ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ofev 100 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 100 mg nintedanib (as esilate)

Excipient(s) with known effect:
Each capsule contains 1.2 mg of soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Ofev 100 mg soft capsules are peach-coloured, opaque, oblong soft-gelatin capsules imprinted on one side in black with the Boehringer Ingelheim company symbol and "100".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

4.2 Posology and method of administration

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

Posology
The recommended dose is 150 mg nintedanib twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose.

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

Dose adjustments
In addition to symptomatic treatment if applicable, the management of adverse reactions to Ofev (see sections 4.4 and 4.8) could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. Ofev treatment may be resumed at the full 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.

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN), 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 dose (150 mg twice daily) (see sections 4.4 and 4.8).

Special populations

Elderly patients (≥ 65 years)

No overall differences in safety and efficacy were observed for elderly patients. No *a-priori* dose adjustment is required on the basis of a patient's age. Patients ≥75 years may be more likely to require dose reduction to manage adverse effects (see section 5.2).

Renal impairment

Less than 1% of a single dose of nintedanib is excreted via the kidney (see section 5.2). 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 (<30 ml/min creatinine clearance).

Hepatic impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90%; see section 5.2). No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A; see section 4.4). The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Ofev is not recommended.

Paediatric population

The safety and efficacy of Ofev in children aged 0-18 years have not been established. No data are available.

Method of administration

Ofev is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Gastrointestinal disorders

Diarrhoea

In the INPULSIS trials (see section 5.1), diarrhoea was the most frequent gastro-intestinal adverse reaction reported in 62.4% versus 18.4% of patients treated with Ofev and placebo, respectively (see section 4.8). In most patients the adverse reaction was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhoea led to dose reduction in 10.7% of the patients and to discontinuation of nintedanib in 4.4% of the patients.

Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, 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 dose (150 mg twice daily). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with Ofev should be discontinued.

Nausea and vomiting

Nausea and vomiting were frequently reported gastrointestinal adverse reactions (see section 4.8). In most patients with nausea and vomiting, the event was of mild to moderate intensity. Nausea led to discontinuation of nintedanib in 2.0% of patients. Vomiting led to discontinuation in 0.8% of the patients.

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 dose (150 mg twice daily). In case of persisting severe symptoms therapy with Ofev should be discontinued.

Hepatic function
The safety and efficacy of Ofev has 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 sections 4.2).

Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, alkaline phosphatase (ALKP), gamma-glutamyl-transferase (GGT)) with a potentially higher risk for female patients. Transaminase increases were reversible upon dose reduction or interruption. Administration of nintedanib was also associated with elevations of bilirubin. Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with Ofev, and periodically thereafter (e.g. at each patient visit) or as clinically indicated. If transaminase (AST or ALT) elevations > 3x ULN are measured, dose reduction or interruption of the therapy with Ofev is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Ofev may be resumed at the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (see section 4.2). If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Ofev should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

Haemorrhage
Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding. In the INPULSIS trials with Ofev, the frequency of patients who experienced bleeding AEs was slightly higher in the Ofev arm (10.3%) than in the placebo arm (7.8%). 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%).

Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment were not included in the INPULSIS studies. Therefore these patients should only be treated with Ofev if the anticipated benefit outweighs the potential risk.

Arterial thromboembolic events
Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Arterial thromboembolic events were infrequently reported: in 0.7% of patients in the placebo and 2.5% in the nintedanib treated group. While adverse events reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%). Caution should be used 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.

Venous thromboembolism
In the INPULSIS trials no increased risk of venous thromboembolism was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of thromboembolic events.

Gastrointestinal perforations
In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of gastrointestinal perforation. Particular caution should be exercised when treating patients with previous abdominal surgery. Ofev should only be initiated at least 4 weeks after abdominal surgery.

Therapy with Ofev should be permanently discontinued in patients who develop gastrointestinal perforation.

Hypertension
Administration of Ofev may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated.

Wound healing complication
No increased frequency of impaired wound healing was observed in the INPULSIS trials. Based on the mechanism of action nintedanib may impair wound healing. 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.

Co-administration with pirfenidone
Concomitant treatment of nintedanib with pirfenidone was investigated in a parallel group design study in Japanese patients with IPF. Twenty four patients were treated for 28 days with 150 mg nintedanib twice daily (13 patients received nintedanib on top of chronic treatment with standard doses of pirfenidone; 11 patients received nintedanib alone). Due to the short duration of concomitant exposure and low number of patients the benefit/risk of the co-administration with pirfenidone has not been established.

Effect on QT interval
No evidence of QT prolongation was observed for nintedanib in the clinical trial programme (Section 5.1). As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered nintedanib in patients who may develop QTc prolongation.

Allergic reaction
Dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.

4.5 Interaction with other medicinal products and other forms of interaction

P-glycoprotein (P-gp)
Nintedanib is a substrate of P-gp (see section 5.2). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study. In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with Ofev, potent P-gp inhibitors (e.g. ketoconazole, erythromycin or cyclosporine) 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 section 4.2).

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medicinal product with no or minimal P-gp induction potential should be considered.

Cytochrome (CYP)-enzymes
Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. 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 (see section 5.2). The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

Co-administration with other medicinal products
The potential for interactions of nintedanib with hormonal contraceptives was not explored.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception
Nintedanib may cause foetal harm in humans (see section 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Ofev. They should be advised to use adequate contraception during and at least 3 months after the last dose of Ofev. Since the effect of nintedanib on the metabolism and efficacy of hormonal contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.

Pregnancy
There is no information on the use of Ofev in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this active substance (see section 5.3). As nintedanib may cause foetal harm also in humans, it must not be used during pregnancy.

Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Ofev.

If the patient becomes pregnant while receiving Ofev, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Ofev should be considered.

Breast-feeding
There is no information on the excretion of nintedanib and its metabolites 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. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Ofev.

Fertility
Based on preclinical investigations there is no evidence for impairment of male fertility (see section 5.3). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 150 mg twice daily (see section 5.3).

4.7 Effects on ability to drive and use machines

Ofev has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines during treatment with Ofev.

4.8 Undesirable effects

Summary of the safety profile
Nintedanib has been studied in clinical trials of 1,529 patients suffering from IPF. The safety data provided in the following are based on the two Phase III, randomised, double-blind, placebo-controlled studies in 1,061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2).

The most frequently reported adverse reactions associated with the use of nintedanib included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased.

For the management of selected adverse reactions please also refer to section 4.4.

Tabulated list of adverse reactions
The below table provides a summary of the adverse reactions by MedDRA System Organ Class (SOC) and frequency category.

Table 1 summarizes the frequencies of adverse drug reactions (ADRs) that were reported in the nintedanib group (638 patients) pooled from the two placebo-controlled Phase III clinical trials of 52 weeks duration.

Frequency categories are defined using the following convention:
very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping adverse reactions are presented in order of decreasing seriousness.

Table 1: Summary of ADRs per frequency category

Frequency **System Organ Class**	**Very common (≥ 1/10)**	**Common (≥ 1/100 < 1/10)**	**Uncommon (≥ 1/1,000 < 1/100)**
Metabolism and nutrition disorders		Weight decreased, Decreased appetite	
Vascular disorders			Hypertension
Gastrointestinal Disorder	Diarrhoea, Nausea, Abdominal pain	Vomiting	
Hepatobiliary disorders	Hepatic enzyme increased	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Gamma glutamyl transferase (GGT) increased	Hyperbilirubinaemia, Blood alkaline phosphatase (ALKP) increased

Description of selected adverse reactions

Diarrhoea
Diarrhoea was reported in 62.4% of patients treated with nintedanib. The event was reported to be of severe intensity in 3.3% of nintedanib treated patients. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. Diarrhoea led to permanent treatment discontinuation in 4.4% of patients; otherwise the events were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption (see section 4.4).

Hepatic enzyme increased
Liver enzyme elevations (see section 4.4) were reported in 13.6% of nintedanib treated patients. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease. For further information about special populations, recommended measures and dosing adjustments in case of diarrhoea and hepatic enzyme increased, refer additionally to sections 4.4 and 4.2, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote or treatment for Ofev overdose. Two patients in the oncology programme had an overdose of maximum 600 mg twice daily up to eight days. Observed adverse reactions 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 INPULSIS 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE31

Mechanism of action
Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling. In addition nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases.

Pharmacodynamic effects
Nintedanib inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis. The potential impact of VEGFR inhibition by nintedanib and the anti-angiogenic activity of nintedanib on IPF pathology are currently not fully elucidated. In preclinical disease models of lung fibrosis nintedanib exerts potent anti-fibrotic and anti-inflammatory activity. Nintedanib inhibits proliferation, migration and fibroblast to myofibroblast transformation of human lung fibroblasts from patients with IPF.

Clinical efficacy and safety
The clinical efficacy of nintedanib has been studied in patients with IPF in two phase III, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 (1199.32) and INPULSIS-2 (1199.34)). Patients with FVC baseline < 50% predicted or carbon monoxide diffusing capacity (DLCO, corrected for haemoglobin) < 30% predicted at baseline were excluded from the trials. Patients were randomized in a 3:2 ratio to treatment with Ofev 150 mg or placebo twice daily for 52 weeks.

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

Annual rate of decline in FVC
The annual rate of decline of 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 2 for individual and pooled study results.

Table 2: Annual rate of decline in FVC (mL) in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

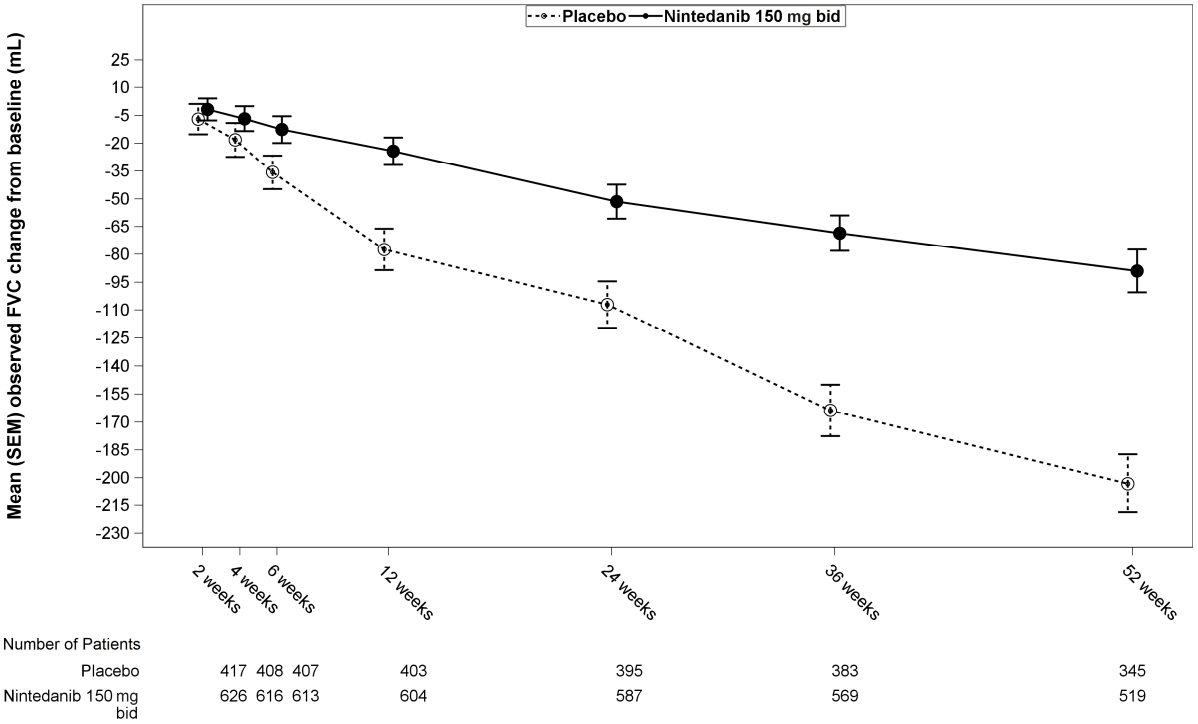
	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 Pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
Rate[1] (SE) of decline over 52 weeks	−239.9 (18.71)	−114.7 (15.33)	−207.3 (19.31)	−113.6 (15.73)	−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.
CI: confidence interval

The robustness of the effect of nintedanib in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses. In patients with missing data, the primary analysis assumes that the decline in FVC after the last observed value would be similar to the decline in other patients in the same treatment group. In a sensitivity analysis which assumed that in patients with missing data at week 52 the FVC decline after the last observed value would be the same as in all placebo patients, the adjusted difference in the annual rate of decline between nintedanib and placebo was 113.9 mL/year (95% CI 69.2, 158.5) in INPULSIS-1 and 83.3 mL/year (95% CI 37.6, 129.0) in INPULSIS-2**.**

In addition, similar effects were observed on other lung function endpoints e.g. change from baseline in FVC at week 52 and FVC responder analyses providing further substantiation of the effects of nintedanib on slowing disease progression. See Figure 1 for the evolution of change from baseline over time in both treatment groups, based on the pooled analysis of studies INPULSIS-1 and INPULSIS-2.

Figure 1: Mean (SEM) observed FVC change from baseline (mL) over time, studies INPULSIS-1 and INPULSIS-2 pooled



Number of Patients							
Placebo	417	408	407	403	395	383	345
Nintedanib 150 mg bid	626	616	613	604	587	569	519

bid = twice daily

FVC responder analysis

In both INPULSIS trials, the proportion of FVC responders, defined as patients with an absolute decline in FVC % predicted no greater than 5% (a threshold indicative of the increasing risk of mortality in IPF), was significantly higher in the nintedanib group as compared to placebo. Similar results were observed in analyses using a conservative threshold of 10%. See Table 3 for individual and pooled study results.

Table 3: Proportion of FVC responders at 52 weeks in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
5% threshold						
Number (%) of FVC responders[1]	78 (38.2)	163 (52.8)	86 (39.3)	175 (53.2)	164 (38.8)	338 (53.0)
Comparison vs placebo						
Odds ratio		1.85		1.79		1.84
95% CI		(1.28, 2.66)		(1.26, 2.55)		(1.43, 2.36)
p-value[2]		0.0010		0.0011		<0.0001
10% threshold						
Number (%) of FVC responders[1]	116 (56.9)	218 (70.6)	140 (63.9)	229 (69.6)	256 (60.5)	447 (70.1)
Comparison vs placebo						
Odds ratio		1.91		1.29		1.58
95% CI		(1.32, 2.79)		(0.89, 1.86)		(1.21, 2.05)
p-value[2]		0.0007		0.1833		0.0007

[1]Responder patients are those with no absolute decline greater than 5% or greater than 10% in FVC % predicted, depending on the threshold and with an FVC evaluation at 52 weeks.
[2]Based on a logistic regression.

Time to progression (≥ 10% absolute decline of FVC % predicted or death)
In both INPULSIS trials, the risk of progression was statistically significantly reduced for patients treated with nintedanib compared with placebo. In the pooled analysis, the HR was 0.60 indicating a 40% reduction in the risk of progression for patients treated with nintedanib compared with placebo.

Table 4: Frequency of patients with ≧ 10% absolute decline of FVC % predicted or death over 52 weeks and time to progression in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	83 (40.7)	75 (24.3)	92 (42.0)	98 (29.8)	175 (41.4)	173 (27.1)
Comparison vs placebo[1]						
p-value[2]		0.0001		0.0054		<0.0001
Hazard ratio[3]		0.53		0.67		0.60
95% CI		(0.39, 0.72)		(0.51, 0.89)		(0.49, 0.74)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

Change from baseline in SGRQ total score at week 52
SGRQ total score measuring health related quality of life (HRQoL) was analysed at 52 weeks. In INPULSIS-2, patients receiving placebo had a larger increase from baseline SGRQ total score as compared to patients receiving nintedanib 150 mg twice daily. The deterioration of HRQoL was smaller in the nintedanib group; the difference between the treatment groups was statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197).

In INPULSIS-1, 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 the pooled analysis of the INPULSIS trials, the estimated mean change from baseline to week 52 in SGRQ total score was smaller in the nintedanib group (3.53) than in the placebo group (4.96), with a difference between the treatment groups of -1.43 (95% CI: -3.09, 0.23; p=0.0923). Overall, the effect of nintedanib on health-related quality of life as measured by the SGRQ total score is modest, indicating less worsening compared to placebo.

Time to first acute IPF exacerbation
In the INPULSIS-2 trial, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving nintedanib compared to placebo, in the INPULSIS-1 trial there was no difference between the treatment groups. In the pooled analysis of the INPULSIS trials, a numerically lower risk of first acute exacerbation was observed in patients receiving nintedanib compared to placebo. See Table 5 for individual and pooled study results.

Table 5: Frequency of patients with acute IPF exacerbations over 52 weeks and time to first exacerbation analysis based on investigator-reported events in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	11 (5.4)	19 (6.1)	21 (9.6)	12 (3.6)	32 (7.6)	31 (4.9)
Comparison vs placebo[1]						
p-value[2]		0.6728		0.0050		0.0823
Hazard ratio[3]		1.15		0.38		0.64
95% CI		(0.54, 2.42)		(0.19, 0.77)		(0.39, 1.05)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

All adverse events of acute IPF exacerbation reported by the investigator were adjudicated by a blinded adjudication committee. A pre-specified sensitivity analysis of the time to first 'confirmed' or 'suspected' adjudicated acute IPF exacerbation was performed on the pooled data. The frequency of patients with at least 1 adjudicated exacerbation occurring within 52 weeks was lower in the nintedanib group (1.9% of patients) than in the placebo group (5.7% of patients). Time to event analysis of the adjudicated exacerbation events using pooled data yielded a hazard ratio (HR) of 0.32 (95% CI 0.16, 0.65; p=0.0010). This indicates that the risk of having a first acute adjudicated IPF exacerbation was statistically significantly lower in the nintedanib group than in the placebo group at any time point.

Survival analysis
In the pre-specified pooled analysis of survival data of the INPULSIS trials, overall mortality over 52 weeks was 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.

Table 6: All-cause mortality over 52 weeks in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 Pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	13 (6.4)	13 (4.2)	20 (9.1)	22 (6.7)	33 (7.8)	35 (5.5)
Comparison vs placebo[1]						
p-value[2]		0.2880		0.2995		0.1399
Hazard ratio[3]		0.63		0.74		0.70
95% CI		(0.29, 1.36)		(0.40, 1.35)		(0.43, 1.12)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

Supportive evidence from the phase II trial (1199.30) Ofev 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 twice daily dose group.

The primary endpoint, rate of decline in FVC over 52 weeks was lower in the 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). The difference between the treatment groups reached nominal statistical significance (p=0.0136).

The estimated mean change from baseline in SGRQ total score at 52 weeks was 5.46 for placebo, indicating worsening of the health-related quality of life and -0.66 for nintedanib, indicating stable health-related quality of life. The estimated mean difference for nintedanib compared with placebo was -6.12 (95% CI: -10.57, -1.67; p=0.0071).

The number of patients with acute IPF exacerbations over 52 weeks was lower in the nintedanib group (2.3%, N=86) compared to placebo (13.8%, N=87). The estimated hazard ratio of nintedanib versus placebo was 0.16 (95% CI 0.04, 0.71; p=0.0054).

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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Ofev in all subsets of the paediatric population in IPF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Nintedanib reached maximum plasma concentrations approximately 2 - 4 h after oral administration as soft gelatine capsule under fed conditions (range 0.5 - 8 h). The absolute bioavailability of a 100 mg dose was 4.69% (90% CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (CI: 95.3 - 152.5%) and absorption was delayed (median t_{max} fasted: 2.00 h; fed: 3.98 h).

Distribution
Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution during the terminal phase (V_{ss}: 1,050 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 0.869.

Biotransformation
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 uridine 5'-diphospho-glucuronosyltransferase enzymes (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. Nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes in preclinical studies, either. Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are therefore not expected.

Elimination
Total plasma clearance after intravenous infusion was high (CL: 1,390 mL/min, 28.8% gCV). Urinary excretion of the unchanged active substance within 48 h was about 0.05% of the dose (31.5% gCV) after oral and about 1.4% of the dose (24.2% gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6% gCV). 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, 2.61% gCV). The contribution of renal excretion to the total clearance was low (0.649% of dose, 26.3% gCV). The overall recovery was considered complete (above 90%) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50%).

Linearity/non-linearity
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). Accumulation upon multiple administrations was 1.04-fold for C_{max} and 1.38-fold for AUC_{τ}. Nintedanib trough concentrations remained stable for more than one year.

Transport
Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section 4.5. Nintedanib was shown to be not 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.

Population pharmacokinetic analysis in special populations
The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients. Based on results of a Population PK (PopPK) analysis in patients with IPF and non small cell lung cancer (NSCLC) (N=1,191) and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), alcohol consumption, or P-gp genotype. The PopPK analysis indicated moderate effects on exposure to nintedanib by age, body weight, and race, which are described in the following. Based on the high inter-individual variability of exposure observed moderate effects are considered not clinically relevant (see section 4.4).

Age
Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16% for a 45-year old patient and increased by 13% for a 76-year old patient 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 were older than 75 years. Based on a PopPK model, an increase in nintedanib exposure of approximately 20 - 25% was observed in patients ≥ 75 years compared with patients under 65 years.

Studies in paediatric populations have not been performed.

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.

Race
The geometric mean exposure to nintedanib was 33% higher in Chinese, Taiwanese, and Indian patients while it was 22% lower in Koreans compared to Caucasians (body weight corrected). Data from Black individuals was very limited but in the same range as for Caucasians.

Hepatic impairment
Pharmacokinetic data for nintedanib was collected in patients with abnormalities in hepatic parameters defined by elevations in AST, ALT and bilirubin levels. A trend to elevated exposure was observed in patients with AST- and ALT-values (up to 10x ULN) and elevated bilirubin levels (up to 1.5x ULN) at baseline as compared to patients with normal AST, ALT and bilirubin levels. In patients with ALT or AST > 10x ULN and bilirubin > 1.5x ULN, data were too limited to draw conclusions.

Concomitant treatment with pirfenidone
In a small parallel group design study in Japanese patients with IPF (13 patients received nintedanib on top of chronic treatment with standard doses of pirfenidone; 11 patients received nintedanib alone), exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on Cmax upon co-administration with pirfenidone pirfenidone compared to administration of nintedanib alone. Nintedanib had no effect on the PK of pirfenidone (see section 4.4).

5.3 Preclinical safety data

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.

Diarrhoea 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 diarrhoea were only observed in Rhesus monkeys.

Reproduction toxicity
In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the MRHD of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

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.

In a pre- and postnatal development study in rats, effects on pre- and post-natal development were seen at an exposure below the MRHD.

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).

From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.

Genotoxicity studies indicated no mutagenic potential for nintedanib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
triglycerides, medium-chain
hard fat
lecithin (soya) (E322)

Capsule shell
gelatin
glycerol (85%)
titanium dioxide (E171)
iron oxide red (E172)
iron oxide yellow (E172)

Printing ink
shellac glaze
iron oxide black (E172)
propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Ofev 100 mg soft capsules are available in the following pack-sizes:
- 30 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters
- 60 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/979/001
EU/1/14/979/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ofev 150 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 150 mg nintedanib (as esilate)

Excipient(s) with known effect:
Each capsule contains 1.8 mg of soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Ofev 150 mg soft capsules are brown-coloured, opaque, oblong soft-gelatin capsules imprinted on one side in black with the Boehringer Ingelheim company symbol and "150".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

4.2 Posology and method of administration

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

Posology
The recommended dose is 150 mg nintedanib twice daily administered approximately 12 hours apart.

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

Dose adjustments
In addition to symptomatic treatment if applicable, the management of adverse reactions to Ofev (see sections 4.4 and 4.8) could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. Ofev treatment may be resumed at the full 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.

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN), 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 dose (150 mg twice daily) (see sections 4.4 and 4.8).

Special populations

Elderly patients (≥ 65 years)

No overall differences in safety and efficacy were observed for elderly patients. No *a-priori* dose adjustment is required on the basis of a patient's age. Patients ≥75 years may be more likely to require dose reduction to manage adverse effects (see section 5.2).

Renal impairment

Less than 1% of a single dose of nintedanib is excreted via the kidney (see section 5.2). 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 (<30 ml/min creatinine clearance).

Hepatic impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90%; see section 5.2). No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A; see section 4.4). The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Ofev is not recommended.

Paediatric population

The safety and efficacy of Ofev in children aged 0-18 years have not been established. No data are available.

Method of administration

Ofev is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Gastrointestinal disorders

Diarrhoea

In the INPULSIS trials (see section 5.1), diarrhoea was the most frequent gastro-intestinal adverse reaction reported in 62.4% versus 18.4% of patients treated with Ofev and placebo, respectively (see section 4.8). In most patients the adverse reaction was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhoea led to dose reduction in 10.7% of the patients and to discontinuation of nintedanib in 4.4% of the patients.

Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, 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 dose (150 mg twice daily). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with Ofev should be discontinued.

Nausea and vomiting

Nausea and vomiting were frequently reported gastrointestinal adverse reactions (see section 4.8). In most patients with nausea and vomiting, the event was of mild to moderate intensity. Nausea led to discontinuation of nintedanib in 2.0% of patients. Vomiting led to discontinuation in 0.8% of the patients.

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 dose (150 mg twice daily). In case of persisting severe symptoms therapy with Ofev should be discontinued.

Hepatic function
The safety and efficacy of Ofev has 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 sections 4.2).

Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, alkaline phosphatase (ALKP), gamma-glutamyl-transferase (GGT)) with a potentially higher risk for female patients. Transaminase increases were reversible upon dose reduction or interruption. Administration of nintedanib was also associated with elevations of bilirubin. Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with Ofev, and periodically thereafter (e.g. at each patient visit) or as clinically indicated. If transaminase (AST or ALT) elevations > 3x ULN are measured, dose reduction or interruption of the therapy with Ofev is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Ofev may be resumed at the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (see section 4.2). If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Ofev should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

Haemorrhage
Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding. In the INPULSIS trials with Ofev, the frequency of patients who experienced bleeding AEs was slightly higher in the Ofev arm (10.3%) than in the placebo arm (7.8%). 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%).

Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment were not included in the INPULSIS studies. Therefore these patients should only be treated with Ofev if the anticipated benefit outweighs the potential risk.

Arterial thromboembolic events
Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Arterial thromboembolic events were infrequently reported: in 0.7% of patients in the placebo and 2.5% in the nintedanib treated group. While adverse events reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%). Caution should be used 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.

Venous thromboembolism
In the INPULSIS trials no increased risk of venous thromboembolism was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of thromboembolic events.

Gastrointestinal perforations
In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of gastrointestinal perforation. Particular caution should be exercised when treating patients with previous abdominal surgery. Ofev should only be initiated at least 4 weeks after abdominal surgery. Therapy with Ofev should be permanently discontinued in patients who develop gastrointestinal perforation.

Hypertension
Administration of Ofev may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated.

Wound healing complication
No increased frequency of impaired wound healing was observed in the INPULSIS trials. Based on the mechanism of action nintedanib may impair wound healing. 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.

Co-administration with pirfenidone
Concomitant treatment of nintedanib with pirfenidone was investigated in a parallel group design study in Japanese patients with IPF. Twenty four patients were treated for 28 days with 150 mg nintedanib twice daily (13 patients received nintedanib on top of chronic treatment with standard doses of pirfenidone; 11 patients received nintedanib alone). Due to the short duration of concomitant exposure and low number of patients the benefit/risk of the co-administration with pirfenidone has not been established.

Effect on QT interval
No evidence of QT prolongation was observed for nintedanib in the clinical trial programme (Section 5.1). As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered nintedanib in patients who may develop QTc prolongation.

Allergic reaction
Dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.

4.5 Interaction with other medicinal products and other forms of interaction

P-glycoprotein (P-gp)
Nintedanib is a substrate of P-gp (see section 5.2). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study. In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with Ofev, potent P-gp inhibitors (e.g. ketoconazole, erythromycin or cyclosporine) 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 section 4.2).

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medicinal product with no or minimal P-gp induction potential should be considered.

Cytochrome (CYP)-enzymes
Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. 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 (see section 5.2). The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

Co-administration with other medicinal products
The potential for interactions of nintedanib with hormonal contraceptives was not explored.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception
Nintedanib may cause foetal harm in humans (see section 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Ofev. They should be advised to use adequate contraception during and at least 3 months after the last dose of Ofev. Since the effect of nintedanib on the metabolism and efficacy of hormonal contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.

Pregnancy
There is no information on the use of Ofev in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this active substance (see section 5.3). As nintedanib may cause foetal harm also in humans, it must not be used during pregnancy.

Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Ofev.

If the patient becomes pregnant while receiving Ofev, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Ofev should be considered.

Breast-feeding
There is no information on the excretion of nintedanib and its metabolites 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. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Ofev.

Fertility
Based on preclinical investigations there is no evidence for impairment of male fertility (see section 5.3). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 150 mg twice daily (see section 5.3).

4.7 Effects on ability to drive and use machines

Ofev has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines during treatment with Ofev.

4.8 Undesirable effects

Summary of the safety profile
Nintedanib has been studied in clinical trials of 1,529 patients suffering from IPF. The safety data provided in the following are based on the two Phase III, randomised, double-blind, placebo-controlled studies in 1,061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2).

The most frequently reported adverse reactions associated with the use of nintedanib included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased.

For the management of selected adverse reactions please also refer to section 4.4.

Tabulated list of adverse reactions
The below table provides a summary of the adverse reactions by MedDRA System Organ Class (SOC) and frequency category.

Table 1 summarizes the frequencies of adverse drug reactions (ADRs) that were reported in the nintedanib group (638 patients) pooled from the two placebo-controlled Phase III clinical trials of 52 weeks duration.

Frequency categories are defined using the following convention:
very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping adverse reactions are presented in order of decreasing seriousness.

Table 1: Summary of ADRs per frequency category

Frequency **System Organ Class**	**Very common (≥ 1/10)**	**Common (≥ 1/100 < 1/10)**	**Uncommon (≥ 1/1,000 < 1/100)**
Metabolism and nutrition disorders		Weight decreased, Decreased appetite	
Vascular disorders			Hypertension
Gastrointestinal Disorder	Diarrhoea, Nausea, Abdominal pain	Vomiting	
Hepatobiliary disorders	Hepatic enzyme increased	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Gamma glutamyl transferase (GGT) increased	Hyperbilirubinaemia, Blood alkaline phosphatase (ALKP) increased

Description of selected adverse reactions

Diarrhoea
Diarrhoea was reported in 62.4% of patients treated with nintedanib. The event was reported to be of severe intensity in 3.3% of nintedanib treated patients. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. Diarrhoea led to permanent treatment discontinuation in 4.4% of patients; otherwise the events were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption (see section 4.4).

Hepatic enzyme increased
Liver enzyme elevations (see section 4.4) were reported in 13.6% of nintedanib treated patients. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease. For further information about special populations, recommended measures and dosing adjustments in case of diarrhoea and hepatic enzyme increased, refer additionally to sections 4.4 and 4.2, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote or treatment for Ofev overdose. Two patients in the oncology programme had an overdose of maximum 600 mg twice daily up to eight days. Observed adverse reactions 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 INPULSIS 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE31

Mechanism of action
Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling. In addition nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases.

Pharmacodynamic effects
Nintedanib inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis. The potential impact of VEGFR inhibition by nintedanib and the anti-angiogenic activity of nintedanib on IPF pathology are currently not fully elucidated. In preclinical disease models of lung fibrosis nintedanib exerts potent anti-fibrotic and anti-inflammatory activity. Nintedanib inhibits proliferation, migration and fibroblast to myofibroblast transformation of human lung fibroblasts from patients with IPF.

Clinical efficacy and safety
The clinical efficacy of nintedanib has been studied in patients with IPF in two phase III, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 (1199.32) and INPULSIS-2 (1199.34)). Patients with FVC baseline < 50% predicted or carbon monoxide diffusing capacity (DLCO, corrected for haemoglobin) < 30% predicted at baseline were excluded from the trials. Patients were randomized in a 3:2 ratio to treatment with Ofev 150 mg or placebo twice daily for 52 weeks.

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

Annual rate of decline in FVC
The annual rate of decline of 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 2 for individual and pooled study results.

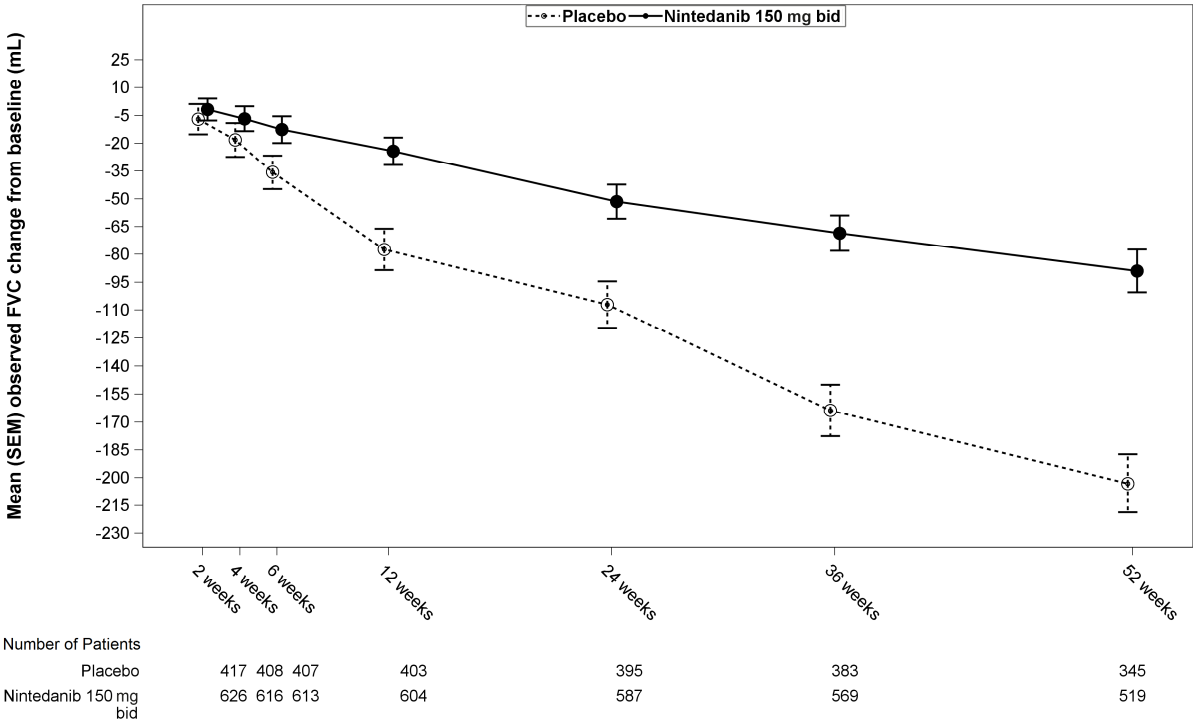
Table 2: Annual rate of decline in FVC (mL) in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 Pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 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.
CI: confidence interval

The robustness of the effect of nintedanib in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses. In patients with missing data, the primary analysis assumes that the decline in FVC after the last observed value would be similar to the decline in other patients in the same treatment group. In a sensitivity analysis which assumed that in patients with missing data at week 52 the FVC decline after the last observed value would be the same as in all placebo patients, the adjusted difference in the annual rate of decline between nintedanib and placebo was 113.9 mL/year (95% CI 69.2, 158.5) in INPULSIS-1 and 83.3 mL/year (95% CI 37.6, 129.0) in INPULSIS-2**.**
In addition, similar effects were observed on other lung function endpoints e.g. change from baseline in FVC at week 52 and FVC responder analyses providing further substantiation of the effects of nintedanib on slowing disease progression. See Figure 1 for the evolution of change from baseline over time in both treatment groups, based on the pooled analysis of studies INPULSIS-1 and INPULSIS-2.

Figure 1: Mean (SEM) observed FVC change from baseline (mL) over time, studies INPULSIS-1 and INPULSIS-2 pooled



Number of Patients							
Placebo	417	408	407	403	395	383	345
Nintedanib 150 mg bid	626	616	613	604	587	569	519

bid = twice daily

FVC responder analysis

In both INPULSIS trials, the proportion of FVC responders, defined as patients with an absolute decline in FVC % predicted no greater than 5% (a threshold indicative of the increasing risk of mortality in IPF), was significantly higher in the nintedanib group as compared to placebo. Similar results were observed in analyses using a conservative threshold of 10%. See Table 3 for individual and pooled study results.

Table 3: Proportion of FVC responders at 52 weeks in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
5% threshold						
Number (%) of FVC responders[1]	78 (38.2)	163 (52.8)	86 (39.3)	175 (53.2)	164 (38.8)	338 (53.0)
Comparison vs placebo						
Odds ratio		1.85		1.79		1.84
95% CI		(1.28, 2.66)		(1.26, 2.55)		(1.43, 2.36)
p-value[2]		0.0010		0.0011		<0.0001
10% threshold						
Number (%) of FVC responders[1]	116 (56.9)	218 (70.6)	140 (63.9)	229 (69.6)	256 (60.5)	447 (70.1)
Comparison vs placebo						
Odds ratio		1.91		1.29		1.58
95% CI		(1.32, 2.79)		(0.89, 1.86)		(1.21, 2.05)
p-value[2]		0.0007		0.1833		0.0007

[1]Responder patients are those with no absolute decline greater than 5% or greater than 10% in FVC % predicted, depending on the threshold and with an FVC evaluation at 52 weeks.
[2]Based on a logistic regression.

Time to progression (≥ 10% absolute decline of FVC % predicted or death)
In both INPULSIS trials, the risk of progression was statistically significantly reduced for patients treated with nintedanib compared with placebo. In the pooled analysis, the HR was 0.60 indicating a 40% reduction in the risk of progression for patients treated with nintedanib compared with placebo.

Table 4: Frequency of patients with ≧ 10% absolute decline of FVC % predicted or death over 52 weeks and time to progression in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	83 (40.7)	75 (24.3)	92 (42.0)	98 (29.8)	175 (41.4)	173 (27.1)
Comparison vs placebo[1]						
p-value[2]		0.0001		0.0054		<0.0001
Hazard ratio[3]		0.53		0.67		0.60
95% CI		(0.39, 0.72)		(0.51, 0.89)		(0.49, 0.74)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

Change from baseline in SGRQ total score at week 52
SGRQ total score measuring health related quality of life (HRQoL) was analysed at 52 weeks. In INPULSIS-2, patients receiving placebo had a larger increase from baseline SGRQ total score as compared to patients receiving nintedanib 150 mg twice daily. The deterioration of HRQoL was smaller in the nintedanib group; the difference between the treatment groups was statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197).

In INPULSIS-1, 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 the pooled analysis of the INPULSIS trials, the estimated mean change from baseline to week 52 in SGRQ total score was smaller in the nintedanib group (3.53) than in the placebo group (4.96), with a difference between the treatment groups of -1.43 (95% CI: -3.09, 0.23; p=0.0923). Overall, the effect of nintedanib on health-related quality of life as measured by the SGRQ total score is modest, indicating less worsening compared to placebo.

Time to first acute IPF exacerbation
In the INPULSIS-2 trial, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving nintedanib compared to placebo, in the INPULSIS-1 trial there was no difference between the treatment groups. In the pooled analysis of the INPULSIS trials, a numerically lower risk of first acute exacerbation was observed in patients receiving nintedanib compared to placebo. See Table 5 for individual and pooled study results.

Table 5: Frequency of patients with acute IPF exacerbations over 52 weeks and time to first exacerbation analysis based on investigator-reported events in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	11 (5.4)	19 (6.1)	21 (9.6)	12 (3.6)	32 (7.6)	31 (4.9)
Comparison vs placebo[1]						
p-value[2]		0.6728		0.0050		0.0823
Hazard ratio[3]		1.15		0.38		0.64
95% CI		(0.54, 2.42)		(0.19, 0.77)		(0.39, 1.05)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

All adverse events of acute IPF exacerbation reported by the investigator were adjudicated by a blinded adjudication committee. A pre-specified sensitivity analysis of the time to first 'confirmed' or 'suspected' adjudicated acute IPF exacerbation was performed on the pooled data. The frequency of patients with at least 1 adjudicated exacerbation occurring within 52 weeks was lower in the nintedanib group (1.9% of patients) than in the placebo group (5.7% of patients). Time to event analysis of the adjudicated exacerbation events using pooled data yielded a hazard ratio (HR) of 0.32 (95% CI 0.16, 0.65; p=0.0010). This indicates that the risk of having a first acute adjudicated IPF exacerbation was statistically significantly lower in the nintedanib group than in the placebo group at any time point.

Survival analysis
In the pre-specified pooled analysis of survival data of the INPULSIS trials, overall mortality over 52 weeks was 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.

Table 6: All-cause mortality over 52 weeks in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	13 (6.4)	13 (4.2)	20 (9.1)	22 (6.7)	33 (7.8)	35 (5.5)
Comparison vs placebo[1]						
p-value[2]		0.2880		0.2995		0.1399
Hazard ratio[3]		0.63		0.74		0.70
95% CI		(0.29, 1.36)		(0.40, 1.35)		(0.43, 1.12)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

Supportive evidence from the phase II trial (1199.30) Ofev 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 twice daily dose group.

The primary endpoint, rate of decline in FVC over 52 weeks was lower in the 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). The difference between the treatment groups reached nominal statistical significance (p=0.0136).

The estimated mean change from baseline in SGRQ total score at 52 weeks was 5.46 for placebo, indicating worsening of the health-related quality of life and -0.66 for nintedanib, indicating stable health-related quality of life. The estimated mean difference for nintedanib compared with placebo was -6.12 (95% CI: -10.57, -1.67; p=0.0071).

The number of patients with acute IPF exacerbations over 52 weeks was lower in the nintedanib group (2.3%, N=86) compared to placebo (13.8%, N=87). The estimated hazard ratio of nintedanib versus placebo was 0.16 (95% CI 0.04, 0.71; p=0.0054).

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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Ofev in all subsets of the paediatric population in IPF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Nintedanib reached maximum plasma concentrations approximately 2 - 4 h after oral administration as soft gelatine capsule under fed conditions (range 0.5 - 8 h). The absolute bioavailability of a 100 mg dose was 4.69% (90% CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (CI: 95.3 - 152.5%) and absorption was delayed (median t_{max} fasted: 2.00 h; fed: 3.98 h).

Distribution
Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution during the terminal phase (V_{ss}: 1,050 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 0.869.

Biotransformation
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 uridine 5'-diphospho-glucuronosyltransferase enzymes (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. Nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes in preclinical studies, either. Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are therefore not expected.

Elimination
Total plasma clearance after intravenous infusion was high (CL: 1,390 mL/min, 28.8% gCV). Urinary excretion of the unchanged active substance within 48 h was about 0.05% of the dose (31.5% gCV) after oral and about 1.4% of the dose (24.2% gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6% gCV). 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, 2.61% gCV). The contribution of renal excretion to the total clearance was low (0.649% of dose, 26.3% gCV). The overall recovery was considered complete (above 90%) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50%).

Linearity/non-linearity
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). Accumulation upon multiple administrations was 1.04-fold for C_{max} and 1.38-fold for AUC_{τ}. Nintedanib trough concentrations remained stable for more than one year.

Transport
Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section 4.5. Nintedanib was shown to be not 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.

Population pharmacokinetic analysis in special populations
The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients. Based on results of a Population PK (PopPK) analysis in patients with IPF and non small cell lung cancer (NSCLC) (N=1,191) and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), alcohol consumption, or P-gp genotype. The PopPK analysis indicated moderate effects on exposure to nintedanib by age, body weight, and race, which are described in the following. Based on the high inter-individual variability of exposure observed moderate effects are considered not clinically relevant (see section 4.4).

Age
Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16% for a 45-year old patient and increased by 13% for a 76-year old patient 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 were older than 75 years. Based on a PopPK model, an increase in nintedanib exposure of approximately 20 - 25% was observed in patients ≥ 75 years compared with patients under 65 years.

Studies in paediatric populations have not been performed.

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.

Race
The geometric mean exposure to nintedanib was 33% higher in Chinese, Taiwanese, and Indian patients while it was 22% lower in Koreans compared to Caucasians (body weight corrected). Data from Black individuals was very limited but in the same range as for Caucasians.

Hepatic impairment
Pharmacokinetic data for nintedanib was collected in patients with abnormalities in hepatic parameters defined by elevations in AST, ALT and bilirubin levels. A trend to elevated exposure was observed in patients with AST- and ALT-values (up to 10x ULN) and elevated bilirubin levels (up to 1.5x ULN) at baseline as compared to patients with normal AST, ALT and bilirubin levels. In patients with ALT or AST > 10x ULN and bilirubin > 1.5x ULN, data were too limited to draw conclusions.

Concomitant treatment with pirfenidone
In a small parallel group design study in Japanese patients with IPF (13 patients received nintedanib on top of chronic treatment with standard doses of pirfenidone; 11 patients received nintedanib alone), exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on Cmax upon co-administration with pirfenidone pirfenidone compared to administration of nintedanib alone. Nintedanib had no effect on the PK of pirfenidone (see section 4.4).

5.3 Preclinical safety data

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.

Diarrhoea 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 diarrhoea were only observed in Rhesus monkeys.

Reproduction toxicity
In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the MRHD of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

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.

In a pre- and postnatal development study in rats, effects on pre- and post-natal development were seen at an exposure below the MRHD.

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).

From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.

Genotoxicity studies indicated no mutagenic potential for nintedanib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
triglycerides, medium-chain
hard fat
lecithin (soya) (E322)

Capsule shell
gelatin
glycerol (85%)
titanium dioxide (E171)
iron oxide red (E172)
iron oxide yellow (E172)

Printing ink
shellac glaze
iron oxide black (E172)
propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Ofev 150 mg soft capsules are available in the following pack-sizes:
- 30 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters
- 60 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/979/003
EU/1/14/979/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer box

1. NAME OF THE MEDICINAL PRODUCT

Ofev 100 mg soft capsules
nintedanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 100 mg nintedanib (as esilate).

3. LIST OF EXCIPIENTS

Contains soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 soft capsules
60 x 1 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/979/001
EU/1/14/979/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ofev 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer box

1. NAME OF THE MEDICINAL PRODUCT

Ofev 150 mg soft capsules
nintedanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 150 mg nintedanib (as esilate).

3. LIST OF EXCIPIENTS

Contains soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 soft capsules
60 x 1 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/979/003
EU/1/14/979/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ofev 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Ofev 100 mg capsules
nintedanib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Ofev 150 mg capsules
nintedanib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ofev 100 mg soft capsules
Nintedanib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ofev is and what it is used for

Ofev contains the active substance nintedanib and it is used for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

IPF is a condition in which the tissue in your lungs becomes thickened, stiff and scarred over time. As a result, scarring reduces the ability to transfer oxygen from the lungs into the bloodstream and it becomes difficult to breathe deeply. Ofev helps to reduce scarring and stiffening of the lungs.

2. What you need to know before you take Ofev

Do not take Ofev:
- if you are allergic to nintedanib, peanut or soya, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Ofev,
- if you have or ever had liver problems,
- if you have or ever had bleeding problems,
- if you take blood-thinning medicines (such as warfarin, phenprocoumon or heparin) to prevent blood clotting,
- if you have or ever had problems with your heart (for example a heart attack),
- if you have recently had surgery. Nintedanib may affect the way your wounds heal. Therefore your treatment with Ofev will usually be stopped for a while if you are having a surgery. Your doctor will decide when to resume your treatment with this medicine.

Based on this information your doctor may do some blood tests, for example to check your liver function. Your doctor will discuss the results of these tests with you and decide whether you may receive Ofev.

Inform your doctor immediately while taking this medicine,
- if you get diarrhoea. Treating diarrhoea early is important (see section 4);
- if you vomit or feel sick (nausea);
- if you have severe pain in your stomach, fever, chills, sickness, vomiting, or abdominal rigidity or bloating, as these could be symptoms of a hole in the wall of your gut ('gastrointestinal perforation');
- if you have pain, swelling, reddening, warmth of a limb as this could be symptoms of a blood clot in one of your veins (a type of blood vessel);
- if you have chest pressure or pain, typically on the left side of the body, pain in the neck, jaw, shoulder or arm, a fast heartbeat, shortness of breath, nausea, vomiting, as this could be symptoms of a heart attack;
- if you have any major bleeding.

Children and adolescents
Ofev should not be taken by children and adolescents under 18 years of age.

Other medicines and Ofev
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

Ofev can interact with certain other medicines. The following medicines are examples that may increase the levels of nintedanib in your blood, and hence may increase the risk for side effects (see section 4):
- a medicine used to treat fungal infections (ketoconazole)
- a medicine used to treat bacterial infections (erythromycin)
- a medicine that affects your immune system (cyclosporine)

The following medicines are examples that may lower the levels of nintedanib in your blood and thus may reduce the effectiveness of Ofev:
- an antibiotic used to treat tuberculosis (rifampicin)
- medicines to treat seizures (carbamazepine, phenytoin)
- a herbal medicine to treat depression (St. John's Wort)

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take this medicine during pregnancy, as it can harm your unborn baby and cause birth defects.

Women who can become pregnant must use an effective combination of birth control methods, including barrier methods as a second form of contraception, while they are taking Ofev and for at least 3 months after stopping treatment. You should discuss the most appropriate methods of contraception for you with your doctor.
Tell your doctor or pharmacist immediately if you become pregnant during treatment with Ofev.

Do not breastfeed during the treatment with Ofev since there may be a risk for harm to the breast-feeding child.

Driving and using machines
Ofev may have minor influence on your ability to drive and use machines. You should not drive or use machines if you feel sick.

Ofev contains soya lecithin
If you are allergic to soya or peanut, do not take this medicine (see section 2).

3. How to take Ofev

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one capsule of 100 mg twice daily (a total of 200 mg per day). Take the capsules 12 hours apart at about the same time every day, for example one capsule in the morning and one capsule in the evening. This ensures that a steady amount of nintedanib is maintained in your blood stream. Swallow the whole capsules with water and do not chew or crush the capsules. It is recommended that you take the capsules with food, i.e. during or immediately before or after a meal.

Do not take more than the recommended dose of two Ofev 100 mg capsules per day.

If you do not tolerate the recommended dose of two Ofev 100 mg capsules per day (see possible side effects in section 4) your doctor may advise you to stop taking this medicine. Do not reduce the dose or stop the treatment by yourself without consulting your doctor first.

If you take more Ofev than you should
Contact your doctor or pharmacist immediately.

If you forget to take Ofev

Do not take two capsules together if you have forgotten to take your earlier dose. You should take your next 100mg dose of Ofev as planned at the next scheduled time recommended by your doctor or pharmacist.

If you stop taking Ofev
Do not stop taking Ofev without consulting your doctor first. It is important to take this medicine every day, as long as your doctor prescribes it for you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You need to pay special attention if you get the following side effects during treatment with Ofev:

Diarrhoea *(very common, may affect more than 1 in 10 people):*
Diarrhoea may lead to dehydration: a loss of fluid and important salts (electrolytes, such as sodium or potassium) from your body. At the first signs of diarrhoea drink plenty of fluids and contact your doctor immediately. Start appropriate anti-diarrhoeal treatment, e.g. with loperamide, as soon as possible.

The following other side effects were observed during treatment with this medicine:

Very common side effects (may affect more than 1 in 10 people)
- Feeling sick (nausea)
- Pain in the lower body (abdomen)
- Abnormal liver test results.

Common side effects (may affect up to 1 in 10 people)
- Vomiting
- Loss of appetite
- Weight loss

Uncommon side effects (may affect up to 1 in 100 people)
- High blood pressure (hypertension)
- Jaundice, that is a yellow colour to the skin and whites of the eyes due to high levels of bilirubin

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ofev

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

Do not store Ofev above 25°C.
Store in the original package 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.

6. Contents of the pack and other information

What Ofev contains
- The active substance is nintedanib. Each capsule contains 100 mg nintedanib (as esilate).
- The other ingredients are:

Capsule fill:	Triglycerides, medium-chain, hard fat, soya lecithin (E322)
Capsule shell:	Gelatin, glycerol (85%), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)
Printing ink:	Shellac glaze, iron oxide black (E172), propylene glycol (E1520)

What Ofev looks like and contents of the pack
Ofev 100 mg capsules are peach-coloured, opaque, oblong soft-gelatin capsules imprinted on one side in black with the Boehringer Ingelheim company symbol and the figure “100”.

Two pack-sizes of Ofev 100 mg capsules are available:
- 30 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters
- 60 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters

Not all pack-sizes may be marketed.

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Manufacturer

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Ofev 150 mg soft capsules
Nintedanib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ofev is and what it is used for

Ofev contains the active substance nintedanib and it is used for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

IPF is a condition in which the tissue in your lungs becomes thickened, stiff and scarred over time. As a result, scarring reduces the ability to transfer oxygen from the lungs into the bloodstream and it becomes difficult to breathe deeply. Ofev helps to reduce scarring and stiffening of the lungs.

2. What you need to know before you take Ofev

Do not take Ofev:
- if you are allergic to nintedanib, peanut or soya, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Ofev,
- if you have or ever had liver problems,
- if you have or ever had bleeding problems,
- if you take blood-thinning medicines (such as warfarin, phenprocoumon or heparin) to prevent blood clotting,
- if you have or ever had problems with your heart (for example a heart attack),
- if you have recently had surgery. Nintedanib may affect the way your wounds heal. Therefore your treatment with Ofev will usually be stopped for a while if you are having a surgery. Your doctor will decide when to resume your treatment with this medicine.

Based on this information your doctor may do some blood tests, for example to check your liver function. Your doctor will discuss the results of these tests with you and decide whether you may receive Ofev.

Inform your doctor immediately while taking this medicine,
- if you get diarrhoea. Treating diarrhoea early is important (see section 4);
- if you vomit or feel sick (nausea);
- if you have severe pain in your stomach , fever, chills, sickness, vomiting, or abdominal rigidity or bloating, as these could be symptoms of a hole in the wall of your gut ('gastrointestinal perforation');
- if you have pain, swelling, reddening, warmth of a limb as this could be symptoms of a blood clot in one of your veins (a type of blood vessel);
- if you have chest pressure or pain, typically on the left side of the body, pain in the neck, jaw, shoulder or arm, a fast heartbeat, shortness of breath, nausea, vomiting, as this could be symptoms of a heart attack;
- if you have any major bleeding.

Children and adolescents
Ofev should not be taken by children and adolescents under 18 years of age.

Other medicines and Ofev
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

Ofev can interact with certain other medicines. The following medicines are examples that may increase the levels of nintedanib in your blood, and hence may increase the risk for side effects (see section 4):
- a medicine used to treat fungal infections (ketoconazole)
- a medicine used to treat bacterial infections (erythromycin)
- a medicine that affects your immune system (cyclosporine)

The following medicines are examples that may lower the levels of nintedanib in your blood and thus may reduce the effectiveness of Ofev:
- an antibiotic used to treat tuberculosis (rifampicin)
- medicines to treat seizures (carbamazepine, phenytoin)
- a herbal medicine to treat depression (St. John's Wort)

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take this medicine during pregnancy, as it can harm your unborn baby and cause birth defects.

Women who can become pregnant must use an effective combination of birth control methods, including barrier methods as a second form of contraception, while they are taking Ofev and for at least 3 months after stopping treatment. You should discuss the most appropriate methods of contraception for you with your doctor.
Tell your doctor or pharmacist immediately if you become pregnant during treatment with Ofev.

Do not breastfeed during the treatment with Ofev since there may be a risk for harm to the breast-feeding child.

Driving and using machines
Ofev may have minor influence on your ability to drive and use machines. You should not drive or use machines if you feel sick.

Ofev contains soya lecithin
If you are allergic to soya or peanut, do not take this medicine (see section 2).

3. How to take Ofev

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one capsule of 150 mg twice daily (a total of 300 mg per day). Take the capsules twice daily approximately 12 hours apart at about the same time every day, for example one capsule in the morning and one capsule in the evening. This ensures that a steady amount of nintedanib is maintained in your blood stream. Swallow the whole capsules with water and do not chew or crush the capsules. It is recommended that you take the capsules with food, i.e. during or immediately before or after a meal.

Do not take more than the recommended dose of two Ofev 150 mg capsules per day.

If you do not tolerate the recommended dose of two Ofev 150 mg capsules per day (see possible side effects in section 4) your doctor may reduce the daily dose of Ofev. Do not reduce the dose or stop the treatment by yourself without consulting your doctor first.

Your doctor may reduce your recommended dose to two times 100 mg per day (a total of 200 mg per day). In this case your doctor will prescribe Ofev 100 mg capsules for your treatment. Do not take more than the recommended dose of two Ofev 100 mg capsules per day if your daily dose was reduced to 200 mg per day.

If you take more Ofev than you should
Contact your doctor or pharmacist immediately.

If you forget to take Ofev

Do not take two capsules together if you have forgotten to take your earlier dose.You should take your next 150 mg dose of Ofev as planned at the next scheduled time recommended by your doctor or pharmacist.

If you stop taking Ofev
Do not stop taking Ofev without consulting your doctor first. It is important to take this medicine every day, as long as your doctor prescribes it for you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You need to pay special attention if you get the following side effects during treatment with Ofev:

Diarrhoea *(very common, may affect more than 1 in 10 people):*
Diarrhoea may lead to dehydration: a loss of fluid and important salts (electrolytes, such as sodium or potassium) from your body. At the first signs of diarrhoea drink plenty of fluids and contact your doctor immediately. Start appropriate anti-diarrhoeal treatment, e.g. with loperamide, as soon as possible.

The following other side effects were observed during treatment with this medicine:

Very common side effects (may affect more than 1 in 10 people)
- Feeling sick (nausea)
- Pain in the lower body (abdomen)
- Abnormal liver test results.

Common side effects (may affect up to 1 in 10 people)
- Vomiting
- Loss of appetite
- Weight loss

Uncommon side effects (may affect up to 1 in 100 people)
- High blood pressure (hypertension)
- Jaundice, that is a yellow colour to the skin and whites of the eyes due to high levels of bilirubin

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ofev

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

Do not store Ofev above 25°C.
Store in the original package 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.

6. Contents of the pack and other information

What Ofev contains
- The active substance is nintedanib. Each capsule contains 150 mg nintedanib (as esilate).
- The other ingredients are:

Capsule fill:	Triglycerides, medium-chain, hard fat, soya lecithin (E322)
Capsule shell:	Gelatin, glycerol (85%), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)
Printing ink:	Shellac glaze, iron oxide black (E172), propylene glycol (E1520)

What Ofev looks like and contents of the pack
Ofev 150 mg capsules are brown-coloured, opaque, oblong soft-gelatin capsules imprinted on one side in black with the Boehringer Ingelheim company symbol and the figure “150”.

Two pack-sizes of Ofev 150 mg capsules are available:
- 30 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters
- 60 x 1 soft capsules in Aluminium/aluminium perforated unit dose blisters

Not all pack-sizes may be marketed.

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