gastrointestinal

Diarrhea

Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively (see ADVERSE REACTIONS section). In most patients, diarrhea was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction or discontinuation of medication in more patients taking nintedanib than taking placebo.

Diarrhea should be treated at first signs with adequate hydration and anti-diarrheal medication (e.g., loperamide) and may require treatment interruption. OFEV treatment may be resumed at a reduced dose (100 mg twice daily) or at the full recommended dose (150 mg twice daily). If

severe diarrhea persists despite symptomatic treatment, treatment with OFEV should be discontinued.

Nausea and vomiting
Nausea and vomiting were frequently reported adverse events (see ADVERSE REACTIONS section). In most patients with nausea and vomiting, the event was of mild to moderate intensity. In clinical trials, nausea or vomiting infrequently led to discontinuation of treatment with nintedanib.

If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full recommended dose (150 mg twice daily). If severe nausea or vomiting persists despite symptomatic treatment, discontinue treatment with OFEV.

Diarrhoea and vomiting may lead to dehydration -with or without electrolyte disturbances which may progress to renal function impairment.

Gastrointestinal perforations
Due to the mechanism of action of nintedanib, patients might have an increased risk of gastrointestinal perforation**.** In the clinical trials, gastrointestinal perforations were reported in 0.3% (2 cases, both serious) of patients treated with OFEV compared to 0 cases in placebo-treated patients. Cases of gastrointestinal perforations have been reported in the post-marketing period, many of them were serious and some have resulted in fatal outcomes, although a definitive causal relationship to OFEV has not been established.

Particular caution should be exercised when treating patients with previous abdominal surgery, a recent history of hollow organ perforation, previous history of peptic ulceration, diverticular disease, or receiving concomitant corticosteroids or NSAIDs. OFEV should only be initiated at least 4 weeks after abdominal surgery. **Only use OFEV in patients with a known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk. Therapy with OFEV should be permanently discontinued in patients who develop gastrointestinal perforation.**

**Hemorrhage**
Based on the mechanism of action of nintedanib, vascular endothelial growth factor receptor (VEGFR) inhibition, OFEV increases the risk of bleeding. In clinical trials, bleeding events were reported for 10% of patients treated with OFEV and in 8% of patients treated with placebo.

Non-serious epistaxis was the most frequent bleeding event. Serious bleeding events occurred with low and similar frequencies in the 2 treatment groups (placebo: 1.4%; Ofev: 1.3%).

Serious and fatal bleeding events have been reported in clinical trials and post-marketing surveillance systems. **Use OFEV in patients with known risk of bleeding (e.g. patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment) only if the anticipated benefit outweighs the potential risk.**

**Hepatic Function**

The safety and efficacy of OFEV have not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore, treatment with OFEV is not recommended in such patients *(*see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics section*).*

A pharmacokinetics study showed that both AUC and Cmax were 2.2-fold higher in subjects with mild hepatic impairment (Child-Pugh A) (AUC: 90% CI: 1.2 – 3.8 and Cmax: 90% CI: 1.3 – 3.7). Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A group). Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of OFEV (see sections DOSAGE AND ADMINISTRATION and Pharmacokinetics). However, this PK study showed that AUC was 8.7-fold (90% CI: 5.7 – 13.1) and Cmax was 7.6-fold (90% CI: 4.4 – 13.2) higher in subjects with moderate hepatic impairment (Child-Pugh B group) when compared with the respective matched healthy subjects.

*Drug-Induced Liver Injury (DILI)*

Cases of drug-induced liver injury have been observed with nintedanib treatment in both clinical trials and post-marketing surveillance database. In the post-marketing period, non-serious and serious, cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported. In clinical trials drug-induced liver injury has been reported in 0.3% versus 0% of patients treated with nintedanib and placebo, respectively.

*Liver Enzyme Elevations*

In clinical trials, administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with these risk factors.

*Monitoring Liver Function*

The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated just before initiation of treatment with OFEV, then at regular intervals (monthly) during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated (see Monitoring and Laboratory Tests). In the majority of cases, elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyl-transferase (GGT)) and bilirubin were reversible upon dose reduction or treatment interruption (see DOSAGE AND ADMINISTRATION, Dose adjustments due to adverse reactions).

**Hypertension**

Treatment with OFEV may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated.

**Renal**
Less than 1% of a single dose of nintedanib is excreted via the kidney (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics section). Adjustment of the recommended dose (150 mg twice daily) 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).

**Venous thromboembolism**
Based on the mechanism of action of nintedanib, patients might have potential for an increased risk of thromboembolic events. In the clinical trials, no increased risk of venous thromboembolism was observed in nintedanib treated patients.

**Wound healing complication**
Based on the mechanism of action, nintedanib may impair wound healing. No increased frequency of impaired wound healing was observed in the clinical trials. No dedicated studies investigating the effect of nintedanib on wound healing were performed. Treatment with OFEV should therefore only be initiated or, in case of perioperative interruption, resumed based on clinical judgement of adequate wound healing.

**Special Populations**

Fertility
Based on preclinical investigations, there is no evidence for impairment of male fertility in rats (see TOXICOLOGY section). In rats, nintedanib reduced female fertility at exposure levels approximately 3 times the maximum recommended human dose (MRHD) of 150 mg twice daily (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 was only observed at exposures approximately equal to the MRHD (on an AUC basis at an oral dose of 20 mg/kg/day (see TOXICOLOGY section).

**Women of Childbearing Potential**
The use of OFEV is contraindicated during pregnancy. Women of childbearing potential being treated with OFEV should be advised to use adequate contraception during OFEV treatment and for at least 3 months after the last dose of OFEV. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. Since the effect of nintedanib on the metabolism and efficacy of hormonal contraceptives has not been investigated, a second form of contraception, e.g. a barrier method, should be applied.

**Pregnant Women**
Use of OFEV is contraindicated during pregnancy. OFEV may cause fetal harm when administered to pregnant women, therefore treatment with OFEV should not be initiated during pregnancy and pregnancy testing should be conducted prior to initiating treatment with OFEV.

Pre-clinical studies have shown that nintedanib is teratogenic and embryo-foetocidal in rats and rabbits (see TOXICOLOGY section). There is no information on the use of OFEV in pregnant women.

**Nursing Women:**
It is not known if nintedanib or its metabolites are excreted in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) were secreted into milk of lactating rats.

Risk to the nursing infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue treatment with OFEV, taking into account the benefits of breast-feeding for the child and of OFEV treatment for the mother.

**Pediatrics**:
The safety and efficacy of OFEV in pediatric patients have not been studied in clinical trials. Toxicology studies in rodents showed hypertrophy of epiphyseal growth plates and abnormalities in growing incisors (see TOXICOLOGY). OFEV is not recommended for use in children and adolescents.

**Geriatrics (>65 years of age)**:
No overall differences in safety and efficacy were observed for elderly patients compared to patients aged 65 years or younger. No adjustment of the recommended dose (150 mg twice daily) is required on the basis of a patient's age (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics section).

**Monitoring and Laboratory Tests**
Hepatic transaminase and bilirubin levels should be investigated just before initiation of treatment with OFEV, then at regular intervals (monthly) during the first three months of treatment, periodically thereafter (e.g. at each patient visit) or as clinically indicated. (See WARNINGS AND PRECAUTIONS, Hepatic section and DOSAGE AND ADMINISTRATION section).

## ADVERSE REACTIONS

**Adverse Drug Reaction Overview**
Physicians should advise patients the following potential adverse drug reactions:

- Liver Enzyme and Bilirubin Elevations
- Gastrointestinal Disorders
- Risk of Bleeding

Most gastrointestinal adverse events with nintedanib were managed with supportive treatment, dose reduction and/or treatment interruption. For the management of selected adverse reactions, please also refer to WARNINGS AND PRECAUTIONS section.

## Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Common Adverse Events in 1199.32 and 1199.34

Nintedanib has been studied in clinical trials of 1529 patients suffering from Idiopathic Pulmonary Fibrosis (IPF). The following safety data are based on the two Phase III, randomised, double-blind, placebo-controlled studies in 1061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (1199.32 and 1199.34).

The most frequently reported adverse events associated with the use of nintedanib included diarrhea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased. Serious adverse events were balanced between the treatment groups. Adverse events leading to discontinuation of study medication and permanent dose reduction were more frequent in the OFEV 150 mg bid group than in the placebo group. Common adverse events in 1199.32 and 1199.34, i.e. those that occurred in >3% of patients treated with nintedanib and more frequently than with placebo by ≥1.5% are shown in Table 1.

**Table 1: Adverse events occurring in >3% of patients treated with nintedanib and more frequently than with placebo by ≥ 1.5%, by SOC and preferred term, sorted by frequency in the nintedanib 150 mg group**

| System organ class/ Preferred term | Placebo N (%) | Nintedanib 150 mg bid N (%) |
|---|---|---|
| Patients | 423 (100.0) | 638 (100.0) |
| Patients with any AE | 379 (89.6) | 609 (95.5) |
| Gastrointestinal disorders | | |
| Diarrhea | 78 (18.4) | 398 (62.4) |
| Nausea | 28 (6.6) | 156 (24.5) |
| Vomiting | 11 (2.6) | 74 (11.6) |
| Constipation | 17 (4.0) | 38 (6.0) |
| Abdominal pain[a] | 26 (6.1) | 96 (15.0) |
| Gastroesophageal reflux disease | 10 (2.4) | 31 (4.9) |
| Flatulence | 4 (0.9) | 30 (4.7) |
| Investigations | | |

| System organ class/ Preferred term | Placebo N (%) | Nintedanib 150 mg bid N (%) |
|---|---|---|
| Weight decreased[d] | 15 (3.5) | 62 (9.7) |
| Liver enzyme elevation[b] | 11 (2.6) | 87 (13.6) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 24 (5.7) | 68 (10.7) |
| Nervous system disorders | | |
| Headache | 19 (4.5) | 43 (6.7) |
| Vascular disorders | | |
| Hypertension[c] | 17 (4.0) | 33 (5.2) |

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy
[d] Weight decreased is equivalent to weight loss.

Adverse Events Leading to Discontinuation of Study Medication in trials 1199.32 and 1199.34

Adverse events leading to discontinuation of study medication were more frequent in the nintedanib 150 mg bid group (19%) than in the placebo group (13%). Adverse events leading to discontinuation that were more common in the nintedanib than the placebo group by at least 1% were diarrhea (nintedanib 4.4%, placebo 0.2 %), nausea (nintedanib 2.0%, placebo 0%) and decreased appetite (nintedanib 1.4%, placebo 0.2%).

Adverse Events Leading to Permanent Dose Reduction in trials 1199.32 and 1199.34

Adverse events leading to permanent dose reduction were reported for 16% of patients treated with OFEV compared to 2 patients (0.5%) treated with placebo. The most frequent adverse reaction that led to dose reduction was diarrhea (11%) followed by nausea (1.7%), vomiting (1.1%) and abdominal pain (0.9%). Other adverse events leading to dose reduction that occurred in more than 0.5% of patients were hepatic function abnormal (0.6%), weight decreased (0.6%) and decreased appetite (0.6%).

Serious Adverse Events

Serious adverse events were balanced between the treatment groups (nintedanib: 30.4%, placebo: 30.0%). The most frequent serious adverse events that were reported more frequently with OFEV compared to placebo were bronchitis (nintedanib: 1.3%, placebo: 0.5%) and myocardial infarction (nintedanib: 1.6%, placebo: 0.5%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.8% vs. 0.5%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (MI) (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV treated patients and 1.4% of placebo-treated patients.

**Less Common Clinical Trial Adverse Drug Reactions (<3%)**
Adverse drug reactions occurring in <3% of patients treated with OFEV and more than placebo in trials 1199.32 and 1199.34 are listed below:

**Hepatobiliary Disorders:** hyperbilirubinemia

**Post-Market Adverse Drug Reactions**
The following additional adverse reactions have been identified during post-approval 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.

**Gastrointestinal disorders:** Pancreatitis

**Vascular disorders**: Non-serious and serious bleeding events (involving different organ systems including gastrointestinal, respiratory and central nervous organ systems), some of which were fatal

**Blood and lymphatic system disorders**: Thrombocytopenia

**Hepatobiliary Disorders:** Drug-induced liver injury

**Skin and subcutaneous tissue disorders:** rash, pruritus

## DRUG INTERACTIONS

### Overview

### Drug-Drug Interactions

P-glycoprotein (P-gp) and Cytochrome (CYP)-3A4
Nintedanib is a substrate of P-gp and to a minor extent CYP3A4 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics section). Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies.

Co-administration with the potent P-gp and CYP3A4 inhibitor ketoconazole increased exposure to nintedanib by 1.61 fold for AUC and by 1.83 fold for Cmax in a drug-drug interaction study. Concomitant use of P-gp and CYP3A4 inhibitors with OFEV may increase exposure to nintedanib.

Co-administration with the potent P-gp and CYP3A4 inducer rifampicin decreased exposure to nintedanib to 50 % based on AUC and to 60 % based on Cmax.

Hormonal contraceptives
The potential for interactions of nintedanib with hormonal contraceptives was not evaluated.

**Table 2 - Established or Potential Drug-Drug Interactions**

| Nintedanib | Ref | Effect | Clinical comment |
|---|---|---|---|
| Inhibitors of P-gp and CYP3A4<br>ketoconazole or erythromycin | CT | Co-administration with the potent P-gp and CYP 3A4 inhibitor ketoconazole increased exposure to nintedanib.<br>If co-administered with OFEV, potent P-gp and CYP 3A4 inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. | In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with OFEV (see DOSAGE AND ADMINISTRATION section). |
| Inducers of P-gp and CYP3A4<br>rifampicin, carbamazepine, phenytoin, and St. John's Wort | CT | Co-administration with the potent P-gp and CYP 3A4 inducer rifampicin decreased exposure to nintedanib.<br>Potent P-gp and CYP 3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. | Co-administration with OFEV should be carefully considered.<br>Selection of an alternate concomitant medication with no or minimal P-gp induction potential should be considered. |

Legend: CT = Clinical Trial

Pirfenidone

Concomitant treatment with nintedanib and pirfenidone has been investigated in an exploratory open-label, randomised 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 105 randomised patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to week 12. The incidence of investigator-defined drug-related adverse events was higher for patients on nintedanib with add-on pirfenidone (79.2%) than on nintedanib alone (58.8%). Gastrointestinal adverse events were frequent and in line with the established safety profile of each component. Diarrhoea, nausea and vomiting were the most frequent adverse events reported in 20 (37.7%) versus 16 (31.4%), in 22 (41.5%) versus 6 (11.8%) and in 15 (28.3%) versus 6 (11.8%) patients, treated with pirfenidone added to nintedanib versus nintedanib alone, respectively.

## Drug-Food Interactions

OFEV is recommended to be taken with food (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics sections).

Grapefruit juice contains one or more components that moderately inhibit CYP3A and P-gp and its co-administration may increase plasma concentrations of nintedanib. Food containing grapefruit or Seville oranges should be avoided during treatment with OFEV.

## Drug-Lifestyle Interactions

Effects on ability to drive and use machines
No studies of the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines during treatment with OFEV.

# DOSAGE AND ADMINISTRATION

## Dosing Considerations

Treatment with OFEV should be initiated by physicians experienced in the diagnosis and treatment of IPF.

Hepatic transaminase and bilirubin levels should be investigated upon initiation of treatment with OFEV, and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Pregnancy testing should be conducted prior to initiating treatment with OFEV.

## Recommended Dose and Dosage Adjustment

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

Dose adjustments due to adverse reactions

In addition to symptomatic treatment if applicable, the management of adverse reactions of OFEV could include dose reduction (to 100 mg twice daily) and temporary interruption of OFEV treatment until the specific adverse reaction has resolved to levels that allow continuation of therapy. OFEV treatment may be resumed at the full recommended dose (150 mg twice daily) or a reduced dose (100 mg twice daily). If a patient does not tolerate 100 mg twice daily, treatment with OFEV should be discontinued (see WARNINGS AND PRECAUTIONS section and ADVERSE REACTIONS section).

Cases of drug-induced liver injury (DILI), have been reported in patients treatment with OFEV (nintedanib). In the majority of cases, the DILI was reversible when the dose was reduced or treatment was stopped.

- If transaminase (AST or ALT) elevations >3 x upper limit of normal (ULN) are measured, dose reduction or interruption of the therapy with OFEV is recommended and the patient should be monitored closely. Alternative causes of the liver enzyme elevations should be investigated. Once transaminases have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full recommended dose (150 mg twice daily) (see WARNINGS AND PRECAUTIONS section and ADVERSE REACTIONS section).

- Treatment with OFEV should be permanently discontinued if any liver test elevations are associated with clinical signs or symptoms of liver injury (e.g. jaundice) (see WARNINGS AND PRECAUTIONS section and ADVERSE REACTIONS section).

Hepatic impairment

***Mild hepatic impairment:*** In patients with mild hepatic impairment (Child Pugh A), the recommended dose of OFEV is 100 mg twice daily approximately 12 hours apart. Treatment interruption or discontinuation for management of adverse reactions should be considered.

***Moderate and severe hepatic impairment:*** Treatment of patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment with OFEV is not recommended. The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Exposure to nintedanib increased significantly in patients with moderate hepatic impairment (see section ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Race

Safety data for black patients is limited.

Renal impairment

Adjustment of the recommended dose (150 mg twice daily) 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).

Geriatrics (>65 years of age):

No dose adjustment is required on the basis of a patient's age.

**Administration**

OFEV capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed.

**Missed Dose**

If a dose of OFEV is missed, administration should resume at the next scheduled time at the recommended dose. If a dose is missed the patient should not be given an additional dose. The recommended maximum daily dose of 300 mg should not be exceeded.

## OVERDOSAGE

| |
|---|
| For management of a suspected drug overdose, contact your regional Poison Control Centre. |

There is no specific antidote or treatment for OFEV overdose. The highest single dose of nintedanib administered in phase I studies was 450 mg once daily. In addition, 2 patients had an overdose of maximum 600 mg bid up to eight days. Observed adverse events were consistent with the known safety profile of nintedanib, i.e. increased liver enzymes and gastrointestinal symptoms. Both patients recovered from these adverse reactions.

In the clinical 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

In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases including: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling. Activation of FGFR and PDGFR signalling cascades is critically involved in proliferation and migration of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of IPF. The potential impact of VEGFR inhibition on IPF pathology is currently not fully elucidated. In addition, nintedanib inhibits non-tyrosine kinases including: Fms-like tyrosine kinase-3 (Flt-3), Lck, Lyn and Src kinases. In *in vivo* studies, nintedanib was shown to have potent anti-fibrotic and anti-inflammatory activity.

### Pharmacodynamics

*QT interval*
In a dedicated 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.

### Pharmacokinetics

The pharmacokinetics (PK) of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data) and dose. Accumulation upon multiple administrations was 1.04-fold for $C_{max}$ and 1.38-fold for AUCτ. Nintedanib trough concentrations remained stable for more than one year.

**Table 3 Pharmacokinetic parameters of nintedanib after single oral administration of 150 mg nintedanib to healthy volunteers**

| Nintedanib | N | gMean | %gCV |
|---|---|---|---|
| $C_{max}$ [ng/mL] | 26 | 22.1 | 51.8 |
| $t_{max}$ [1] [h] | 26 | 3.00 | 0.500–6.00 |
| $AUC_{0-□}$ [ng·h/mL] | 26 | 183 | 36.1 |

[1] median and range

**Absorption:**
Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 hours). The absolute bioavailability of a 100 mg dose was 4.7% in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

Steady state plasma concentrations were achieved within one week of dosing at the latest.

Although the impact of food on the extent of nintedanib absorption is variable, when administered after food intake, nintedanib exposure generally increased by 20-50% compared to administration under fasted conditions and absorption was delayed (median $T_{max}$ fasted: 2.00 hours; fed: 3.98 hours).

**Distribution:**
Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (Vss: 1050 L, 45.0% gCV) 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.

**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 ADME study. *In vitro*, CYP-dependent metabolism accounted for about 5% compared to about 25% ester cleavage.

In preclinical *in vivo* experiments, BIBF 1202 did not show efficacy despite its activity at target receptors of the drug.

**Elimination:**
Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min). Urinary excretion of unchanged drug within 48 h 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. The major route of elimination of drug related radioactivity after oral administration of [$^{14}$C] nintedanib was via faecal/biliary excretion (93.4% of dose). 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. The terminal half-life of nintedanib was between 10 and 15 hours.

**Transport:**
Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see DRUG INTERACTIONS section. Nintedanib was shown not to be a substrate or inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2 or MRP-2 *in vitro*. Nintedanib was also not a substrate of BCRP. Only a weak inhibitory potential on OCT-1, BCRP, and P-gp was observed in vitro which is considered to be of low clinical relevance. The same applies for nintedanib being a substrate of OCT-1.

Exposure-response relationship
In exploratory pharmacokinetic (PK)-adverse event analyses based on the Phase II IPF data, higher exposure to nintedanib tended to be associated with liver enzyme elevations (see WARNINGS AND PRECAUTIONS section).

Intrinsic and Extrinsic Factors; Special Populations
The PK properties of nintedanib were similar in healthy volunteers and patients with IPF. Based on results of a Population PK analysis and descriptive investigations, moderate effects on exposure to nintedanib by age, body weight, smoking status and race were observed. Based on the high inter-individual variability of exposure, the observed moderate effects are not sufficient to warrant a dose adjustment (see WARNINGS AND PRECAUTIONS section).

## Special Populations and Conditions

**Pediatrics:**
Studies in pediatric populations have not been performed.

**Geriatrics:**
Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16% for a 45-year old patient ($5^{th}$ percentile) and increased by 13% for a 76-year old patient ($95^{th}$ percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5% of the population was older than 75 years.

**Race:**
The population mean exposure to nintedanib was 33-50% higher in Chinese, Taiwanese, and Indian patients and 16% higher in Japanese patients while it was 16-22% lower in Koreans compared to Caucasians (body weight corrected).

**Hepatic Insufficiency:**

A dedicated single-dose phase I study compared the pharmacokinetics of OFEV in 8 subjects with mild hepatic impairment (Child Pugh A) and 8 subjects with moderate hepatic impairment (Child Pugh B) to healthy matched control subjects (N=8 per hepatic impairment group). In subjects with mild hepatic impairment, the mean exposure to nintedanib was 2.2-fold higher based on $C_{max}$ (90% CI 1.3 – 3.7) and $AUC_{0-\infty}$ (90% CI 1.2 – 3.8) compared to healthy subjects. In subjects with moderate hepatic impairment, exposure was 7.6-fold higher based on $C_{max}$ (90%

CI 4.4 – 13.2) and 8.7-fold higher (90% CI 5.7 – 13.1) based on $AUC_{0-\infty}$ compared to healthy volunteers. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

**Renal Insufficiency:**
Based on a population PK analysis of data from patients with IPF, exposure to nintedanib was not influenced by mild (CrCl: 60 to 90 mL/min) or moderate (CrCl: 30 to 60 mL/min) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) were limited.

**Body Weight:**
An inverse correlation between body weight and exposure to nintedanib was observed. $AUC_{\tau,ss}$ increased by 25% for a 50 kg patient ($5^{th}$ percentile) and decreased by 19% for a 100 kg patient ($95^{th}$ percentile) relative to a patient with the median weight of 71.5 kg.

**Smokers:**
Smoking was associated with a 21% lower exposure to nintedanib compared to ex- and never-smokers. No dose adjustment is warranted.

**Concomitant Treatment with Pirfenidone:**
In a dedicated pharmacokinetic study, concomitant treatment of nintedanib with pirfenidone was investigated in patients with IPF. Group 1 received a single dose of 150 mg nintedanib before and after uptitration to 801 mg pirfenidone three times a day at steady state. Group 2 received steady state treatment of 801 mg pirfenidone three times a day and had a PK profiling before and after at least 7 days of co-treatment with 150 mg nintedanib twice daily. In group 1, the adjusted geometric mean ratios (90% confidence interval (CI)) were 93% (57% - 151%) and 96% (70% - 131%) for Cmax and AUC0-tz of nintedanib, respectively (n=12). In group 2, the adjusted geometric mean ratios (90% CI)) were 97% (86% - 110%) and 95% (86% - 106%) for Cmax,ss and AUCτ,ss of pirfenidone, respectively (n=12).

## STORAGE AND STABILITY

Store at 15 – 25°C.

## SPECIAL HANDLING INSTRUCTIONS

Store in the original package in order to protect from moisture.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

OFEV soft capsules are available in two different strengths of 100 and 150 mg of nintedanib (as a free base) corresponding to 120.40 mg and 180.60 mg of nintedanib ethanesulfonate (esilate), respectively:

- 100 mg soft capsules are peach-colored, opaque, oblong soft-gelatin capsules imprinted on one side in black with the Boehringer Ingelheim company symbol and “100”.
- 150 mg soft capsules are brown-colored, opaque, oblong soft-gelatin capsule imprinted

on one side in black with the Boehringer Ingelheim company symbol and “150”

Excipients

| | |
|---|---|
| *Capsule fill:* | Medium chain triglycerides, hard fat, soya lecithin (E322) |
| *Capsule shell:* | Gelatin, glycerol 85 %, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), black ink (Opacode®) |
| *Black ink:* | Shellac glaze, iron oxide black (E172), propylene glycol (E1520) |

OFEV soft capsules are packaged in unit dose blister cards with push-through foil and individually molded cavities (10-count blister card with cross perforation). The blister cards are composed of a laminated aluminum bottom foil and a printed aluminum lidding foil.

OFEV 100 mg soft capsules are available in the following packaging sizes: Six blister cards are packed into a folding box resulting in pack sizes of 6 x 10 capsules per pack.

OFEV 150 mg soft capsules are available in the following packaging sizes: Six blister cards are packed into a folding box resulting in pack sizes of 6 x 10 capsules per pack and three blister cards are packed into a folding box resulting in pack sizes of 3 x 10 capsules per pack.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

Common name: nintedanib esilate

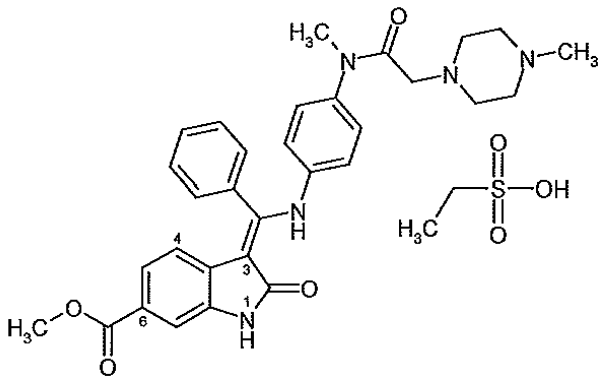
Chemical name:

CAS Index name:
1H-indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]-amino]phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3Z)-, ethanesulfonate (1:1)

Molecular formula and molecular mass:

$C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$ ($C_{33}H_{39}N_5O_7S$)
649.76 g/mol (ethanesulfonate salt), 539.62 g/mol (free base)

Structural formula:



Physicochemical properties:

Physical description: bright yellow powder.

Melting Point: $T_{fus}$ = 305 ± 5 °C
$\Delta H_{fus}$ = 82 ± 5 J/g

Dissociation Constants: $pKa_1$ = 7.9 ± 0.2 (piperazine moiety)
$pKa_2$ = 2.1 ± 0.2 (piperazine moiety)

Partition Coefficient: Log D (pH 7.4) = 3.0

pH Solubility Profile: nintedanib shows good solubility behaviour (> 1 mg/ml) in acidic media. Above pH 3 solubility of nintedanib drops by at least three orders of magnitude to the lower solubility of the monocationic form and its free base (< 0.001 mg/ml at pH≥7). The intrinsic dissolution rate is fast in acidic media (> 1000 μg/cm$^2$/min up to pH 2.0). In water a solubility of 2.8 mg/ml was found; the resulting solution shows an intrinsic pH of 5.7.

## CLINICAL TRIALS

The clinical efficacy of nintedanib has been studied in patients with IPF in two phase 3, randomised, double-blind, placebo-controlled studies with identical design (1199.32 and 1199.34). Patients were randomised in a 3:2 ratio to treatment with nintedanib 150 mg or placebo twice daily for 52 weeks. Dose reduction to 100 mg twice daily and dose interruptions were allowed to manage adverse events.

The two phase 3 trials included male and female patients 40 years of age and older, with a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for < 5 years. Diagnoses were centrally adjudicated based on radiological and, if available, histopathological confirmation. Patients were required to have an FVC ≥ 50% predicted of normal and a carbon monoxide diffusing capacity (DLCO, corrected for hemoglobin) 30% to 79% predicted of normal. 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.

The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC). The key secondary endpoints were change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at 52 weeks and time to first acute IPF exacerbation.

### Study demographics and trial design

**Table 4 - Summary of patient demographics for clinical trials in specific indication**

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n=number) | Mean age (Standard Deviation (StD)) | Gender |
|---|---|---|---|---|---|
| 1199.32 | Multicentre, randomised, double-blind | Eligible patients were randomised in 3:2 ratio to receive nintedanib 150 mg bid or placebo for 52 weeks. | Nintedanib: n=309<br>Placebo: n=204 | 66.9 (StD 8.4) years | 81% male and 19% female |
| 1199.34 | Multicentre, randomised, double-blind | Eligible patients were randomised in 3:2 ratio to receive nintedanib 150 mg bid or placebo for 52 weeks. | Nintedanib: n=329<br>Placebo: n=219 | 66.4 (StD 7.9) years | 78% male and 22% female |

**Study results**

Annual rate of decline in FVC

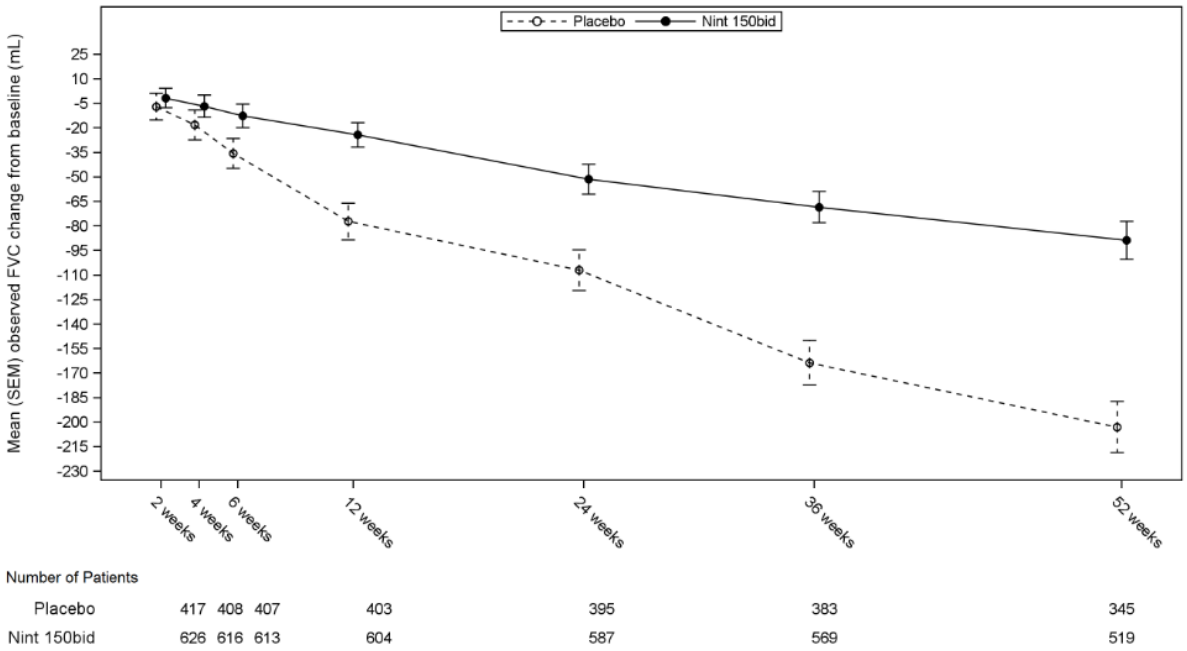
The annual rate of decline in FVC (in mL) was significantly reduced in patients receiving nintedanib compared to patients receiving placebo. The treatment effect was consistent in both trials. See Table 5 for individual and pooled study results.

**Table 5: Annual rate of decline in FVC (mL) in trials 1199.32, 1199.34 and their pooled data - treated set**

| | **1199.32** | | **1199.34** | | **1199.32 and 1199.34 pooled** | |
|---|---|---|---|---|---|---|
| | Placebo | Nintedanib150 mg twice daily | Placebo | Nintedanib 150 mg twice daily | Placebo | Nintedanib 150 mg twice daily |
| Number of analysed patients | 204 | 309 | 219 | 329 | 423 | 638 |
| Rate[1] (SE) of decline over 52 weeks | −239.9 (18.71) | −114.7 (15.33) | −207.3 (19.31) | −113.6 (15.73) | −223.5 (13.45) | −113.6 (10.98) |
| Comparison vs. placebo Difference[1] | | 125.3 | | 93.7 | | 109.9 |
| 95% CI | | (77.7, 172.8) | | (44.8, 142.7) | | (75.9, 144.0) |
| p-value | | <0.0001 | | 0.0002 | | <0.0001 |
| [1] Estimated based on a random coefficient regression model. | | | | | | |

The robustness of the effect of nintedanib in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses. See Figure 1 for the evolution of change from baseline over time in both treatment groups, based on the pooled analyses of studies 1199.32 and 1199.34.

**Figure 1: Mean (SEM) observed FVC change from baseline (mL) over time, studies 1199.32 and 1199.34 pooled**




bid = twice daily

Time to first acute IPF exacerbation

The time to first acute IPF exacerbation was a key secondary endpoint in trials 1199.32 and 1199.34. In trial 1199.34, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving nintedanib compared to placebo (Hazard ratio (HR): 0.38; 95% CI 0.19, 0.77), whereas in trial 1199.32 there was no difference between the treatment groups (Hazard ratio: 1.15; 95% CI 0.54, 2.42). In the pooled analysis of the clinical trials, a numerically lower risk of first acute exacerbation was observed in patients receiving nintedanib compared to placebo (Hazard ratio: 0.64; 95% CI 0.39, 1.05).

All adverse events of acute IPF exacerbation reported by the investigator were adjudicated by a blinded adjudication committee. An analysis of the time to first ‘confirmed’ or 'suspected' adjudicated acute IPF exacerbation was performed. The frequency of patients with at least 1 adjudicated exacerbation occurring within 52 weeks was lower in the nintedanib group than in the placebo group for both clinical trials. Time to event analysis of the adjudicated exacerbation events yielded an HR 0.55 (95% CI: 0.20, 1.54) for trial 1199.32 and an HR of 0.20 (95% CI: 0.07, 0.56) for trial 1199.34.

Change from baseline in St. George’s Respiratory Questionnaire total score at week 52

St. George’s Respiratory Questionnaire (SGRQ) total score measuring health related quality of life was analysed at 52 weeks as a key secondary endpoint in the two clinical trials. In trial

1199.32, the increase from baseline in SGRQ total score at week 52 was comparable between nintedanib and placebo (difference between treatment groups: -0.05; 95% CI: -2.50, 2.40; p=0.9657).

In trial 1199.34, patients receiving placebo had a larger increase (i.e. worsening) from baseline in SGRQ total score as compared to patients receiving nintedanib 150 mg bid, and the difference between the treatment groups was statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197).

Survival analysis

Survival was evaluated in trials 1199.32 and 1199.34 as an exploratory analysis to support the primary endpoint (FVC). In the pre-specified pooled analysis of survival data of the clinical trials, all-cause mortality over 52 weeks was numerically lower in the nintedanib group (5.5%) compared with the placebo group (7.8%). The analysis of time to death resulted in a HR of 0.70 (95% CI 0.43, 1.12; p=0.1399). The results of all survival endpoints (such as on-treatment mortality and respiratory mortality) showed a consistent numerical difference in favour of nintedanib.

Supportive evidence from the phase II trial (1199.30) Nintedanib 150 mg twice daily results:

Additional evidence of efficacy is provided by the randomised, double-blind, placebo-controlled, dose finding phase II trial including a nintedanib 150 mg bid dose group. This was a 52 week study in patients with IPF and included a total of 432 randomized patients with 85 patients treated with nintedanib 150 mg and 85 patients treated with placebo.

The primary endpoint, rate of decline in FVC over 52 weeks, was lower in the 150 mg nintedanib arm (-0.060 L/year, N=84) than the placebo arm (-0.190 L/year, N=83). The estimated difference between the treatment groups was 0.131 L/year (95% CI 0.027, 0.235) reaching nominal statistical significance (p=0.0136).

## DETAILED PHARMACOLOGY

Nintedanib exerted anti-inflammatory and anti-fibrotic activity in three animal models of bleomycin- or silica-induced pulmonary fibrosis. Anti-inflammatory activity was demonstrated by reduced lymphocytes and neutrophils in the bronchoalveolar lavage, by attenuated interleukin (IL)-1β, IL-6, CXCL1/KC levels in lung tissue and by reduced inflammatory scores in lung histology. Anti-fibrotic activity was shown by reduced procollagen-1 mRNA expression and total collagen and tissue inhibitor of metalloproteinase 1 levels in lung tissue and reduced fibrotic scores in lung histology.

## TOXICOLOGY

General toxicology

Single dose toxicity studies in rats and mice indicated a low acute toxic potential of nintedanib. In repeat dose toxicology studies in rats, adverse effects (e.g. thickening of epiphyseal plates, lesions of the incisors) were mostly related to the mechanism of action (i.e. VEGFR-2 inhibition)

of nintedanib. These changes are known from other VEGFR-2 inhibitors and can be considered class effects.

Diarrhea and vomiting accompanied by reduced food consumption and loss of body weight were observed in toxicity studies in non-rodents.

There was no evidence of liver enzyme increases in rats, dogs, and Cynomolgus monkeys. Mild liver enzyme increases which were not due to serious adverse effects such as diarrhea were only observed in Rhesus monkeys.

Reproduction toxicity

In rats, nintedanib reduced female fertility, including increases in resorption and post-implantation loss, at exposures below the maximum recommended human dose (MRHD) of 150 mg b.i.d. based on AUC. A decrease in the number and size of corpora lutea in the ovaries was observed in chronic toxicity studies in rats and mice.

In rats, embryo-foetal lethality and teratogenic effects were observed at an exposure approximately 3.6 to 7.2 times lower than at the MRHD. At an exposure of approximately 12 to 18 times lower than the exposure at the MRHD, slight effects on the development of the axial skeleton and on the development of the great arteries were noted.

In rabbits, embryo-foetal lethality and teratogenic effects were observed at an exposure approximately 3 times higher than at the MRHD but equivocal effects on the embryo-foetal development of the axial skeleton and the heart were noted already at an exposure below that at the MRHD of 150 mg twice daily.

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5 % of the administered dose).

Carcinogenicity

From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib. Nintedanib was dosed up to 10 mg/kg/day in rats and 30 mg/kg/day in mice. These doses were less than (in rats) and approximately 4 times (in mice) the MRHD based on plasma drug AUC.

Genotoxicity

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

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6. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365(12): 1079-87.

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9. Supplementary Appendix to: Richeldi L, du Boi RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.

10. Wollin L, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Resp J 2015;45:1434-45.

## PART III: CONSUMER INFORMATION

**PrOfev®**
Nintedanib Capsules

**Read this carefully before you start taking OFEV and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about OFEV.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
Use OFEV to treat Idiopathic Pulmonary Fibrosis (IPF) in adults.

**What it does:**
OFEV works to reduce the fibrosis in your lungs.

**When it should not be used:**
- If you are allergic to nintedanib, peanut or soya, or any of the other ingredients in OFEV.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking OFEV.
- Do not take OFEV during pregnancy. It can cause birth defects.
- If you are younger than 18 years of age.

**What the medicinal ingredient is:**
Nintedanib esilate

**What the non-medicinal ingredients are:**
Gelatin, glycerol, hard fat, iron oxide black, iron oxide red, iron oxide yellow, medium chain triglycerides, propylene glycol, shellac glaze, soya lecithin, titanium dioxide

**What dosage forms it comes in:**
Capsules: 100 and 150 mg

## WARNINGS AND PRECAUTIONS

BEFORE you use OFEV, talk to your doctor or pharmacist if you:
- have or had liver problems;
- have or had bleeding problems;
- have high blood pressure;
- have or had peptic ulcers;
- take blood-thinning medicines to prevent blood clotting;
- have or had problems with your heart;
- recently had surgery or will be having surgery;
- are pregnant or planning to become pregnant;
- are taking NSAIDS or corticosteroids.

**Serious Liver Problems:** In some patients, OFEV has been associated with drug-induced liver injuries (DILIs), in rare cases these can be serious and life-threatening. Before and during treatment, your doctor should do blood tests, for example to check your liver function, to determine if you may be treated with OFEV.

Stop taking OFEV and inform your doctor immediately if you have unexplained symptoms such as yellowing of your skin or the white part of your eyes (jaundice), dark or brown (tea coloured) urine, pain on the upper right side of your stomach area (abdomen), bleeding or bruising more easily than normal, nausea, vomiting or loss of appetite, or feeling tired.

While taking OFEV, tell your doctor immediately if you:
- experience diarrhea. It is important to treat diarrhea early;
- vomit or have nausea;
- experience severe abdominal pain and swelling, nausea, vomiting, chills and fever as these could be symptoms of a hole in the wall of your gut (gastrointestinal perforation);
- experience swelling, redness and pain in one part of the body as these could be symptoms of a blood clot;
- experience chest pressure or pain, in the centre of the chest or spread over the shoulder or arm, a fast heartbeat, shortness of breath, nausea or vomiting, as these could be symptoms of a heart attack;
- have any bleeding that does not stop.

**Birth Control:** Women who can become pregnant must use effective birth control while taking OFEV and for at least 3 months after the last dose. Also use a second form of birth control, such as, a barrier method while taking OFEV. Tell your doctor or pharmacist right away if you become pregnant while taking OFEV.

**Breastfeeding / Lactation:**
Do not breastfeed. OFEV may harm the infant.

**Driving and using machines:** Before doing tasks that require special attention, wait until you know how you respond to OFEV.

## INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about **all** the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

**The following may interact with OFEV:**
- Ketoconazole used to treat fungal infections;
- Erythromycin used to treat bacterial infections;
- Rifampicin, an antibiotic used to treat tuberculosis;
- Carbamazepine or phenytoin used to treat seizures;
- St. John's Wort, a herbal medicine;
- Grapefruits, grapefruit juice or Seville oranges.

## PROPER USE OF THIS MEDICATION

OFEV should only be prescribed and monitored by physicians with the appropriate training and experience in the diagnosis and treatment of IPF.

Swallow the capsule **whole** with water. DO NOT chew or crush the capsule.

Take OFEV:
- exactly as prescribed;
- every day;
- every 12 hours, at about the same time every day;
- with food.

**Usual Adult Dose:**

Recommended and maximum daily dose is 150 mg twice a day.

For patients with mild liver disease the recommended daily dose is 100 mg twice a day.

Your doctor probably will not prescribe OFEV if you have moderate or severe liver disease.

If you have side effects, your doctor may:
- decrease your dose to 100 mg twice a day;
- or advise you to interrupt temporarily or stop taking OFEV.

Do not reduce the dose or stop taking OFEV without consulting your doctor. It is important to take OFEV every day, as long as your doctor prescribes it for you.

Do not take more than the maximum daily dose.

**Overdose:**

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
If you have forgotten to take your dose, carry on and take your next dose at the usual time. Do not double dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients using OFEV may experience side effects, although not everybody gets them.

**Side effects may include:**
- Diarrhea, which may lead to a loss of fluid and important electrolytes in your body. At the first signs of diarrhea, drink plenty of fluids and start anti-diarrheal treatment.
- Constipation;
- Gas;
- Heartburn.

OFEV can cause abnormal blood test results. Your doctor will do blood tests regularly to check how well your liver function is working during your treatment. Your doctor will decide when to perform blood tests and will interpret the results.

**If any of these affects you severely, tell your doctor, nurse or pharmacist.**

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| **Very Common** | Diarrhea | | ✓ | |
| | Nausea | ✓ | | |
| | Abdominal pain | | ✓ | |
| **Common** | Vomiting | | ✓ | |
| | Decreased weight | ✓ | | |
| | Decreased appetite | ✓ | | |
| | Bleeding | | | ✓ |
| **Uncommon** | **Serious liver problems or Jaundice:** Increased blood bilirubin and liver enzymes levels (liver test), yellowing of the skin or the white part of the eyes, dark or brown (tea coloured) urine, abdominal pain, nausea, vomiting, loss of appetite, bleeding or bruising more easily than normal, or feeling tired | | | ✓ |
| | **Hypertension** (blood pressure increased): headache, vision disorders, nausea and vomiting | ✓ | | |
| | **Gastrointestinal perforation:** severe constant abdominal pain with tenderness, distension, nausea and vomiting | | | ✓ |
| | **Heart Attack**: pain in the chest or spread over the shoulder or arm; a fast heartbeat; shortness of breath; nausea or vomiting | | ✓ | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and call your doctor or pharmacist** |
| | | **Only if severe** | **In all cases** | |
| **Uncommon** | **Pancreatitis:** severe upper abdominal pain radiating to the back, fever, nausea and vomiting | | ✓ | |
| | **Thrombocytopenia:** easily bruised, rash with reddish-purplish spots usually on the lower legs, longer than usual bleeding from a cut, bleeding from your gums or nose, bleeding in urine or in your stool (black like tar stool), fatigue. | | ✓ | |
| | **Rash/itchy skin** | ✓ | | |

***This is not a complete list of side effects. For any unexpected effects while taking OFEV, contact your doctor or pharmacist.***

## HOW TO STORE IT

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on carton.

Store at 15-25°C. Store in the original blister in order to protect from moisture.

Do not use this medicine if you notice that the blister containing the capsules is opened or a capsule is broken.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

**If you want more information about OFEV:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (http://www.boehringer-ingelheim.ca), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, ext. 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

Last revised: August 10, 2018