OFEV®

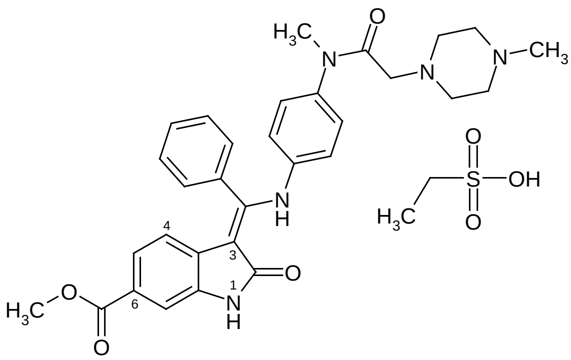
soft capsules

nintedanib (as nintedanib esilate)

NAME OF THE MEDICINE

Active Ingredient:	nintedanib esilate
Chemical name:	1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[-(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1)
Molecular formula:	$C_{31}H_{33}N_5O_4.C_2H_6O_3S$
CAS number:	656247-18-6
Molecular weight:	649.76

Structural formula:



DESCRIPTION

Nintedanib esilate is a bright yellow powder. The octanol-water partition coefficient (log P_{ow}) for nintedanib esilate free base was determined to be 3.6, which demonstrates the lipophilic character of the molecule. Due to the ionisable groups in nintedanib esilate, the lipophilicity profile is strongly pH dependent. At physiological pH (pH = 7.4), the apparent partition coefficient (log *D*) was calculated to 3.0. The molecule is less lipophilic in the acidic pH range (log D ≤ 1 for pH < 5).

Nintedanib esilate is soluble in water. A saturated solution in water was found to have a concentration of 2.8 mg/mL and exhibited an intrinsic pH of 5.7. The solubility of nintedanib esilate is strongly pH dependent with an increased solubility at acidic pH, particularly for pH < 3. The highest solubility of nintedanib esilate in organic solvents is observed in methanol and *N*-methylpyrrolidone. The best solubility in pharmaceutically relevant co-solvents is observed in propylene glycol.

OFEV are soft gelatin capsules for oral administration containing 100 mg or 150 mg nintedanib (as nintedanib esilate).

Excipients: Each OFEV capsule also contains medium chain triglycerides, hard fat and lecithin.

The capsule shell contains gelatin, glycerol 85%, titanium dioxide, iron oxide red (CI 77491), iron oxide yellow (CI 77492).

The black printing ink (Opacode® Type S-1-17823) contains shellac, ethanol, propylene glycol, and iron oxide black (CI 77499).

PHARMACOLOGY

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitors.

ATC code: L01XE31.

Pharmacodynamics

Mechanism of Action

Non-small Cell Lung Cancer (NSCLC):

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells). In addition Fms-like tyrosine-protein kinase-3 (Flt-3), lymphocyte-specific tyrosine-protein kinase (Lck), tyrosine-protein kinase Lyn (Lyn) and proto-oncogene tyrosine-protein kinase Src (Src) are inhibited.

Idiopathic Pulmonary Fibrosis (IPF):

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

NSCLC:

Tumour angiogenesis is an essential feature contributing to tumour growth, progression and metastasis formation and is predominantly triggered by the release of pro-angiogenic factors secreted by the tumour cell (i.e. VEGF and bFGF) to attract host endothelial as well as perivascular cells to facilitate oxygen and nutrient supply through the host vascular system. In preclinical disease models nintedanib, as single agent, effectively interfered with the formation and maintenance of the tumour vascular system resulting in tumour growth inhibition and tumour stasis. Treatment of tumour xenografts with nintedanib led to a reduction in tumour micro vessel density.

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) measurements showed an anti-angiogenic effect of nintedanib in humans. It was not clearly dose dependent, but most responses were seen at doses of ≥ 200 mg. Logistic regression revealed a statistically significant association of the anti-angiogenic effect to nintedanib exposure. DCE-MRI effects were seen 24-48 hours after the first intake of the medicinal product and were preserved or even increased after continuous treatment over several weeks. No correlation of the DCE-MRI response and subsequent clinically significant reduction in target lesion size was found, but DCE-MRI response was associated with disease stabilisation.

IPF:

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 fibroblast 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 anti-fibrotic and anti-inflammatory activity.

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: 0.953 – 1.525) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 hours).

Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (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 (absorption, distribution, metabolism and excretion) study. *In vitro*, CYP-dependent metabolism accounted for about 5% compared to about 25% ester cleavage.

Excretion

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 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 hours (gCV % approximately 50%).

Exposure-response relationship

NSCLC:

In exploratory PK - adverse event analyses, higher exposure to nintedanib tended to be associated with liver enzyme elevations, but not with gastrointestinal adverse events.

PK-efficacy analyses were not performed for clinical endpoints. Logistic regression revealed a statistically significant association between nintedanib exposure and DCE-MRI response.

IPF:

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 diarrhoea of any intensity, even if plasma exposure as risk determining factor could not be ruled out (see 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 analyses and descriptive investigations, exposure to nintedanib was not influenced by gender (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 the intrinsic and extrinsic factors age, body weight, and race which are described in the following. Based on the high inter-individual variability of exposure observed in the clinical trials these effects are not considered clinically relevant (see PRECAUTIONS).

Age

Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16% for a 45-year old patient (5th percentile) and increased by 13% for a 76-year old patient (95th 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 (5th percentile) and decreased by 19% for a 100 kg patient (95th 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). However, based on the high inter-individual variability of exposure these effects are not considered clinically relevant in NSCLC.

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 C_{max} and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for C_{max} 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 C_{max} (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

IPF: 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 metabolised 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 INTERACTIONS WITH OTHER MEDICINES. Nintedanib was shown not to be a substrate or inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2 or MRP-2 *in vitro*. Nintedanib was also not a substrate of BCRP. Only a weak inhibitory potential on OCT-1, BCRP, and P-gp was observed *in vitro* which is considered to be of low clinical relevance. *In vitro* studies also showed that nintedanib was a substrate of OCT-1, which is of low clinical relevance.

CLINICAL TRIALS

NSCLC:

Efficacy in the pivotal phase 3 trial LUME-Lung 1

The efficacy and safety of OFEV was investigated in 1314 patients with locally advanced, metastatic or recurrent NSCLC after one prior line of chemotherapy. The trial included 658 patients (50.1%) with adenocarcinoma, 555 patients (42.2%) with squamous cell carcinoma, and 101 patients (7.7%) with other tumour histologies.

Patients were randomised (1:1) to receive nintedanib 200 mg orally twice daily in combination with 75 mg/m^2 of i.v. docetaxel every 21 days (n = 655) or placebo orally twice daily in combination with 75 mg/m^2 of docetaxel every 21 days (n = 659). Nintedanib was not given on day 1 of each cycle, i.e. the day when docetaxel was given. Randomisation was stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 vs. 1), bevacizumab pre-treatment (yes vs. no), brain metastasis (yes vs. no) and tumour histology (squamous vs. non-squamous tumour histology).

Patient characteristics were balanced between treatment arms within the overall population and within the adenocarcinoma patients. In the overall population 72.7% of the patients were male. The majority of patients were non-Asian (81.6%), the median age was 60.0 years, the baseline ECOG performance status was 0 (28.6%) or 1 (71.3%); one patient had a baseline ECOG performance status of 2. 5.8% of the patients had stable brain metastasis at study entry and 3.8% had prior bevacizumab treatment.

The disease stage was determined at the time of diagnosis using Union Internationale Contre le Cancer (UICC) / American Joint Committee on Cancer (AJCC) Edition 6 or Edition 7. In the overall population, 16.0% of the patients had disease stage < IIIB/IV, 22.4% had disease stage IIIB and 61.6% had disease stage IV. 9.2% of the patients entered the study with locally recurrent disease stage as had been evaluated at baseline. For patients with tumour of adenocarcinoma histology, 15.8% had disease stage < IIIB/IV, 15.2% had disease stage IIIB and 69.0% had disease stage IV. 5.8% of the adenocarcinoma patients entered the study with locally recurrent disease stage as had been evaluated at baseline. 'Locally recurrent' was defined as local re-occurrence of the tumour without metastases at study entry.

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC) based on the intent-to-treat (ITT) population and tested by histology. Overall survival (OS) was the key secondary endpoint. Other efficacy outcomes included objective response, disease control, change in tumour size and health-related quality of life.

As shown in Table 1, the addition of nintedanib to docetaxel led to a statistically significant reduction in the risk of progression or death by 21% for the overall population (HR 0.79; 95% CI: 0.68 - 0.92; p = 0.0019) as determined by the IRC. This result was confirmed in the follow-up PFS analysis (HR 0.85, 95% CI: 0.75 - 0.96; p = 0.0070) which included all events collected at the time of the final OS analysis. OS analysis in the overall population did not reach statistical significance (HR 0.94; 95% CI: 0.83 – 1.05). Of note, pre-planned analyses according to histology showed statistically significant difference in OS between treatment arms in the adenocarcinoma population only.

The addition of nintedanib to docetaxel led to a statistically significant reduction in the risk of progression or death by 23% for the adenocarcinoma population (HR 0.77; 95% CI: 0.62 – 0.96). In line with these observations, related study endpoints such as disease control and change in tumour size showed significant improvements.

Table 1: Efficacy results for study LUME-Lung 1 for all patients and for patients with adenocarcinoma tumour histology

	All patients		Adenocarcinoma tumour histology	
	OFEV (n = 565)	**Placebo (n = 569)**	**OFEV (n = 277)**	**Placebo (n = 285)**
Progression free survival*				
Number of Deaths or Progressions, n (%)	339 (60.0)	375 (65.9)	152 (54.9)	180 (63.2)
Median PFS [months]	3.4	2.7	4.0	2.8
HR (95% CI)**	0.79 (0.68, 0.92)		0.77 (0.62, 0.96)	
Stratified Log-Rank Test p-value**	0.0019		0.0193	
Disease control [%]	48.5	37.6	60.6	43.9
Odds ratio (95% CI)+	1.56 (1.23, 1.98)		1.98 (1.41, 2.77)	
p-value+	0.0002		<0.0001	
Objective response [%]	3.4	1.9	4.3	3.5
Odds ratio (95% CI)+	1.77 (0.85, 3.89)		1.25 (0.53, 3.01)	
p-value+	0.1283		0.6122	
Overall Survival***	**(n= 655)**	**(n= 659)**	**(n= 322)**	**(n= 336)**
Number of OS events, n (%)	564 (86.1)	557 (84.5)	259 (80.4)	276 (82.1)
Median OS [months]	10.1	9.1	12.6	10.3
HR (95% CI)	0.94 (0.83, 1.05)		0.83 (0.70, 0.99)	
Stratified Log-Rank Test p-value*	0.2720		0.0359	

* Primary PFS analysis based on a total of 713th PFS events in the overall population. Recruitment was ongoing when the primary analysis was conducted.

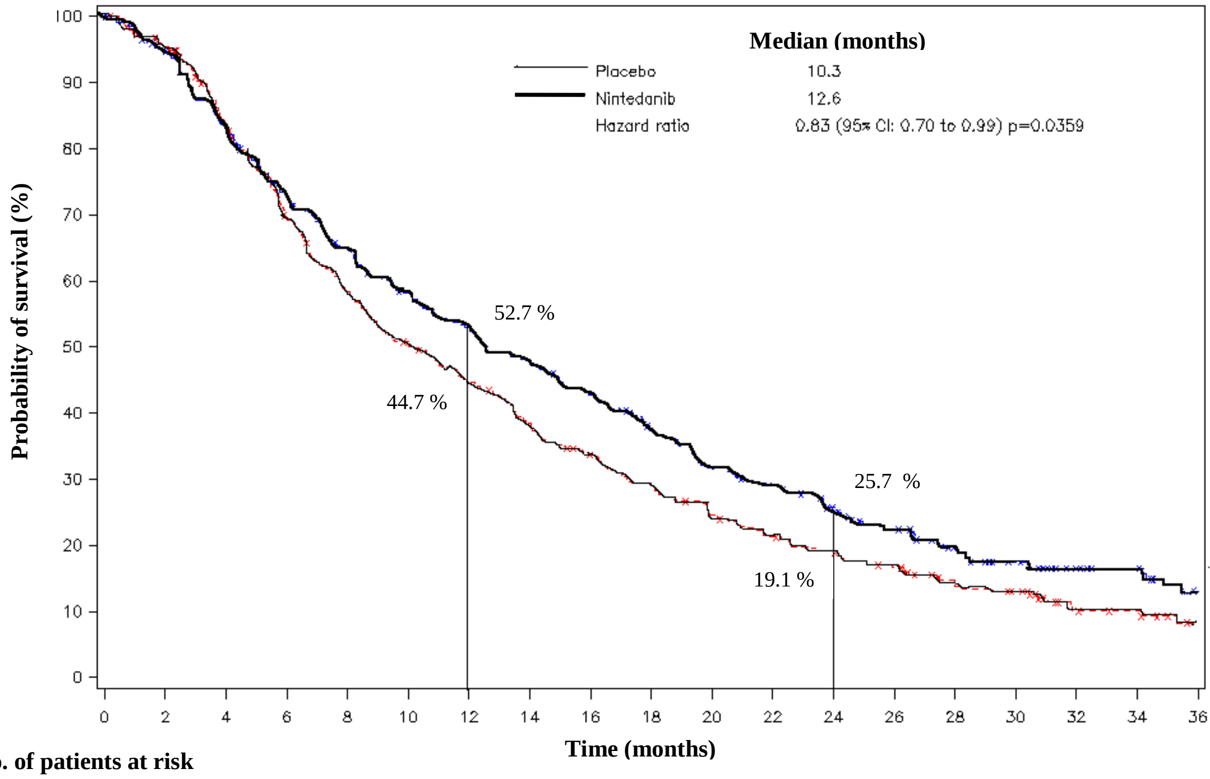
** Stratified by baseline ECOG PS (0 *vs*. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes *vs*. no) and in the all patients population additionally stratified by tumour histology (squamous *vs*. non−squamous).

*** OS analysis based on a total of 1121 deaths in the overall population

\+ Odds ratio and p-value are obtained from a logistic regression model adjusted for baseline ECOG Performance Score (0 *vs*. 1) and in the all patients population it is additionally adjusted by tumour histology (squamous vs. non-squamous).

A statistically significant improvement in OS favouring treatment with nintedanib plus docetaxel was demonstrated in patients with adenocarcinoma with a 17% reduction in the risk of death (HR 0.83, p = 0.0359) and a median OS improvement of 2.3 months (10.3 vs. 12.6 months, Figure 1).

Figure 1: Kaplan-Meier Curve for overall survival for patients with adenocarcinoma tumour histology by treatment group in trial LUME-Lung 1



No. of patients at risk

Placebo	336	312	269	219	184	159	139	119	101	88	73	62	55	46	33	29	15	13	7
Nintedanib	322	302	263	230	203	180	163	149	131	113	96	87	72	59	46	36	25	22	10

A pre-specified evaluation was performed in the population of adenocarcinoma patients considered to have entered the study with a particularly poor treatment prognosis, namely, patients who progressed during or shortly after 1st line therapy prior to study entry. This population included those adenocarcinoma patients identified at baseline as having progressed and entered the study less than 9 months since start of their first-line therapy. Treatment of these patients with nintedanib in combination with docetaxel reduced the risk of death by 25%, compared with placebo plus docetaxel (HR 0.75; 95% CI: 0.60 - 0.92; p = 0.0073). Median OS improved by 3 months (nintedanib: 10.9 months; placebo: 7.9 months).

In a post-hoc analysis in adenocarcinoma patients having progressed and entered the study ≥ 9 months since start of their first-line therapy the difference did not reach statistical significance (HR for OS: 0.89, 95% CI 0.66 – 1.19).

The proportion of adenocarcinoma patients with stage < IIIB/IV at diagnosis was small and balanced across treatment arms (placebo: 54 patients (16.1%); nintedanib: 50 patients, (15.5%)). The HR for these patients for PFS and OS was 1.24 (95% CI: 0.68, 2.28) and 1.09 (95% CI: 0.70, 1.70), respectively. However, the sample size was small, there was no significant interaction and the CI was wide and included the HR for OS of the overall adenocarcinoma population.

<u>Quality of Life</u>

Treatment with nintedanib did not significantly change the time to deterioration of the pre-specified symptoms cough, dyspnoea and pain. Patients receiving nintedanib plus docetaxel reported a statistically significant, small deterioration in the symptom assessment of diarrhoea used in the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30. This finding did not compromise patients' self-reported Global health status/Quality of life. Patients receiving nintedanib plus docetaxel reported statistically significant improvements in other individual lung cancer symptoms (e.g. pain in chest and pain in arm and shoulder).

IPF:

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). The studies enrolled subjects with FVC ≥ 50% of predicted and DL_{CO} corrected for haemoglobin 30-79% of predicted at baseline. Patients were randomised 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.

<u>Annual rate of decline in FVC</u>

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.

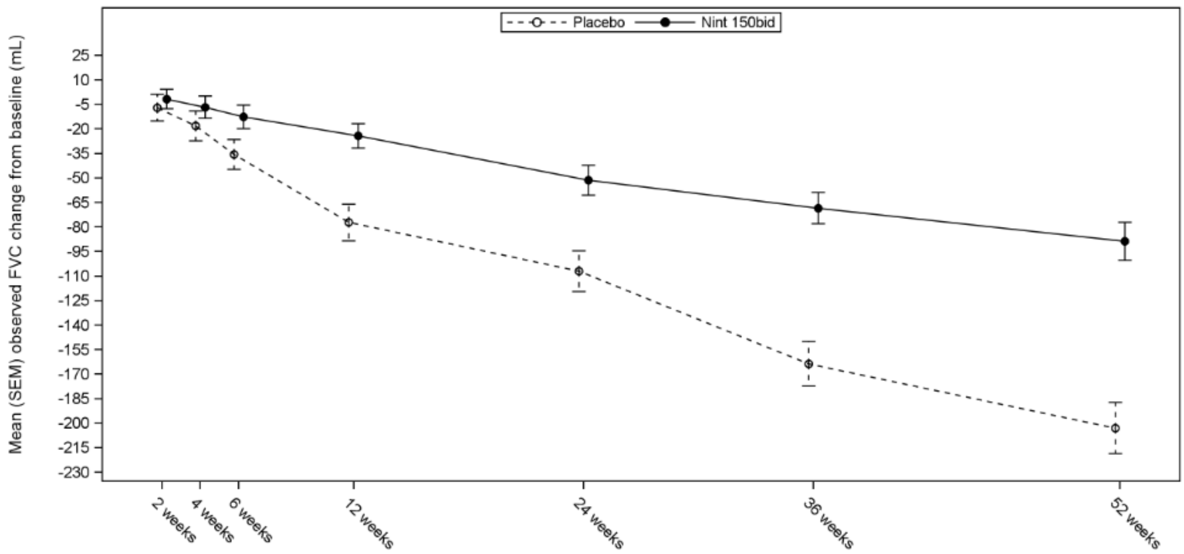
Table 2: Annual rate of decline in FVC (mL) in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

	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
Rate1 (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 2: 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
Nint 150bid	626	616	613	604	587	569	519

bid = twice daily
SEM = standard error of the mean

<u>FVC responder analysis</u>
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		<.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

<u>Time to progression (≥ 10% absolute decline of FVC % predicted or death)</u>

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

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 modest, but statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197). The clinical significance of this finding is unknown.

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. The clinical significance of this finding is unknown.

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 ‘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 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

The INPULSIS trials were not statistically powered for overall mortality. In a pre-specified pooled analysis, overall mortality over 52 weeks was numerically lower in the nintedanib group (5.5%) compared with the placebo group (7.8%). The difference did not reach statistical significance. 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). Although the difference between the treatments was not significant according to the primary analysis, it reached statistical significance (p=0.0136) using a pre-specified sensitivity analysis.

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).

Effect on QT interval

QT/QTc measurements were recorded and analysed from a dedicated study comparing nintedanib monotherapy against sunitinib monotherapy in patients with renal cell carcinoma. In this study single oral doses 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.

NSCLC: No thorough QT-trial of nintedanib administered in combination with docetaxel was conducted.

Paediatric studies

No clinical trials have been conducted in children and adolescents.

INDICATIONS

OFEV is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.

OFEV is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

CONTRAINDICATIONS

OFEV is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients.

OFEV is contraindicated during pregnancy.

NSCLC: For contraindications related to docetaxel please refer to the corresponding product information for docetaxel.

PRECAUTIONS

Gastrointestinal disorders

<u>Diarrhoea</u>

NSCLC:

Diarrhoea was the most frequently reported gastrointestinal event (see ADVERSE EFFECTS). In the clinical trial LUME-Lung 1 (see CLINICAL TRIALS), the majority of patients had mild to moderate diarrhoea. 6.3% of the patients had diarrhoea of grade ≥ 3 in combination treatment compared to 3.6% treated with docetaxel alone. Dehydration was reported in 1.9% of patients in the combination arm and in none of the patients treated with docetaxel alone. Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with OFEV (see DOSAGE AND ADMINISTRATION).

IPF:

In the INPULSIS trials (see 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 ADVERSE EFFECTS). In most patients the event 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.

<u>Nausea and vomiting</u>

NSCLC:

Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events (see ADVERSE EFFECTS). If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction, treatment interruption or discontinuation of therapy with OFEV (see DOSAGE AND ADMINISTRATION) may be required.

In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

IPF:

Nausea and vomiting were frequently reported adverse events (see ADVERSE 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.

Gastrointestinal perforations

Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. OFEV should therefore only be initiated at least 4 weeks after major, including abdominal, surgery. Therapy with OFEV should be permanently discontinued in patients who develop gastrointestinal perforation.

NSCLC:

The frequency of gastrointestinal perforation was comparable between the treatment arms in the LUME-Lung 1 study.

IPF:

In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients.

Neutropenia and sepsis

NSCLC: A higher frequency of neutropenia of CTCAE grade $\geq$ 3 was observed in patients treated with OFEV in combination with docetaxel as compared to treatment with docetaxel alone. Subsequent complications such as sepsis or febrile neutropenia have been observed. Febrile neutropenia was reported in 7.5% of patients in the combination arm compared to 4.5% of patients during treatment with docetaxel alone. Fatal sepsis was reported in 0.9% of patients treated with OFEV in combination with docetaxel. Fatal sepsis was not reported during treatment with docetaxel alone.

Blood counts should be monitored during therapy, in particular during the combination treatment with docetaxel. Frequent monitoring of complete blood counts should be performed at the beginning of each treatment cycle and around the nadir for patients receiving treatment with nintedanib in combination with docetaxel, and as clinically indicated after the administration of the last combination cycle.

Hepatic function

Use in patients with hepatic impairment

Subjects with baseline AST, ALT or bilirubin levels > 1.5 times the upper limit of normal were excluded from the pivotal studies. Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics). 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 PHARMACOLOGY, Pharmacokinetics).

Liver enzyme elevations and hyperbilirubinaemia

Cases of drug-induced liver injury have been observed with nintedanib treatment.

NSCLC:

Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALP) gamma-glutamyltransferase (GGT) and bilirubin. These increases were reversible in the majority of cases. Liver related adverse events of grade ≥ 3 were reported in 15.3% of patients treated with the combination of OFEV and docetaxel compared to 1.8% of patients treated with docetaxel alone.

Female and Asian patients have a higher risk of elevations in liver enzymes. Nintedanib exposure increased linearly with patient age and was inversely correlated to weight which may also result in a higher risk of developing liver enzyme elevations (see PHARMACOKINETICS). Close monitoring is recommended in patients with these risk factors.

Transaminase, ALP and bilirubin levels should be investigated before the initiation of the combination treatment with OFEV plus docetaxel. The values should be monitored as clinically indicated or periodically during treatment, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle and monthly in case OFEV is continued as monotherapy after discontinuation of docetaxel.

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with OFEV may be required (see DOSAGE AND ADMINISTRATION, Table 12). Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary.

In case of specific changes in liver values (AST/ALT > 3 x ULN in conjunction with bilirubin ≥ 2 x ULN and ALP < 2 x ULN) treatment with OFEV should be interrupted. Unless there is an alternative cause established, OFEV should be permanently discontinued (see DOSAGE AND ADMINISTRATION, Table 12).

IPF:

Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of OFEV (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics).

Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALP, gamma-glutamyl-transferase (GGT)) and bilirubin. Transaminase and bilirubin increases were reversible upon dose reduction or interruption. 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.

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 PHARMACOKINETICS). Close monitoring is recommended in patients with these risk factors.

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 DOSAGE AND ADMINISTRATION). 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

NSCLC:

VEGFR inhibition might be associated with an increased risk of bleeding. In the clinical trial LUME-Lung 1 with OFEV, the frequency of bleeding in both treatment arms was comparable. Mild to moderate epistaxis represented the most frequent bleeding event. The majority of fatal bleeding events were tumour-associated. There were no imbalances of respiratory or fatal bleedings and no intracerebral bleeding was reported.

Patients with recent pulmonary bleeding (> 2.5 mL of red blood) as well as patients with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours have been excluded from clinical trials. Therefore, it is not recommended to treat these patients with OFEV.

<u>Brain metastasis</u>

Stable brain metastasis: No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for ≥ 4 weeks before start of treatment with OFEV was observed. However, such patients should be closely monitored for signs and symptoms of cerebral bleeding.

Active brain metastasis: Patients with active brain metastasis were excluded from clinical trials and are not recommended for treatment with OFEV.

<u>Therapeutic anticoagulation</u>

There are no data available for patients with inherited predisposition to bleeding or for patients receiving a full dose of anticoagulative treatment prior to start of treatment with OFEV. In patients on chronic low dose therapy with low molecular weight heparins or acetylsalicylic acid, no increased frequency of bleeding was observed. Patients who developed thromboembolic events during treatment and who required anticoagulant treatment were allowed to continue OFEV and did not show an increased frequency of bleeding events. Patients taking concomitant anticoagulation, such as warfarin should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes.

IPF:

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. Cases of haemorrhage have been reported in postmarketing period (including patients with or without anticoagulant therapy or other drugs that could cause bleeding). Therefore these patients should only be treated with OFEV if the anticipated benefit outweighs the potential risk.

Arterial thromboembolic events

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.

NSCLC:

The frequency of arterial thromboembolic events was comparable between the two treatment arms in the phase 3 study 1199.13 (LUME-Lung 1). Patients with a recent history of myocardial infarction or stroke were excluded from this study. However, an increased frequency of arterial thromboembolic events was observed in patients with IPF when treated with nintedanib monotherapy.

IPF:

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%).

Venous thromboembolism

NSCLC:

Patients treated with OFEV have an increased risk of venous thromboembolism including deep vein thrombosis. Patients should be closely monitored for thromboembolic events. OFEV should be discontinued in patients with life-threatening venous thromboembolic reactions.

IPF:

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.

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 CONTRAINDICATIONS).

Special populations

In study 1199.13 (LUME-Lung 1), there was a higher frequency of serious adverse events in patients treated with nintedanib plus docetaxel with a body weight of less than 50 kg compared to patients with a weight ≥ 50 kg; however the number of patients with a body weight of less than 50 kg was small. Therefore close monitoring is recommended in patients weighing < 50 kg.

Effects on fertility

Based on preclinical investigations, there is no evidence for impairment of male fertility. A study of male fertility and early embryonic development up to implantation in rats at 100 mg/kg/day did not reveal effects on the male reproductive tract and male fertility. In the same species, nintedanib reduced female fertility at 100 mg/kg/day (slightly above the clinical exposure on an AUC basis), and increased early resorptions at ≥ 20 mg/kg/day (below clinical exposure based on AUC). Ovarian follicles and corpora lutea (increased luteinised follicles and increased number and decreased size of corpora lutea) were adversely affected in mice and rats at subclinical exposures.

Use in pregnancy (Category D)

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.

NSCLC: In rats, embryo-fetal lethality and teratogenic effects were observed at an exposure significantly lower (below the level of quantification, at 2.5 mg/kg/day) than at the maximal recommended human dose (MRHD) of 200 mg twice daily.

In rabbits, embryo-fetal lethality and teratogenic effects were observed at 15 mg/kg/day with an exposure approximately 4 times higher than at the MHRD but equivocal effects on the embryo-fetal development of the axial skeleton and the heart were noted already at an exposure below than at the MRHD of 200 mg twice daily.

IPF: In rats, embryo-fetal lethality and teratogenic effects were observed at an exposure significantly lower (below the level of quantification, at 2.5 mg/kg/day) than at the maximal recommended human dose (MRHD) of 150 mg twice daily.

In rabbits, embryo-fetal lethality and teratogenic effects were observed at 15 mg/kg/day with an exposure approximately 5 times higher than at the MHRD but equivocal effects on the embryo-fetal development of the axial skeleton and the heart were noted already at an exposure below that at the MRHD of 150 mg twice daily.

Fetal abnormalities included brachydactyly, major artery anomalies (missing, additional, altered position or size), abnormal heart shape, missing urogenital organs (kidneys, ureter, uterus, ductus deferens, ovaries), vertebral anomalies (missing, fused, displaced, cleft, asymmetrical ossification), and rib anomalies (flat, thickened, additional, fused).

As nintedanib may cause fetal harm also in humans, it must not be used 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 they become pregnant during therapy with OFEV. If the patient becomes pregnant while receiving OFEV the patient should be apprised of the potential hazard to the fetus. Discontinuation of the treatment should be considered.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. 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. Since the effect of OFEV 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.

Use in 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/or its metabolites ($\leq$ 0.5% of the administered dose) were secreted into milk of lactating rats.

Decreased postnatal viability during the first 4 postnatal days was observed in rats dosed with 10 mg/kg/day nintedanib from gestation day 6 to postnatal day 20 (exposure less than the clinical exposure based on AUC).

Because of the potential for serious adverse effects in breastfeeding infants, breastfeeding should be discontinued during treatment with OFEV.

Genotoxicity

Nintedanib was not genotoxic in the bacterial reverse mutation assay, *in vitro* mouse lymphoma cell forward mutation assay, and *in vivo* rat micronucleus assay.

Carcinogenicity

There was no evidence of carcinogenicity in a 103-week study in mice at oral doses of nintedanib up to 30 mg/kg/day, or in a 104-week study in rats at oral doses up to 10 mg/kg/day, resulting in approximately 2.5 and 0.15 times the human exposure (AUC) at the maximum recommended human dose (MRHD) of 200 mg twice daily, respectively.

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.

Docetaxel

For precautions related to docetaxel please refer to the corresponding product information for docetaxel.

INTERACTIONS WITH OTHER MEDICINES

P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see PHARMACOLOGY, 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 by 50 % based on AUC and by 40 % 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 or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with OFEV (see DOSAGE AND ADMINISTRATION).

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

Co-administration with other drugs

NSCLC: Co-administration of nintedanib with docetaxel (75 mg/m²) did not alter the pharmacokinetics of either drug to a relevant extent.

IPF: For co-administration of nintedanib with pirfenidone (see PHARMACOLOGY, Pharmacokinetics).

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

ADVERSE EFFECTS

Summary of the safety profile

NSCLC:

The safety data provided below are based on the global, double-blind randomised pivotal phase 3 trial 1199.13 (LUME-Lung 1) comparing treatment with nintedanib plus docetaxel against placebo plus docetaxel in patients with locally advanced, or metastatic, or recurrent NSCLC after first-line chemotherapy. Adverse events in all patients occurring in at least 10% of patients in either treatment arm in the pivotal trial LUME-Lung 1 are summarised in Table 7.

Table 7: Adverse events in all patients in LUME-Lung 1 (incidence >10% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses - TS

	Placebo			Nintedanib		
	Any grade n (%)	Grade 1/2 n (%)	Grade 3/4/5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3/4/5 n (%)
Patients	655 (100.0)	655 (100.0)	655 (100.0)	652 (100.0)	652 (100.0)	652 (100.0)
Patients with AEs	609 (93.0)	188 (28.7)	421 (64.3)	610 (93.6)	145 (22.2)	465 (71.3)
Diarrhoea	143 (21.8)	126 (19.2)	17 (2.6)	276 (42.3)	233 (35.7)	43 (6.6)
Neutrophil count decreased	235 (35.9)	39 (6.0)	196 (29.9)	242 (37.1)	33 (5.1)	209 (32.1)
Fatigue	176 (26.9)	151 (23.1)	24 (3.7)	198 (30.4)	161 (24.7)	37 (5.7)
ALT increased	55 (8.4)	49 (7.5)	6 (0.9)	186 (28.5)	135 (20.7)	51 (7.8)
WBC decreased	160 (24.4)	60 (9.2)	100 (15.3)	160 (24.5)	53 (8.1)	107 (16.4)
Nausea	118 (18.0)	112 (17.1)	6 (0.9)	158 (24.2)	153 (23.5)	5 (0.8)
AST increased	43 (6.6)	40 (6.1)	3 (0.5)	147 (22.5)	125 (19.2)	22 (3.4)
Decreased appetite	102 (15.6)	94 (14.4)	8 (1.2)	145 (22.2)	136 (20.9)	9 (1.4)
Dyspnoea	110 (16.8)	75 (11.5)	35 (5.3)	124 (19.0)	92 (14.1)	32 (4.9)
Vomiting	61 (9.3)	58 (8.9)	3 (0.5)	110 (16.9)	105 (16.1)	5 (0.8)
Alopecia	119 (18.2)	118 (18.0)	0	107 (16.4)	106 (16.3)	1 (0.2)
Cough	110 (16.8)	106 (16.2)	4 (0.6)	99 (15.2)	93 (14.3)	6 (0.9)
Neutropenia	94 (14.4)	15 (2.3)	79 (12.1)	90 (13.8)	11 (1.7)	79 (12.1)
Pyrexia	98 (15.0)	96 (14.7)	2 (0.3)	83 (12.7)	78 (12.0)	5 (0.8)
Haemoglobin decreased	79 (12.1)	65 (9.9)	14 (2.1)	73 (11.2)	64 (9.8)	9 (1.4)
Constipation	76 (11.6)	73 (11.1)	3 (0.5)	35 (5.4)	35 (5.4)	0

Preferred terms are sorted by frequency in the nintedanib arm

Table 8 summarises the frequencies of adverse drug reactions (ADRs) by System Organ Class (SOC) that were reported in the pivotal study LUME-Lung 1 for patients with NSCLC of adenocarcinoma tumour histology (n = 320). The following terms are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 < 1/10), uncommon (≥ 1/1,000 <

1/100). Within each frequency grouping adverse reactions are presented in order of decreased seriousness. The most frequently reported adverse reactions specific for nintedanib were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting.

Table 8: Summary of ADRs per frequency category

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1,000 < 1/100)
Infections and infestations		Febrile neutropenia[1], Abscesses, Sepsis[1]	
Blood and lymphatic system disorders	Neutropenia[1] (includes febrile neutropenia)	Thrombocytopenia	
Metabolism and nutrition disorders	Decreased appetite, Electrolyte imbalance	Dehydration	
Nervous system disorders	Peripheral neuropathy[1]		
Vascular disorders	Bleeding[2]	Venous thromboembolism, Hypertension	
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Abdominal pain		Perforation[2] Pancreatitis[3]
Hepatobiliary disorders	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased	Hyperbilirubinaemia, Gamma-Glutamyltransferase increased	Drug-induced liver injury
Skin and subcutaneous tissue disorders	Mucositis[1] (including stomatitis), Rash		

1 Please also refer to the product information for docetaxel

2 Frequency was not increased in patients treated with nintedanib plus docetaxel as compared to placebo plus docetaxel. For all other ADRs, the frequency was higher in patients treated with nintedanib plus docetaxel compared to placebo plus docetaxel.

3 Events of pancreatitis have been reported in patients taking nintedanib for the treatment of IPF and NSCLC. The majority of these events were reported for patients in the IPF indication.

IPF:

Nintedanib has been studied in clinical trials of 1529 patients suffering from 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).

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.

Adverse events occuring in at least 5% of patients in either treatment arm in the pivotal trials INPULSIS-1 and INPULSIS-2 are summarised in Table 9.

Table 9: Adverse events occurring in at least 5% of patients in either treatment arm in INPULSIS-1 and INPULSIS-2 – by SOC and preferred term – TS

	Placebo n (%)	Nintedanib 150 mg twice daily n (%)
Patients	423 (100.0)	638 (100.0)
Patients with any AE	379 (89.6)	609 (95.5)
Gastrointestinal disorders	168 (39.7)	488 (76.5)
Diarrhoea	78 (18.4)	398 (62.4)
Nausea	28 (6.6)	156 (24.5)
Vomiting	11 (2.6)	74 (11.6)
Abdominal pain	10 (2.4)	56 (8.8)
Abdominal pain upper	15 (3.5)	41 (6.4)
Constipation	17 (4.0)	38 (6.0)
Infections and infestations	228 (53.9)	359 (56.3)
Nasopharyngitis	68 (16.1)	87 (13.6)
Bronchitis	45 (10.6)	67 (10.5)
Upper respiratory tract infection	42 (9.9)	58 (9.1)
Pneumonia	24 (5.7)	29 (4.5)
Respiratory, thoracic and mediastinal disorders	177 (41.8)	254 (39.8)
Cough	57 (13.5)	85 (13.3)
Idiopathic pulmonary fibrosis	61 (14.4)	64 (10.0)
Dyspnoea	48 (11.3)	49 (7.7)
Investigations	69 (16.3)	185 (29.0)
Weight decreased	15 (3.5)	62 (9.7)
General disorders and administration site conditions	106 (25.1)	152 (23.8)
Fatigue	33 (7.8)	40 (6.3)
Chest pain	22 (5.2)	34 (5.3)
Musculoskeletal and connective tissue disorders	95 (22.5)	118 (18.5)
Back pain	29 (6.9)	37 (5.8)
Arthralgia	21 (5.0)	14 (2.2)
Metabolism and nutrition disorders	60 (14.2)	115 (18.0)
Decreased appetite	24 (5.7)	68 (10.7)
Nervous system disorders	65 (15.4)	105 (16.5)
Headache	19 (4.5)	43 (6.7)

Preferred terms are sorted by frequency in the nintedanib 150 mg twice daily arm

Table 10 summarises the frequencies of ADRs by MedDRA SOC that were reported in the nintedanib group (638 patients) pooled from the two placebo-controlled Phase 3 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 10: Summary of ADRs per frequency category

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1,000 < 1/100)
Metabolism and nutrition disorders		Decreased appetite, Weight decreased	
Vascular disorders		Bleeding[1,2]	Hypertension
Blood and lymphatic system disorders			Thrombocytopenia
Gastrointestinal Disorder	Diarrhoea, Nausea, Abdominal pain	Vomiting	Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Gamma glutamyl transferase (GGT) increased	Hyperbilirubinaemia, Blood alkaline phosphatase (ALP) increased Drug-induced liver injury

1 Term represents a group of events that describe a broader medical concept rather than a single condition or MedDRA preferrred term.

2 Non-serious and serious bleeding events have been observed in the post-marketing period in line with clinical trial experience.

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

DOSAGE AND ADMINISTRATION

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

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.

NSCLC:

Treatment with OFEV should be initiated and supervised by a physician experienced in the use of anticancer therapies.

The recommended dose of OFEV is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21-day docetaxel treatment cycle.

OFEV must not be taken on the same day of docetaxel chemotherapy administration (= day 1).

The recommended maximum daily dose of 400 mg should not be exceeded.

Patients may continue therapy with OFEV after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

For dosage, method of administration and dose modifications of docetaxel, please refer to the corresponding product information for docetaxel.

IPF:

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

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

The recommended maximum daily dose of 300 mg should not be exceeded.

Dose adjustments

NSCLC:

As initial measure for the management of adverse reactions (see Table 11 and Table 12*)* treatment with OFEV should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline). OFEV treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 11 and Table 12.

In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with OFEV should be permanently discontinued.

In case of specific elevations of AST/ALT values to > 3 x upper limit normal (ULN) in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALP < 2 x ULN (see Table 12) treatment with OFEV should be interrupted. Unless there is an alternative cause established, OFEV should be permanently discontinued (see PRECAUTIONS, Hepatic function).

Table 11: Recommended dose adjustments for OFEV in case of diarrhoea, vomiting and other non-haematological or haematological adverse reactions except liver enzyme elevations (see Table 12)

<table>
<tr><th>CTCAE* Adverse reaction</th><th>Dose adjustment</th></tr>
<tr><td>Diarrhoea equal to grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment**
OR
Diarrhoea $\geq$ grade 3
despite anti-diarrhoeal treatment**</td><td rowspan="3">After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and – if a 2nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.</td></tr>
<tr><td>Vomiting ** $\geq$ grade 2
AND/OR
Nausea $\geq$ grade 3
despite anti-emetic treatment**</td></tr>
<tr><td>Other non-haematological or haematological adverse reaction of $\geq$ grade 3</td></tr>
</table>

*CTCAE: Common Terminology Criteria for Adverse Events
** see also PRECAUTIONS

Table 12: Recommended dose adjustments for OFEV in case of AST and/or ALT and bilirubin elevations

AST / ALT and bilirubin elevations	Dose adjustment
Elevation of AST and/or ALT values to > 2.5 x ULN in conjunction with total bilirubin elevation to ≥ 1.5 x ULN OR Elevation of AST and/or ALT values to > 5 x ULN	After treatment interruption and recovery of transaminase values to ≤ 2.5 x ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and, if a 2nd dose reduction is considered necessary, from 150 mg twice daily to 100 mg twice daily.
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALP < 2 x ULN	Unless there is an alternative cause established, OFEV should be permanently discontinued.

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase;

ALP: Alkaline phosphatase; ULN: Upper limit normal

IPF:

In addition to symptomatic treatment if applicable, the management of side effects (see PRECAUTIONS and ADVERSE EFFECTS) of 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 permanently be discontinued.

In case of interruptions due to transaminase (AST or ALT) elevations > 3 x 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 PRECAUTIONS and ADVERSE EFFECTS).

Special populations

Paediatric population

The safety and efficacy of OFEV in paediatric patients have not been studied in clinical trials.

Elderly patients (≥ 65 years)

No overall differences in safety and efficacy were observed for elderly patients compared to patients aged below 65 years. No adjustment of the initial dosing is required on the basis of a patient’s age (see PHARMACOLOGY, Pharmacokinetics).

Race

Based on population PK analyses, no *a priori* dose adjustments of OFEV are necessary (see PRECAUTIONS, Special populations and PHARMACOLOGY, Pharmacokinetics). Safety data for Black patients are limited.

Body weight

Based on population PK analyses, no *a priori* dose adjustments of OFEV are necessary (see PHARMACOLOGY, Pharmacokinetics).

Renal impairment

Less than 1% of a single dose of nintedanib is excreted via the kidney (see PHARMACOLOGY, Pharmacokinetics). Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCL).

<u>Hepatic impairment</u>

Nintedanib is predominantly eliminated via biliary/faecal excretion (>90%). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see PHARMACOLOGY, Pharmacokinetics).

The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended (see PHARMACOLOGY, Pharmacokinetics).

NSCLC: No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A, see PRECAUTIONS).

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

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

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 (IPF), 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.

PRESENTATION AND STORAGE CONDITIONS

OFEV 100 mg capsules are peach-coloured, opaque, oblong, soft gelatin capsules imprinted in black on one side with the Boehringer Ingelheim company logo and “100”. The capsules contain a bright yellow viscous suspension. The capsules are packaged in aluminium/aluminium blisters containing 10 capsules per blister. OFEV 100 mg are supplied in packs of 60 capsules.

OFEV 150 mg capsules are brown-coloured, opaque, oblong, soft gelatin capsules imprinted in black on one side with the Boehringer Ingelheim company logo and “150”. The capsules contain a bright yellow viscous suspension. The capsules are packaged in aluminium/aluminium blisters containing 10 capsules per blister. OFEV 150 mg are supplied in packs of 60 capsules.

Store below 25°C. Store in the original package in order to protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

1 September 2015

DATE OF MOST RECENT AMENDMENT

6 July 2017