SCHEDULING STATUS | S4 |

1. NAME OF THE MEDICINE

OFEV® 100 mg

OFEV® 150 mg

soft gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OFEV 100 mg: each soft gelatin capsule contains 100 mg nintedanib (as esilate).
OFEV 150 mg: each soft gelatin capsule contains 150 mg nintedanib (as esilate).

Sugar free.
Excipient(s) with known effect:
Each 100 mg capsule contains 1,2 mg of soya lecithin.
Each 150 mg capsule contains 1,8 mg of soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft gelatin capsules (capsules).

OFEV 100 mg soft gelatin capsules are peach-coloured, opaque, oblong soft gelatin capsules marked in dark grey on one side with the Boehringer Ingelheim company symbol and “100”, and containing a bright yellow viscous suspension.

OFEV 150 mg soft gelatin capsules are brown-coloured, opaque, oblong soft gelatin capsules marked in dark grey on one side with the Boehringer Ingelheim company symbol and “150”, and containing a bright yellow viscous suspension.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

OFEV is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (see section 5.1).

OFEV is indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Treatment with OFEV should be initiated by doctors experienced in the management of diseases for which OFEV is approved.

Posology

The recommended dose is 150 mg nintedanib administered 12 hourly.
The 100 mg 12 hourly dose is only recommended to be used in patients who do not tolerate the 150 mg 12 hourly dose.

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

Dose adjustments

In addition to symptomatic treatment if applicable, the management of adverse reactions to OFEV (see sections 4.4 and 4.8) could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dose (150 mg 12 hourly) or a reduced dose (100 mg 12 hourly). If a patient does not tolerate 100 mg 12 hourly, treatment with OFEV should be discontinued.

If diarrhoea, nausea and/or vomiting 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 12 hourly) or at the full dose (150 mg 12 hourly). In case of persisting severe diarrhoea, nausea and/or vomiting despite symptomatic treatment, therapy with OFEV should be discontinued (see section 4.4).

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 12 hourly) which subsequently may be increased to the full dose (150 mg 12 hourly) (see sections 4.4 and 4.8).

Special populations

Elderly patients (≥ 65 years)

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

Renal impairment

Less than 1 % of a single dose of nintedanib is excreted via the kidney (see section 5.2). Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min creatinine clearance).

Hepatic impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see section 5.2). In patients with mild hepatic impairment (Child Pugh A), the recommended dose of OFEV is 100 mg 12 hourly. 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 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 section 5.2).

Paediatric population

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

Method of administration
OFEV is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed. The capsule should not be opened or crushed (see section 6.6).

4.3 CONTRAINDICATIONS
Hypersensitivity to nintedanib, to peanuts or soya, or to any of the excipients listed in section 6.1.
Pregnancy (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Gastrointestinal disorders
Diarrhoea
In the clinical trials, diarrhoea was the most frequent gastro-intestinal adverse reaction reported (see section 4.8). In most patients the adverse reaction was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhoea led to dose reduction in 10,7 % of the patients and to discontinuation of nintedanib in 4,4 % of the patients in clinical trials.

Serious cases of diarrhoea leading to dehydration and electrolyte disturbances have been reported in the post-marketing period. Patients should be treated at first signs with adequate hydration and anti-diarrhoeal medicines, e.g. loperamide. Treatment interruption should be considered if diarrhoea and dehydration do not improve. OFEV treatment may be resumed at a reduced dose (100 mg 12 hourly) or at the full dose (150 mg 12 hourly). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with OFEV should be discontinued.

Nausea and vomiting
Nausea and vomiting were frequently reported gastrointestinal adverse reactions (see section 4.8). In most patients with nausea and vomiting, the event was of mild to moderate intensity. In clinical trials nausea led to discontinuation of OFEV in up to 2,1 % of patients and vomiting led to discontinuation in up to 1,4 % 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 12 hourly) or at the full dose (150 mg 12 hourly). In case of persisting severe symptoms therapy with OFEV should be discontinued.

Hepatic function
The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore, treatment with OFEV is not recommended in such patients (see section 4.2). 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 4.2 and 5.2).

Cases of drug-induced liver injury have been observed with OFEV treatment, including severe liver injury with fatal outcome. The majority of hepatic events occur within the first three

months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated before treatment initiation and during the first month of treatment with OFEV. Patients should then be monitored at regular intervals during the subsequent two months of treatment and periodically thereafter, e.g. at each patient visit or as clinically indicated.

Elevations of liver enzymes (ALT, AST, ALP, gamma-glutamyl-transferase (GGT), see section 4.8) and bilirubin were reversible upon dose reduction or interruption in the majority of cases. If transaminase (AST or ALT) elevations > 3x ULN are measured, dose reduction or interruption of the therapy with OFEV is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with OFEV may be resumed at the full dose (150 mg 12 hourly) or reintroduced at a reduced dose (100 mg 12 hourly) which subsequently may be increased to the full dose (see section 4.2). If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with OFEV should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations of liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations (see section 5.2). Close monitoring is recommended in patients with these risk factors.

Renal Function
Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with OFEV use (see section 4.8).
Patients should be monitored during OFEV therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered (see section 4.2 Dose adjustments).

Haemorrhage
Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding.
Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulant medicines were not included in the clinical trials. Non-serious and serious bleeding events, some of which were fatal, have been reported in the post-marketing period (including patients with or without anticoagulant therapy or other medicines that could cause bleeding). Therefore, these patients should only be treated with OFEV if the anticipated benefit outweighs the potential risk.

Arterial thromboembolic events
Patients with a recent history of myocardial infarction or stroke were excluded from the clinical trials. In the clinical trials, arterial thromboembolic events were infrequently reported (OFEV 2,5 % versus placebo 0,7 % for INPULSIS; OFEV 0,9 % versus placebo 0,9 % for INBUILD; OFEV 0,7 % versus placebo 0,7 % for SENSCIS). In the INPULSIS trials, a higher percentage of patients experienced myocardial infarctions in the OFEV group (1,6 %) compared to the placebo group (0,5 %), while adverse events reflecting ischaemic heart disease were balanced between the OFEV and placebo groups. In the INBUILD trial, myocardial infarction was observed with low frequency: OFEV 0,9 % versus placebo 0,9 %. In the SENSCIS trial, myocardial infarction was observed with low frequency in the placebo group (0,7 %) and not observed in the OFEV group.

Regular cardiac monitoring (e.g. ECG, echocardiography) should be used when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating OFEV, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

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

Gastrointestinal perforations and ischaemic colitis
In the clinical trials, the frequency of patients with gastrointestinal perforation was up to 0,3 % in both treatment groups. Due to the mechanism of action of OFEV patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations and cases of ischaemic colitis, 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, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. OFEV should only be initiated at least 4 weeks after abdominal surgery. Therapy with OFEV should be permanently discontinued in patients who develop gastrointestinal perforation or ischaemic colitis. Exceptionally, OFEV can be reintroduced after complete resolution of ischaemic colitis and careful assessment of the patient's condition and other risk factors.

Nephrotic range proteinuria and thrombotic microangiopathy
Very few cases of nephrotic range proteinuria with or without renal function impairment have been reported post-marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of the symptoms has been observed after Ofev was discontinued, with residual proteinuria in some cases. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.

VEGF pathway inhibitors have been associated with thrombotic microangiopathy (TMA), including very few case reports for nintedanib. If laboratory or clinical findings associated with TMA occur in a patient receiving nintedanib, treatment with nintedanib should be discontinued and thorough evaluation for TMA should be completed.

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

Pulmonary hypertension
Data on the use of OFEV in patients with pulmonary hypertension is limited.
Patients with significant pulmonary hypertension (cardiac index $\leq$ 2 L/min/m², or parenteral epoprostenol/treprostinil, or significant right heart failure) were excluded from the INBUILD

and SENSCIS trials.
OFEV should not be used in patients with severe pulmonary hypertension. Close monitoring is recommended in patients with mild to moderate pulmonary hypertension.

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

Co-administration with pirfenidone
In a dedicated pharmacokinetic study, concomitant treatment of OFEV with pirfenidone was investigated in patients with IPF. Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between OFEV and pirfenidone when administered in combination (see section 5.2). Given the similarity in safety profiles for both medicinal products, additive adverse events, including gastrointestinal and hepatic adverse events, may be expected. The benefit-risk balance of concomitant treatment with pirfenidone has not been established.

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

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

P-glycoprotein (P-gp)
Nintedanib is a substrate of P-gp (see section 5.2). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1,61-fold based on AUC and 1,83-fold based on C_{max} in a dedicated drug-drug interaction study. In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50,3 % based on AUC and to 60,3 % based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with OFEV, potent P-gp inhibitors (e.g. ketoconazole, erythromycin or ciclosporin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with OFEV (see section 4.2).

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

Cytochrome (CYP)-enzymes
Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies (see section 5.2). The likelihood of drug-drug interactions with OFEV based on CYP metabolism is therefore considered to be low.

Co-administration with other medicinal products
Co-administration of OFEV with oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent (see section 5.2).

Co-administration of OFEV with bosentan did not alter the pharmacokinetics of nintedanib (see section 5.2).

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential / Contraception
Nintedanib may cause foetal harm in humans (see section 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraceptive methods at initiation of, during and at least 3 months after the last dose of OFEV. Nintedanib does not relevantly affect the plasma exposure of ethinylestradiol and levonorgestrel (see section 5.2). The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives experiencing these conditions should be advised to use an alternative highly effective contraceptive measure.

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 medicine (see section 5.3). As nintedanib may cause foetal harm also in humans, it must not be used during pregnancy (see section 4.3) and pregnancy testing must be conducted prior to treatment with OFEV and during treatment as appropriate.

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, treatment must be discontinued and she should be apprised of the potential hazard to the foetus.

Breast-feeding
There is no information on the excretion of nintedanib and its metabolites in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites ($\leq$ 0,5 % of the administered dose) were secreted into milk of lactating rats. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with OFEV.

Fertility
Based on preclinical investigations there is no evidence for impairment of male fertility (see

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The undesirable effects (section 4.8) of OFEV may impair the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines during treatment with OFEV.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

In clinical trials and during the post-marketing experience, the most frequently reported adverse reactions associated with the use of OFEV included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, decreased weight and increased hepatic enzymes.

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

Tabulated list of adverse reactions

Table 1 provides a summary of the adverse drug reactions (ADRs) by MedDRA System Organ Class (SOC) and frequency category 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).

Table 1: Summary of ADRs per frequency category

	Frequency		
System Organ Class preferred term	**Idiopathic pulmonary fibrosis**	**Other chronic fibrosing ILDs with a progressive phenotype**	**Systemic sclerosis associated interstitial lung disease**
Blood and lymphatic system disorders			
Thrombocytopenia	Uncommon	Uncommon	Uncommon
Metabolism and nutrition disorders			
Decreased weight	Common	Common	Common
Decreased appetite	Common	Very common	Common
Dehydration	Uncommon	Uncommon	Not known
Cardiac disorders			
Myocardial infarction	Uncommon	Uncommon	Not known
Vascular disorders			
Bleeding (see section 4.4)	Common	Common	Common
Hypertension	Uncommon	Common	Common
Aneurysms and artery dissections	Not known	Not known	Not known
Gastrointestinal disorder			

	Frequency		
System Organ Class preferred term	**Idiopathic pulmonary fibrosis**	**Other chronic fibrosing ILDs with a progressive phenotype**	**Systemic sclerosis associated interstitial lung disease**
Diarrhoea	Very common	Very common	Very common
Nausea	Very common	Very common	Very common
Abdominal pain	Very common	Very common	Very common
Vomiting	Common	Very common	Very common
Pancreatitis	Uncommon	Uncommon	Not known
Colitis	Uncommon	Uncommon	Uncommon
Hepatobiliary disorders			
Drug induced liver injury	Uncommon	Common	Uncommon
Increased hepatic enzyme	Very common	Very common	Very common
Increased alanine aminotransferase (ALT)	Common	Very common	Common
Increased aspartate aminotransferase (AST)	Common	Common	Common
Increased gamma glutamyl transferase (GGT)	Common	Common	Common
Hyperbilirubinaemia	Uncommon	Uncommon	Not known
Increased blood alkaline phosphatase (ALP)	Uncommon	Common	Common
Skin and subcutaneous tissue disorders			
Rash	Common	Common	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon
Alopecia	Uncommon	Uncommon	Not known
Renal and urinary disorders			
Renal failure (see section 4.4)	Not known	Uncommon	Uncommon
Proteinuria	Uncommon	Uncommon	Not known
Nervous system disorders			
Headache	Common	Common	Common

Description of selected adverse reactions

Diarrhoea

In clinical trials, diarrhoea was the most frequent gastrointestinal event reported. In most patients, the event was of mild to moderate intensity. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. In most patients, the events were managed by anti-diarrhoeal therapy, dose

reduction or treatment interruption (see section 4.4). An overview of the reported diarrhoea events in the clinical trials as listed in Table 2 were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption (see section 4.4).

Table 2: Diarrhoea in clinical trials over 52 weeks

	INPULSIS		INBUILD		SENSCIS	
	Placebo	OFEV	Placebo	OFEV	Placebo	OFEV
Diarrhoea	18,4 %	62,4 %	23,9 %	66,9 %	31,6 %	75,7 %
Severe diarrhoea	0,5 %	3,3 %	0,9 %	2,4 %	1,0 %	4,2 %
Diarrhoea leading to OFEV dose reduction	0 %	10,7 %	0,9 %	16,0 %	1,0 %	22,2 %
Diarrhoea leading to OFEV discontinuation	0,2 %	4,4 %	0,3 %	5,7 %	0,3 %	6,9 %

Increased hepatic enzyme
In the INPULSIS trials, liver enzyme elevations (see section 4.4) were reported in 13,6 % versus 2,6 % of patients treated with OFEV and placebo, respectively. In the INBUILD trial, liver enzyme elevations were reported in 22,6 % versus 5,7 % of patients treated with OFEV and placebo, respectively. In the SENSCIS trial, liver enzyme elevations were reported in 13,2 % versus 3,1 % of patients treated with OFEV and placebo, respectively. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease.
For further information about special populations, recommended measures and dosing adjustments in case of diarrhoea and hepatic enzyme increases, refer additionally to sections 4.4 and 4.2, respectively.

Bleeding
In clinical trials, the frequency of patients who experienced bleeding was slightly higher in patients treated with OFEV or comparable between the treatment arms (OFEV 10,3 % versus placebo 7,8 % for INPULSIS; OFEV 11,1 % versus placebo 12,7 % for INBUILD; OFEV 11,1 % versus placebo 8,3 % for SENSCIS). Non-serious epistaxis was the most frequent bleeding event reported. Serious bleeding events occurred with low frequencies in the 2 treatment groups (OFEV 1,3 % versus placebo 1,4 % for INPULSIS; OFEV 0,9 % versus placebo 1,5 % for INBUILD; OFEV 1,4 % versus placebo 0,7 % for SENSCIS).
Post-marketing bleeding events include but are not limited to gastrointestinal, respiratory and central nervous organ systems, with the most frequent being gastrointestinal (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 OVERDOSE

There is no specific antidote or treatment for OFEV overdose. Two patients in the oncology programme had an overdose of maximum 600 mg twice daily up to eight days. Observed adverse reactions were consistent with the known safety profile of nintedanib, i.e. increased liver enzymes and gastrointestinal symptoms. Both patients recovered from these adverse reactions. In the INPULSIS trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis*)* occurred and resolved during the period of incorrect dosing, with no onset of other reported events. In case of overdose, treatment should be interrupted, and general supportive measures initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 26 Cytostatic agents

Mechanism of action

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinase (RTKs) 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. FGFR, PDGFR and VEGFR receptors have been implicated in IPF pathogenesis. In addition, nintedanib inhibits Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn), Src (proto-oncogene tyrosine-protein kinase src), and CSFIR (colony stimulating factor 1 receptor) kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases. The role of FLT3 and nRTK inhibition to IPF pathogenesis is unknown.

Pharmacodynamic effects

In *in vitro* studies using human cells nintedanib has been shown to inhibit processes assumed to be involved in the initiation of the fibrotic pathogenesis, the release of pro-fibrotic mediators from peripheral blood monocytic cells and macrophage polarisation to alternatively activated macrophages. Nintedanib has been demonstrated to inhibit fundamental processes in organ fibrosis, proliferation and migration of fibroblasts and transformation to the active myofibroblast phenotype and secretion of extracellular matrix. In animal studies in multiple models of IPF, SSc/SSc-ILD, rheumatoid arthritis-associated-(RA)-ILD and other organ fibrosis, nintedanib has shown anti-inflammatory effects and anti-fibrotic effects in the lung, skin, heart, kidney, and liver. Nintedanib also exerted vascular activity. It reduced dermal microvascular endothelial cell apoptosis and attenuated pulmonary vascular remodelling by reducing the proliferation of vascular smooth muscle cells, the thickness of pulmonary vessel walls and percentage of occluded pulmonary vessels.

QT interval

In a dedicated study in renal cell cancer patients, QT/QTc measurements were recorded and showed that a single oral dose of 200 mg OFEV as well as multiple oral doses of 200 mg OFEV

administered twice daily for 15 days did not prolong the QTcF interval.

Paediatric population
See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Nintedanib reached maximum plasma concentrations approximately 2 - 4 h after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 h). The absolute bioavailability of a 100 mg dose was 4,69 % (90 % CI: 3,615 – 6,078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

After food intake, nintedanib exposure increased by approximately 20 % compared to administration under fasted conditions (CI: 95,3 % – 152,5 %) and absorption was delayed (median t_{max} fasted: 2.00 h; fed: 3.98 h).

Distribution
Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution which was larger than total body volume (V_{ss}: 1,050 L, 45,0 % gCV) was observed.

The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97,8 %. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0,869.

Biotransformation
The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by uridine 5'-diphospho-glucuronosyltransferase enzymes (UGT) enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human absorption, distribution, metabolism and elimination (ADME) study. *In vitro*, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage. Nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes in preclinical studies, either. Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are therefore not expected.

Elimination
The effective half-life of nintedanib in patients with IPF was 9,5 hours (gCV 31,9 %). Total plasma clearance after intravenous infusion was high (CL: 1 390 mL/min, 28,8 % gCV). Urinary excretion of the unchanged active substance within 48 h was about 0,05 % of the dose (31,5 % gCV) after oral and about 1,4 % of the dose (24,2 % gCV) after intravenous administration; the renal clearance was 20 mL/min (32,6 % gCV). The major route of elimination of medicine

related radioactivity after oral administration of [^{14}C] nintedanib was via faecal/biliary excretion (93,4 % of dose, 2,61 % gCV). The contribution of renal excretion to the total clearance was low (0,649 % of dose, 26,3 % gCV). The overall recovery was considered complete (above 90 %) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50 %).

Linearity/non-linearity
The pharmacokinetics (PK) of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). Accumulation upon multiple administrations was 1,04-fold for C_{max} and 1,38-fold for AUC_{τ}. Nintedanib trough concentrations remained stable for more than one year.

Transport
Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section 4.5. Nintedanib was shown to be not a substrate or inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2 *in vitro*. Nintedanib was also not a substrate of BCRP. Only a weak inhibitory potential on OCT-1, BCRP, and P-gp was observed *in vitro* which is considered to be of low clinical relevance. The same applies for nintedanib being a substrate of OCT-1.

Population pharmacokinetic analysis in special populations
The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, patients with other chronic fibrosing ILDs with a progressive phenotype, patients with SSc-ILD, and cancer patients. Based on results of a Population PK (PopPK) analysis in patients with IPF and non small cell lung cancer (NSCLC) (N = 1 191) and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), alcohol consumption, or P-gp genotype. PopPK 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 moderate effects are considered not clinically relevant (see section 4.4).

Age
Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16 % for a 45-year old patient and increased by 13 % for a 76-year old patient relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population were older than 75 years. Based on a PopPK model, an increase in nintedanib exposure of approximately 20 – 25 % was observed in patients ≥ 75 years compared with patients under 65 years.

Studies in paediatric populations have not been performed.

Body weight
An inverse correlation between body weight and exposure to nintedanib was observed. $AUC_{\tau,ss}$ increased by 25 % for a 50 kg patient (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). Data from Black individuals were very limited but in the same range as for Caucasians.

Hepatic impairment
In a dedicated single-dose phase I pharmacokinetic study of nintedanib compared to 8 healthy subjects, exposure to nintedanib based on C_{max} and AUC was 2,2-fold higher in subjects 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 subjects 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 subjects. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Concomitant treatment with pirfenidone
In a dedicated pharmacokinetic study, concomitant treatment of nintedanib with pirfenidone was investigated in patients with IPF. Group 1 received a single dose of 150 mg nintedanib before and after uptitration to 801 mg pirfenidone three times a day at steady state (N = 20 patients treated). Group 2 received steady state treatment of 801 mg pirfenidone three times a day and had a PK profiling before and after at least 7 days of co-treatment with 150 mg nintedanib twice daily (N = 17 patients treated). In group 1, the adjusted geometric mean ratios (90 % confidence interval (CI)) were 93 % (57 % - 151 %) and 96 % (70 % - 131 %) for C_{max} and $AUC_{0\text{-}tz}$ of nintedanib, respectively (n = 12 for intraindividual comparison). In group 2, the adjusted geometric mean ratios (90 % CI)) were 97 % (86 % - 110 %) and 95 % (86 % - 106 %) for $C_{max,ss}$ and $AUC_{\tau,ss}$ of pirfenidone, respectively (n = 12 for intraindividual comparison). Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when administered in combination (see section 4.4).

Concomitant treatment with bosentan
In a dedicated pharmacokinetic study, concomitant treatment of OFEV with bosentan was investigated in healthy volunteers. Subjects received a single dose of 150 mg OFEV before and after multiple dosing of 125 mg bosentan twice daily at steady state. The adjusted geometric mean ratios (90 % confidence interval (CI)) were 103 % (86 % - 124 %) and 99 % (91 % - 107 %) for C_{max} and $AUC_{0\text{-}tz}$ of nintedanib, respectively (n = 13), indicating that co-administration of OFEV with bosentan did not alter the pharmacokinetics of nintedanib.

Concomitant treatment with oral hormonal contraceptives
In a dedicated pharmacokinetic study, female patients with SSc-ILD received a single dose of a combination of 30 µg ethinylestradiol and 150 µg levonorgestrel before and after twice daily dosing of 150 mg OFEV for at least 10 days. The adjusted geometric mean ratios (90 % confidence interval (CI)) were 117 % (108 % - 127 %; C_{max}) and 101 % (93 % - 111 %; AUC_{0-tz}) for ethinylestradiol and 101 % (90 % - 113 %; C_{max}) and 96 % (91 % - 102 %; AUC_{0-tz}) for levonorgestrel, respectively (n = 15), indicating that co-administration of OFEV has no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel.

Exposure-response relationship
Exposure-response analyses of patients with IPF and other chronic fibrosing ILDs with a progressive phenotype, indicated 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 section 4.4).

5.3 Preclinical safety data

General toxicology

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

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

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

Reproduction toxicity

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

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

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

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

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk ($\leq$ 0,5 % of the administered dose).

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

Genotoxicity studies indicated no mutagenic potential for nintedanib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

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

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

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
OFEV soft gelatin capsules are packed in blister strips, consisting of a printed aluminium lidding foil and an aluminium-based forming foil.
Each blister strip consists of 10 soft gelatin capsules; 6 blister strips are packed per printed cardboard carton, in packs of 60 capsules.

6.6 Special precautions for disposal and other handling
In the event of coming in contact with the content of the capsule, hands should be washed off immediately with plenty of water (see section 4.2).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
South Africa
Tel. No.: +27 (011) 348-2400

8. REGISTRATION NUMBER(S)
OFEV 100 mg: 52/26/0153
OFEV 150 mg: 52/26/0154

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of registration: 22 September 2020
Date of Renewal of Authorisation: 10 February 2026

10. DATE OF REVISION OF THE TEXT