OFEV®
Nintedanib

COMPOSITION

Ofev® 100 mg soft capsules

1 capsule contains 100 mg of nintedanib (= free base)
corresponding to 120.4 mg 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl] amino]phenyl] amino]phenylmethylene]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1) (= nintedanib esilate).

Ofev® 150 mg soft capsules

1 capsule contains 150 mg of nintedanib (= free base)
corresponding to 180.6 mg 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl] amino]phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1) (= nintedanib esilate).

Excipients ***

Capsule fill: Medium chain triglycerides, hard fat, soya lecithin (E322)

Capsule shell: Gelatine, glycerol 85 %, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), black ink (Opacode®)

Black ink: Shellac glaze, iron oxide black (E172), propylene glycol (E1520)

INDICATIONS/ USAGE

Ofev® is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF)

DOSAGE AND ADMINISTRATION/ RECOMMENDED INTAKE

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

Posology and method of administration

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 be given 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® 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).

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.

Renal impairment

Less than 1% of a single dose of nintedanib is excreted via the kidney. 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 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B). In patients with mild hepatic impairment (Child Pugh A), the recommended dose of Ofev® is 100 mg twice daily approximately 12 hours apart. In patients with mild hepatic impairment (Child Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered.
The safety and efficacy of nintedanib have not been investigated with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic imapairment 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.

Race

Based on population pharmacokinetic (PK) analyses, no a priori dose adjustments of Ofev® are necessary. Safety data for Black patients are limited.

Body weight

Based on population PK analyses, no a priori dose adjustments of Ofev® are necessary.

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.

CONTRAINDICATIONS

Ofev® is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients (see section ***Composition***).
Ofev® is contraindicated during pregnancy (see sections ***Fertility, Pregnancy and Lactation*** and ***Toxicology***).

SPECIAL WARNINGS AND PRECAUTIONS

Gastrointestinal –Disorders

- *Diarrhoea*
  In the INPULSIS trials (see section ***Clinical trials***), diarrhoea was the most frequent gastro-intestinal event reported in 62.4 % versus 18.4 % of patients treated with **Ofev®** and placebo, respectively (see section ***Side effects***). In most patients the event was of mild to moderate intensity and occured 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 adverse events (see section ***Side effects***). 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.

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

<u>Hepatic Function</u>

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 ***Pharmacokinetics)***.
Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A).
Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of Ofev® (see sections Dosage and Administration, Pharmacokinetics).

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated upon initiation of treatment with **Ofev**®, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyl transferase (GGT) and bilirubin were reversible upon dose reduction or interruption in the majority of cases.
If transaminase (AST or ALT) elevations > 3x upper limit of normal (ULN) are measured, dose reduction or interruption of the therapy with **Ofev**® is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with **Ofev**® may be re-increased to 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 ***Dosage and administration/Recommended intake***). 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.
Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes.

Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations (see section Pharmacokinetics).

Close monitoring is recommended in patients with these risk factors.

Haemorrhage

VEGFR inhibition might be associated with an increased risk of bleeding. In the INPULSIS trials with **Ofev®**, the frequency of patients who experienced bleeding adverse events 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.

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

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%).

Use caution when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

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 nintedanib patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery, a recent history of a hollow organ perforation, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. **Ofev®** should therefore

only be initiated at least 4 weeks after major, incl. abdominal, surgery. Therapy with **Ofev**® should be permanently discontinued in patients who develop gastrointestinal perforation.

Wound healing complication

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

Soya lecithin

Ofev® soft capsules contain soya lecithin (see section ***Contraindications).***

Hypertension

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

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. 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 QT 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.

INTERACTIONS

P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see section ***Pharmacokinetics***). 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-admini- stration with rifampicin compared to administration of nintedanib alone.

If co-administered with **Ofev**®, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with **Ofev**® (see section ***Dosing and administration)***.

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

Food

Ofev® is recommended to be taken with food (see section ***Pharmacokinetics***).

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 ***Pharmacokinetics***). The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

Co-administration with other drugs

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

FERTILITY, PREGNANCY AND LACTATION

Fertility

Based on preclinical investigations, there is no evidence for impairment of male fertility (see section ***Toxicology***). 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 ***Toxicology***).

Contraception

Women of childbearing potential being treated with **Ofev®** should be advised to use adequate contraception during and at least 3 months after the last dose of **Ofev®.** Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with **Ofev®.**

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 drug (see section ***Toxicology***). As nintedanib may cause foetal harm also in humans, it must not be applied during pregnancy and pregnancy testing should be conducted at least prior to treatment with **Ofev®**.
Female patients should be advised to notify their doctor or pharmacist if becoming pregnant during therapy with **Ofev®**.
If the patient becomes pregnant while receiving **Ofev®** the patient should be apprised of the potential hazard to the foetus. Termination of the treatment should be considered.

Breastfeeding / lactation

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. Breastfeeding should be discontinued during treatment with **Ofev®**.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

SIDE EFFECTS

Summary of the safety profile

Nintedanib has been studied in clinical trials of 1529 patients suffering from Idiopathic Pulmonary Fibrosis (IPF).
The safety data provided in the following are based on the two Phase 3, randomised, double-blind, placebo-controlled studies in 1061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2) and based on data observed during the post-marketing period. The most frequently

reported adverse events 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 ***Special Warnings and Precautions*.**

Tabulated list of adverse reactions
The below table provide 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-contolled Phase III clinical trials of 52 weeks duration or from the postmarketing period.

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 Adverse Reactions per frequency category

Frequency **System Organ Class**	**Very common (≥ 1/10)**	**Common (≥ 1/100 < 1/10)**	**Uncommon (≥ 1/1,000 < 1/100)**
Blood and lymphatic system disorders			Thrombocytopenia
Metabolism and nutrition disorders		Weight decreased, Decreased appetite	
Vascular disorders		Bleeding[1)2)]	Hypertension
Gastrointestinal disorders	Diarrhoea, Nausea, Abdominal pain	Vomitting	Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased	Alanine aminotransferase (ALT) increased,	Hyperbilirubinaemia, Blood alkaline phosphatase (ALKP)

		Aspartate aminotransferase (AST) increased, Gamma glutamyl transferase (GGT) increased	increased Drug-induced liver injury
Skin and subcutaneous tissue disorder		Rash	Pruritus

1) Term represents a group of events that describe a broader medical concept rather than a single condition or MedDRA preferred term.
2) Non-serious and serious bleeding events, some of which were fatal, have been observed in the post-marketing period in line with clinical trial experience.

OVERDOSE

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

In the 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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine 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 vascular endothelial growth factor receptor (VEGFR) 1-3. Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration and transformation of fibroblasts representing essential mechanisms of the IPF pathology. In addition nintedanib inhibits Flt-3, Lck, Lyn and Src kinases.

Pharmacodynamic effects

Activation of FGFR and PDGFR signalling cascades is critically involved in proliferation and migration of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis. The potential impact of VEGFR inhibition on IPF

pathology is currently not fully elucidated. On the molecular level, nintedanib is thought to inhibit the FGFR and PDGFR signalling cascades mediating lung fibroblast proliferation and migration by binding to the adenosine triphosphate (ATP) binding pocket of the intracellular receptor kinase domain, thus interfering with cross-activation via auto-phosphorylation of the receptor homodimers. In vitro, the target receptors are inhibited by nintedanib in low nanomolar concentrations. In human lung fibroblasts from patients with IPF nintedanib inhibited PDGF-, FGF-, and VEGF-stimulated cell proliferation with EC_{50} values of 11 nmol/L, 5.5 nmol/L and less than 1 nmol/L, respectively. At concentrations between 100 and 1000 nmol/L nintedanib also inhibited PDGF-, FGF-, and VEGF-stimulated fibroblast migration and TGF-ß2-induced fibroblasts to myofibroblast transformation. In addition, the anti-inflammatory activity of nintedanib is thought to limit fibrotic stimulation by reduction of profibrotic mediators like IL-1β and IL-6 . The contribution of the anti-angiogenic activity of nintedanib to its mechanism of action in fibrotic lung diseases is currently not clarified. In in vivo studies, nintedanib was shown to have potent anti-fibrotic and anti-inflammatory activity.

CLINICAL TRIALS

The clinical efficacy of nintedanib has been studied in patients with IPF in two phase 3, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 and INPULSIS-2). 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

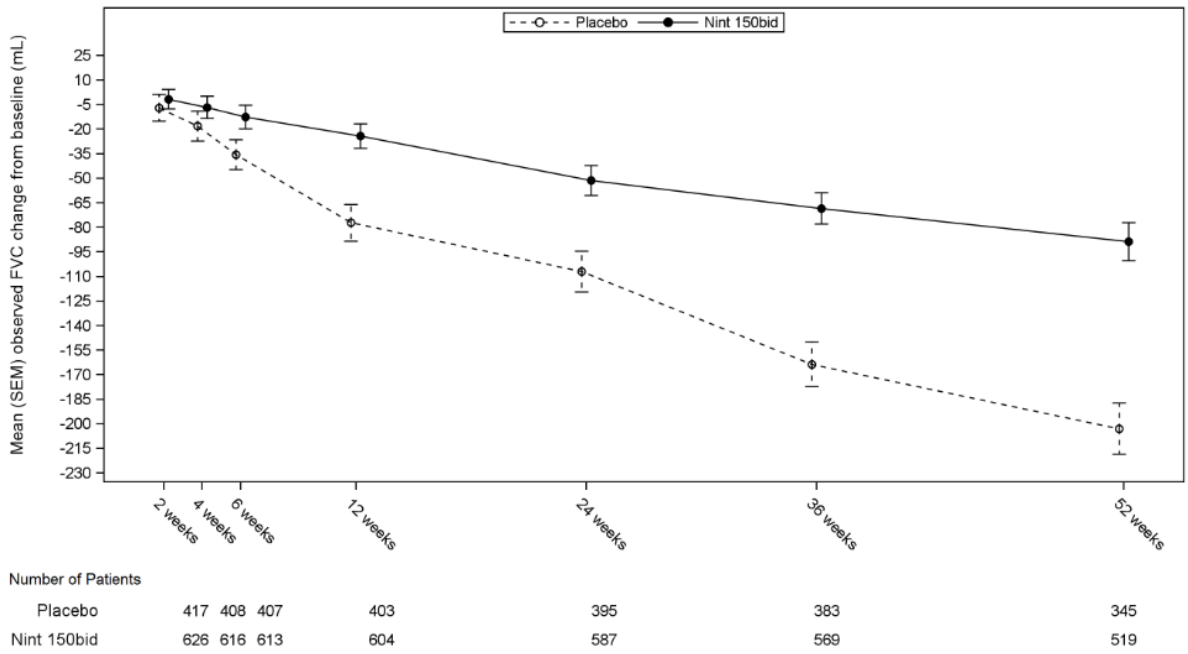
	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	**Ofev**®150 mg twice daily	Placebo	**Ofev**®150 mg twice daily	Placebo	**Ofev**®150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
Rate[1] (SE) of decline over 52 weeks	−239.9 (18.71)	−114.7 (15.33)	−207.3 (19.31)	−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.

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 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 2 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



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, see Table 4.

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

St. George's Respiratory Questionnaire (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 bid. 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 in 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 Time to first acute exacerbation over 52 weeks 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 '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 an HR of 0.32 (95% CI 0.16, 0.65; p = 0.0010).This indicates that the risk of having a first acute 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 (see Table 6).

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 bid 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 pateints, 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 studies of the paedriatic population in IPF.

PHARMACOKINETICS

The pharmacokinetics (PK) of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). 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.

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 hours;). The absolute bioavailability of a 100 mg dose was 4.69 % (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 hours; fed: 3.98 h).

Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (V_{ss} : 1050 L, 45.0 % gCV) was observed.
The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8 %. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869

Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.
Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human ADME study. *In vitro*, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage.

Elimination

Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV). Urinary excretion of the unchanged active substance within 48 hours was about 0.05 % of 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 %;).

Exposure-response relationship

Exposure–response analyses indicated an E_{max}-like relationship between exposure in the range observed in Phase II and III and the annual rate of decline in FVC with an EC_{50} of around 3-5 ng/mL (relative standard errors: 54-67%).
With respect to safety, there seemed to be a weak relationship between nintedanib plasma exposure and ALT and/or AST elevations. Actual administered dose might be the better predictor for the risk of developing diarrhea of any intensity, even if plasma exposure as risk determining factor could not be ruled out.(see section ***Special warnings and precautions***).

Intrinsic and Extrinsic Factors; Special Populations

The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients. Based on results of Population PK (PopPK) analyses and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), liver metastases, ECOG performance score, alcohol consumption, or P-gp genotype. Population PK analyses indicated moderate effects on exposure to nintedanib depending on age, body weight, and race (see below). Based on the high inter-individual variability of exposure observed in the clinical trials these effects are not considered clinically relevant (see section ***Special warnings and precautions***).

Age

Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16 % for a 45-year old patient (5^{th} percentile) and increased by 13 % for a 76-year old patient (95^{th} percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population was older than 75 years.
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 population mean exposure to nintedanib was 33 - 50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patients while it was 16 - 22 % lower in Koreans compared to Caucasians (body weight corrected).

Data from Black individuals was very limited but in the same range as for Caucasians.

Hepatic impairment

In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib based on Cmax and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for Cmax and 1.2 – 3.8 for AUC, respectively). In volunteers with moderate hepatic impairment (Child Pugh B), exposure was 7.6-fold higher based on Cmax (90% CI 4.4 – 13.2) and 8.7-fold higher (90% CI 5.7-13.1) based on AUC, respectively, compared to healthy volunteers.
Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Concomitant treatment 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 bid. In 13 patients, nintedanib was added to chronic treatment with standard doses of pirfenidone. Eleven patients received nintedanib monotherapy. The exposure to nintedanib tended to be lower when nintedanib was administered on top of pirfenidone compared to administration of nintedanib alone. Nintedanib had no effect on the PK of pirfenidone. Due to the short duration of concomitant exposure and low number of patients no conclusion on the safety and efficacy of the combination can be drawn.

Drug-Drug Interaction Potential

Metabolism

Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are not expected, since nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes preclinically nor was nintedanib metabolized by CYP enzymes to a relevant extent.

Transport

Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section ***Interactions***. 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.

TOXICOLOGY

General toxicology

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

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, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (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, embryofoetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats.

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.

SPECIAL PRECAUTIONS FOR DISPOSAL

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

Availability :
Soft Capsules 100 g
Box, 6 Alu Blisters @ 10 Soft Capsules Reg. No: DKI1752503502A1

Soft Capsules 150 mg
Box, 6 Alu Blisters @ 10 Soft Capsules Reg. No: DKI1752503502B1

Storage conditions :
Store below 25°C, in a safe place, out of the reach of children
Store in the original package in order to protect from moisture and light.

Only on doctor's prescription
Harus dengan resep dokter

Bulk Manufactured by :
Catalent Germany Eberbach GmbH, Eberbach, Germany

Packed and Released by :
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein
Germany

PT. Boehringer Ingelheim Indonesia
Medical & Regulatory Affairs

For :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by :
PT Boehringer Ingelheim Indonesia
Bogor, Indonesia

MENGANDUNG BABI

05-1120