PROFESSIONAL INFORMATION FOR

NINTEDANIB CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NINTEDANIB 100 CIPLA (100 mg Capsules)

NINTEDANIB 150 CIPLA (150 mg Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NINTEDANIB CIPLA 100 mg capsule contains 120,40 mg nintedanib esylate equivalent to 100 mg nintedanib.

Each NINTEDANIB CIPLA 150 mg capsule contains 180,60 mg nintedanib esylate equivalent to 150 mg nintedanib.

For the full list of excipients, see **section 6.1**.

Sugar free

3. PHARMACEUTICAL FORM

Capsules

NINTEDANIB 100 CIPLA: Fluorescent yellow coloured homogeneous dispersion filled in brownish yellow, opaque, oblong soft gelatin capsules.

NINTEDANIB 150 CIPLA: Fluorescent yellow coloured homogeneous dispersion filled in light brown; opaque, oblong soft gelatin capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

NINTEDANIB CIPLA 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 NINTEDANIB CIPLA should be initiated by doctors experienced in the management of diseases for which NINTEDANIB CIPLA 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 NINTEDANIB CIPLA (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. NINTEDANIB CIPLA 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 NINTEDANIB CIPLA 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 NINTEDANIB CIPLA 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 NINTEDANIB CIPLA 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 NINTEDANIB CIPLA 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 NINTEDANIB CIPLA is not recommended (see **section 5.2**).

Paediatric population

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

Method of administration

NINTEDANIB CIPLA 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

Diarrhoea is the frequent gastrointestinal adverse reaction reported (see **section 4.8**). In most patients the adverse reaction can be mild to moderate intensity and occur within the first 3 months of treatment. Diarrhoea led to dose reduction in patients and to discontinuation of nintedanib in 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. NINTEDANIB CIPLA 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 NINTEDANIB CIPLA should be discontinued.

Nausea and vomiting

Nausea and vomiting can be frequent 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 and vomiting led to discontinuation of nintedanib as in NINTEDANIB CIPLA in 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 NINTEDANIB CIPLA should be discontinued.

Hepatic function

The safety and efficacy of nintedanib as in NINTEDANIB CIPLA has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore, treatment with NINTEDANIB CIPLA 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 NINTEDANIB CIPLA (see **sections 4.2** and **5.2**).

Cases of drug-induced liver injury have been observed with NINTEDANIB CIPLA 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 NINTEDANIB CIPLA. 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 (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), see **section 4.8**) and bilirubin can be 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 NINTEDANIB CIPLA is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with NINTEDANIB CIPLA 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 NINTEDANIB CIPLA 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 as in NINTEDANIB CIPLA 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 NINTEDANIB CIPLA use (see **section 4.8**).

Patients should be monitored during NINTEDANIB CIPLA 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 studies, 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 NINTEDANIB CIPLA 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. In a clinical trial, a higher percentage of patients experienced myocardial infarctions in the nintedanib group compared to the placebo group, while adverse events reflecting ischaemic heart disease were balanced between the nintedanib as in NINTEDANIB CIPLA and placebo groups. In a clinical trial, myocardial infarction was observed with low frequency: nintedanib as in NINTEDANIB CIPLA versus placebo. In a clinical trial, myocardial infarction was observed with low frequency in the placebo group and not observed in the nintedanib 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 NINTEDANIB CIPLA, 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 nintedanib as in NINTEDANIB CIPLA treated patients. Due to the mechanism of action of NINTEDANIB CIPLA 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 in both treatment groups. Due to the mechanism of action of NINTEDANIB CIPLA 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 Non-Steroidal Anti-inflammatory drugs (NSAIDs). NINTEDANIB CIPLA should only be initiated at least 4 weeks after abdominal surgery. Therapy with NINTEDANIB CIPLA should be permanently discontinued in patients who develop gastrointestinal perforation or ischaemic colitis. Exceptionally, NINTEDANIB CIPLA 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 nintedanib as in NINTEDANIB CIPLA 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 as in NINTEDANIB CIPLA. If laboratory or clinical findings associated with TMA occur in a patient receiving nintedanib as in NINTEDANIB CIPLA, treatment with nintedanib as in NINTEDANIB CIPLA should be discontinued and thorough evaluation for TMA should be completed.

Hypertension

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

Pulmonary hypertension

Data on the use of nintedanib as in NINTEDANIB CIPLA in patients with pulmonary hypertension is limited. Patients with significant pulmonary hypertension (cardiac index ≤ 2 L/min/m², or parenteral epoprostenol / treprostinil, or significant right heart failure) were excluded from the INBUILD and SENSCIS trials.

NINTEDANIB CIPLA 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. Based on the mechanism of action NINTEDANIB CIPLA may impair wound healing. No dedicated studies investigating the effect of nintedanib as in NINTEDANIB CIPLA on wound healing were performed. Treatment with

NINTEDANIB CIPLA 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 nintedanib as in NINTEDANIB CIPLA with pirfenidone was investigated in patients with IPF. Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between NINTEDANIB CIPLA and pirfenidone when administered in combination (see **section 5.2**). Given the similarity in safety profiles for both medicines, 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 as in NINTEDANIB CIPLA (see **section 5.1**). As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administering NINTEDANIB CIPLA in patients who may develop QTc prolongation.

Allergic reaction

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

4.5 Interaction with other medicinal products and other forms of interaction

P-glycoprotein (P-gp)

Nintedanib as in NINTEDANIB CIPLA 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 as in NINTEDANIB CIPLA 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 as in NINTEDANIB CIPLA alone. If co-administered with NINTEDANIB CIPLA, potent P-gp inhibitors (e.g., ketoconazole, erythromycin or ciclosporin) may increase exposure to nintedanib as in NINTEDANIB CIPLA. In such cases, patients should be monitored closely for tolerability of nintedanib as in NINTEDANIB CIPLA. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with NINTEDANIB CIPLA (see **section 4.2**).

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

Cytochrome (CYP)-enzymes

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

Co-administration with other medicines

Co-administration of nintedanib as in NINTEDANIB CIPLA with oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent (see **section 5.2**).

Co-administration of nintedanib as in NINTEDANIB CIPLA with bosentan did not alter the pharmacokinetics of nintedanib as in NINTEDANIB CIPLA (see **section 5.2**).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Nintedanib as in NINTEDANIB CIPLA may cause foetal harm in humans. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with NINTEDANIB CIPLA and to use highly effective contraceptive methods at initiation of, during and at least 3 months after the last dose of NINTEDANIB CIPLA. Nintedanib as in NINTEDANIB CIPLA 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 NINTEDANIB CIPLA in pregnant women. As nintedanib as in NINTEDANIB CIPLA 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 NINTEDANIB CIPLA and during treatment as appropriate.

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

If the patient becomes pregnant while receiving NINTEDANIB CIPLA, treatment must be discontinued, and she should be apprised of the potential hazard to the foetus.

Breastfeeding

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

Fertility

Based on preclinical investigations there is no evidence for impairment of male fertility. 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.

4.7 Effects on ability to drive and use machines

The undesirable effects (see **section 4.8**) of NINTEDANIB CIPLA may impair the ability to drive and use machines. NINTEDANIB CIPLA has minor influence on the ability to drive and use machines.

Patients should be advised to be cautious when driving or using machines during treatment with NINTEDANIB CIPLA.

4.8 Undesirable effects

a) Summary of the safety profile

In clinical studies and during the post-marketing experience, the frequently reported adverse reactions associated with the use of nintedanib as in NINTEDANIB CIPLA 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**.

b) Tabulated summary of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

	Frequency		
MedDRA system organ Class	**Idiopathic pulmonary fibrosis**	**Other chronic fibrosing ILDs with a progressive phenotype**	**Systemic sclerosis associated interstitial lung disease**
Blood and lymphatic system disorders			
Thrombocytopenia	*Less frequent*	*Less frequent*	*Less frequent*
Metabolism and nutrition disorders			
Decreased weight	*Frequent*	*Frequent*	*Frequent*
Decreased appetite	*Frequent*	*Frequent*	*Frequent*
Dehydration	*Less frequent*	*Less frequent*	*Frequency unknown*
Cardiac disorders			

	Frequency		
MedDRA system organ Class	**Idiopathic pulmonary fibrosis**	**Other chronic fibrosing ILDs with a progressive phenotype**	**Systemic sclerosis associated interstitial lung disease**
Myocardial infarction	*Less frequent*	*Less frequent*	*Frequency unknown*
Vascular disorders			
Bleeding (see **section 4.4**)	*Frequent*	*Frequent*	*Frequent*
Hypertension	*Less frequent*	*Frequent*	*Frequent*
Aneurysms and artery dissections	*Frequency unknown*	*Frequency unknown*	*Frequency unknown*
Gastrointestinal disorder			
Diarrhoea	*Frequent*	*Frequent*	*Frequent*
Nausea	*Frequent*	*Frequent*	*Frequent*
Abdominal pain	*Frequent*	*Frequent*	*Frequent*
Vomiting	*Frequent*	*Frequent*	*Frequent*
Pancreatitis	*Less frequent*	*Less frequent*	*Frequency unknown*
Colitis	*Less frequent*	*Less frequent*	*Less frequent*
Hepatobiliary disorders			
Drug induced liver injury	*Less frequent*	*Frequent*	*Less frequent*
Increased hepatic enzyme	*Frequent*	*Frequent*	*Frequent*

	Frequency		
MedDRA system organ Class	**Idiopathic pulmonary fibrosis**	**Other chronic fibrosing ILDs with a progressive phenotype**	**Systemic sclerosis associated interstitial lung disease**
Increased alanine aminotransferase (ALT)	*Frequent*	*Frequent*	*Frequent*
Increased aspartate aminotransferase (AST)	*Frequent*	*Frequent*	*Frequent*
Increased gamma glutamyl transferase (GGT)	*Frequent*	*Frequent*	*Frequent*
Hyperbilirubinemia	*Less frequent*	*Less frequent*	*Frequency unknown*
Increased blood alkaline phosphatase (ALP)	*Less frequent*	*Frequent*	*Frequent*
Skin and subcutaneous tissue disorders			
Rash	*Frequent*	*Frequent*	*Less frequent*
Pruritus	*Less frequent*	*Less frequent*	*Less frequent*
Alopecia	*Less frequent*	*Less frequent*	*Frequency unknown*
Renal and urinary disorders			
Renal failure (see **section 4.4**)	*Frequency unknown*	*Less frequent*	*Less frequent*

	Frequency		
MedDRA system organ Class	**Idiopathic pulmonary fibrosis**	**Other chronic fibrosing ILDs with a progressive phenotype**	**Systemic sclerosis associated interstitial lung disease**
Proteinuria	*Less frequent*	*Less frequent*	*Frequency unknown*
Nervous system disorders			
Headache	*Frequent*	*Frequent*	*Frequent*

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**).

Increased hepatic enzymes

In the clinical trials, liver enzyme elevations (see **section 4.4**) were reported in patients treated with nintedanib as in NINTEDANIB CIPLA and placebo, respectively. In a clinical trial, liver enzyme elevations were reported in patients treated with nintedanib as in NINTEDANIB CIPLA and placebo, respectively. In a clinical trial, liver enzyme elevations were reported in patients treated with nintedanib as in NINTEDANIB CIPLA 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 nintedanib as in NINTEDANIB CIPLA or comparable between the treatment arms. Non-serious epistaxis was the most frequent bleeding event reported. Serious bleeding events occurred with low frequencies in the 2 treatment groups.

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**).

Proteinuria

In clinical trials, the frequency of patients who experienced proteinuria was low and comparable between the treatment arms. Nephrotic syndrome has not been reported in clinical trials. 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 nintedanib as in NINTEDANIB CIPLA was discontinued, with residual proteinuria in some cases. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome (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. Health care providers are asked

to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

There is no specific antidote or treatment for NINTEDANIB CIPLA 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 as in NINTEDANIB CIPLA, 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

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01 EX09

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 nintedanib as in NINTEDANIB CIPLA as well as multiple oral doses of 200 mg nintedanib as in NINTEDANIB CIPLA 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 to 4 h after oral administration as soft gelatin capsule under fed conditions (range 0,5 to 8 h). The absolute bioavailability of a 100 mg dose was 4,69 % (90 % CI: 3,615 to 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 to 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) 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. $AUC_{T,ss}$ 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 to 25 % was observed in patients ≥ 75 years compared with patients under 65 years.

Body weight

An inverse correlation between body weight and exposure to nintedanib was observed. $AUC_{T,ss}$ increased by 25 % for a 50 kg patient (5th percentile) and decreased by 19 % for a 100 kg patient (95^{th} percentile) relative to a patient with the median weight of 71,5 kg.

Race

The population mean exposure to nintedanib was 33 – 50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patients while it was 16 – 22 % lower in Koreans compared to Caucasians (body weight corrected). Data from Black individuals 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 Cmax (90 % CI 4,4 – 13,2) and 8,7-fold higher (90 % CI 5,7 – 13,1) based on AUC, respectively, compared to healthy 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. Group 2 received steady state treatment of 801 mg pirfenidone three times a day and had a PK profiling before and after at least 7 days of co-treatment with 150 mg nintedanib twice daily. In group 1, the adjusted geometric mean ratios (90 % confidence interval (CI)) were 93 % (57 % to 151 %) and 96 % (70 % to 131 %) for C_{max} and $AUC_{0\text{-}tz}$ of nintedanib, respectively. In group 2, the adjusted geometric mean ratios (90 % CI) were 97 % (86 % to 110 %) and 95 % (86 % to 106 %) for $C_{max,ss}$ and $AUC_{T,ss}$ of pirfenidone, respectively.

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 nintedanib as in NINTEDANIB CIPLA with bosentan was investigated in healthy volunteers. Subjects received a single dose of 150 mg nintedanib as in NINTEDANIB CIPLA 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 % to 124 %) and 99 % (91 % to 107 %) for C_{max} and $AUC_{0\text{-}tz}$ of nintedanib, respectively, indicating that co-administration of nintedanib as in NINTEDANIB CIPLA 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 microgram ethinylestradiol and 150 microgram levonorgestrel before and after twice daily dosing of 150 mg nintedanib as in NINTEDANIB CIPLA for at least 10 days. The adjusted geometric mean ratios (90 % confidence interval (CI)) were 117 % (108 % to 127 %; C_{max}) and 101 % (93 % to 111 %; $AUC_{0–tz}$) for ethinylestradiol and 101 % (90 % to 113 %; C_{max}) and 96 % (91 % to 102 %; $AUC_{0–tz}$) for levonorgestrel, respectively, indicating that co-administration of nintedanib as in NINTEDANIB CIPLA 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**).

Paediatric population

Studies in paediatric populations have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Hard fat (softisan 378)

Lecithin (topcithin SB PCR Negative)

Medium chain triglyceride (miglyol 812 N)

Capsule shell

Ferric oxide (red) (colour index number: 77491, E-number: E172)

Ferric oxide (yellow) (colour index number: 77492, E-number: E172)

Gelatin (gelita RXL)

Glycerin

Purified water

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in the original package and protect from exposure to high humidity and avoid excessive heat.

6.5 Nature and contents of container

NINTEDANIB100 CIPLA capsules are packed in a 50 CC white round HDPE container with 33 MM 400 Argus LOC Blue Child Resistant cap or in a 100 CC white HDPE container with 38 MM 400 Argus LOC Blue Child Resistant cap.

NINTEDANIB 150 CIPLA capsules are packed in a 50 CC white round HDPE container with 33 MM 400 Argus LOC Blue Child Resistant cap or in a 75 CC white HDPE container with 38 MM 400 Argus LOC Blue Child Resistant cap.

Pack sizes:

NINTEDANIB 100 CIPLA: 30’s and 60’s

NINTEDANIB 150 CIPLA: 30’s and 60’s

Not all pack sizes may be marketed.

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 medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

Nintedanib 100 Cipla: 56/26/0704.702

Nintedanib 150 Cipla: 56/26/0705.703

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 26 September 2023

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

Not applicable