

For the use of only Registered Medical Practitioner or a Hospital or a Laboratory

### Colour code

Oncology

Idiopathic pulmonary fibrosis (IPF)

Both indications

Oncology indication Information highlighted in blue colour and IPF indication information highlighted in purple colour. Information not highlighted in any colour is common for both the indication

## Nintedanib Soft Gelatin Capsules

**CYENDIV<sup>®</sup>**

### COMPOSITION

#### **CYENDIV<sup>®</sup> 100 mg**

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

#### **CYENDIV<sup>®</sup> 150 mg**

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

### **Excipients**

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

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

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

### **INDICATIONS/ USAGE**

**CYENDIV<sup>®</sup>** is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy.

**CYENDIV<sup>®</sup>** is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF)

### **DOSAGE AND ADMINISTRATION/ RECOMMENDED INTAKE**

Treatment with **CYENDIV<sup>®</sup>** should be initiated and supervised by a physician experienced in the use of anticancer therapies.

For posology, method of administration, and dose modifications of docetaxel, please refer to

the corresponding product information for docetaxel.  
The recommended dose of **CYENDIV<sup>®</sup>** is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21-day docetaxel treatment cycle.

**CYENDIV<sup>®</sup>** must not be taken on the same day of docetaxel chemotherapy administration (= day 1).

Treatment with **CYENDIV<sup>®</sup>** should be initiated by physicians experienced in the diagnosis and treatment of IPF.

The recommended dose of **CYENDIV<sup>®</sup>** is 150 mg twice daily administered approximately 12 hours apart.

**CYENDIV<sup>®</sup>** 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.

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

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

Patients may continue therapy with **CYENDIV<sup>®</sup>** after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

### Dose adjustments

As initial measure for the management of adverse reactions (see Table 1 and 2) treatment with **CYENDIV<sup>®</sup>** should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline).  
**CYENDIV<sup>®</sup>** 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 1 and Table 2**.

In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with **CYENDIV<sup>®</sup>** should be permanently discontinued.

In case of specific elevations of aspartate aminotransferase (AST) / alanine aminotransferase (ALT) values to > 3 x upper limit normal (ULN) in conjunction with an increase of total bilirubin to  $\geq 2$  x ULN and alkaline phosphatase ALKP < 2 x ULN (see Table 2) treatment with **CYENDIV<sup>®</sup>** should be interrupted. Unless there is an alternative cause established, **CYENDIV<sup>®</sup>** should be permanently discontinued (see also section 4.4).

Table 1 Recommended dose adjustments for **CYENDIV<sup>®</sup>** in case of diarrhoea, vomiting and other non-haematological or haematological adverse reactions except liver enzyme elevations (see Table 2)

CTCAE* Adverse reaction	Dose adjustment
Diarrhoea equal to grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment** <b>OR</b>	<b>The geometric mean exposure to nintedanib was 33 % higher in Chinese, Taiwanese, and Indian patients.</b>

Diarrhoea $\geq$ grade 3 despite anti-diarrhoeal treatment**	<p><b>The dose reduction was required in 31% Indian patients as observed in the Phase-III NSCLC study</b></p> <p>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 2<sup>nd</sup> dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.</p>
Vomiting ** $\geq$ grade 2 <b>AND/OR</b> Nausea $\geq$ grade 3 despite anti-emetic treatment**	
Other non-haematological or haematological adverse reaction of $\geq$ grade 3	

\*CTCAE: Common Terminology Criteria for Adverse Events

\*\* see also section *Special warnings and precautions*

Table 2 Recommended dose adjustments for **CYENDIV<sup>®</sup>** (nintedanib) 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 $> 2.5 \times$ ULN in conjunction with total bilirubin elevation to $\geq 1.5 \times$ ULN  <b>OR</b> Elevation of AST and/or ALT values to $> 5 \times$ ULN	After treatment interruption and recovery of transaminase-values to $\leq 2.5 \times$ ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2 <sup>nd</sup> dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.
Elevation of AST and/or ALT values to $> 3 \times$ ULN in conjunction with an increase of total bilirubin to $\geq 2 \times$ ULN and ALKP $< 2 \times$ ULN	Unless there is an alternative cause established, <b>CYENDIV<sup>®</sup></b> should be permanently discontinued.

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase;

ALKP: Alkaline phosphatase; ULN: Upper limit normal

In addition to symptomatic treatment if applicable, the management of side effects (see section *Special warnings and Precautions, Side effects*) of **CYENDIV<sup>®</sup>** could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. **CYENDIV<sup>®</sup>** 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 **CYENDIV<sup>®</sup>** should be discontinued.

In case of interruptions due to transaminase (AST or ALT) elevations  $> 3 \times$  upper limit of normal (ULN), once transaminases have returned to baseline values, treatment with **CYENDIV<sup>®</sup>** 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 section *Special Warnings and Precautions, Side effects*)

### **Special populations**

#### Paediatric population

The safety and efficacy of **CYENDIV<sup>®</sup>** 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 section **Pharmacokinetics**).

### Race

Based on population pharmacokinetic (PK) analyses, no *a priori* dose adjustments of **CYENDIV<sup>®</sup>** are necessary (see section **Special warnings and precautions**, special populations, **Pharmacokinetics**). Safety data for Black patients are limited.

### Body weight

Based on population PK analyses, no *a priori* dose adjustments of **CYENDIV<sup>®</sup>** are necessary (see section **Pharmacokinetics**).

### Renal impairment

Less than 1 % of a single dose of nintedanib is excreted via the kidney (see section **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).

### 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 **Pharmacokinetics**).

No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A, see section **Special warnings and precautions**).

In patients with mild hepatic impairment (Child Pugh A), the recommended dose of Cyendiv<sup>®</sup> is 100 mg twice daily approximately 12 hours apart.

In patients with mild hepatic impairment (Child Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered.

The safety and efficacy of nintedanib have not been investigated 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 Cyendiv<sup>®</sup> is not recommended *see section Pharmacokinetics*

## **CONTRAINDICATIONS**

**CYENDIV<sup>®</sup>** is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients .

**CYENDIV<sup>®</sup>** is contraindicated during pregnancy (see sections **Fertility, Pregnancy and Lactation** and **Toxicology**).

For contraindications of docetaxel please refer to the corresponding product information for docetaxel.

## **SPECIAL WARNINGS AND PRECAUTIONS**

### Gastrointestinal -Disorders

- *Diarrhoea*  
Diarrhoea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel (see section *Side effects*). In the clinical trial LUME-Lung 1 (see section *Clinical trials*), the majority of patients had mild to moderate diarrhoea. 6.3 % of the patients had diarrhoea of grade  $\geq 3$  in combination treatment compared to 3.6 % 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 **CYENDIV<sup>®</sup>** (see section *Dosage and administration/ Recommended intake*).
- *Nausea and vomiting*  
Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events (see section *Side effects*). If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction, treatment interruption or discontinuation of therapy with **CYENDIV<sup>®</sup>** (see section *Dosage and administration/ Recommended intake*) may be required.

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

#### *Diarrhoea*

In the INPULSIS trials (see section Clinical trials), diarrhoea was the most frequent gastro-intestinal event reported in 62.4 % versus 18.4 % of patients treated with **CYENDIV<sup>®</sup>** and placebo, respectively (see section *Side 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. **CYENDIV<sup>®</sup>** 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 **CYENDIV<sup>®</sup>** should be discontinued.

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

If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe symptoms therapy with **CYENDIV<sup>®</sup>** -should

be discontinued.

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

### Neutropenia and Sepsis

A higher frequency of neutropenia of CTCAE grade > 3 was observed in patients treated with **CYENDIV**<sup>®</sup> in combination with docetaxel as compared to treatment with docetaxel alone. Subsequent complications such as sepsis or febrile neutropenia have been observed.

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

The safety and efficacy of **CYENDIV**<sup>®</sup> has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with **CYENDIV**<sup>®</sup> is not recommended in such patients.

Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see sections *Dosage and Administration*, *Pharmacokinetics*).

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, severe liver injury with fatal outcome has been reported. Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyltransferase (GGT) and bilirubin were reversible upon dose reduction or interruption in the majority of cases.

Transaminase, ALKP and bilirubin levels should be investigated upon initiation of the combination treatment with **CYENDIV**<sup>®</sup> 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 **CYENDIV**<sup>®</sup> is continued as monotherapy after discontinuation of docetaxel.

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with **CYENDIV**<sup>®</sup> may be required (see section *Dosage and administration/Table 2*). 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  $\geq$  2 x ULN and ALKP < 2 x ULN) treatment with **CYENDIV**<sup>®</sup> should be interrupted. Unless there is an alternative cause established, **CYENDIV**<sup>®</sup> should be permanently discontinued (see section *Dosage and administration/Table 2*).

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



section Pharmacokinetics).

Close monitoring is recommended in patients with these risk factors.

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 CYENDIV<sup>®</sup> (see sections Dosage and Administration, Pharmacokinetics)

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported.

The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated upon initiation of treatment with CYENDIV<sup>®</sup>, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyl-transferase (GGT)) and bilirubin were reversible upon dose reduction or interruption in the majority of cases. If transaminase (AST or ALT) elevations > 3x upper limit of normal (ULN) are measured, dose reduction or interruption of the therapy with CYENDIV<sup>®</sup> is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with CYENDIV<sup>®</sup> may be re-increased to the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose. (see section *Dosage and administration/Recommended intake*). If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with CYENDIV<sup>®</sup> should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes.

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

Close monitoring is recommended in patients with these risk factors

### Haemorrhage

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

In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed. In patients who experience grade 3/4 bleeding events, the benefits and risks of continuing treatment with CYENDIV<sup>®</sup> should be carefully weighed and discontinuation of CYENDIV<sup>®</sup> may be considered. If treatment with CYENDIV<sup>®</sup> is resumed, a reduced daily dose is recommended (see section *Dosage and administration/Table 1*).

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 cavitory or necrotic tumours have been excluded from clinical trials. Therefore, it is not recommended to treat these patients with CYENDIV<sup>®</sup>.

- Brain metastasis

- Stable brain metastasis

- No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for  $\geq 4$  weeks before start of treatment with **CYENDIV**<sup>®</sup> 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 **CYENDIV**<sup>®</sup>.

- Therapeutic anticoagulation

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 **CYENDIV**<sup>®</sup>. 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 **CYENDIV**<sup>®</sup> and did not show an increased frequency of bleeding events. Patients taking concomitant anticoagulation, such as warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes.

VEGFR inhibition might be associated with an increased risk of bleeding. In the INPULSIS trials with **CYENDIV**<sup>®</sup>, the frequency of patients who experienced bleeding adverse events was slightly higher in the **CYENDIV**<sup>®</sup> 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%; Cyendiv: 1.3%). Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment were not included in the INPULSIS studies. Therefore these patients should only be treated with **CYENDIV**<sup>®</sup> if the anticipated benefit outweighs the potential risk. In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed.

### Arterial thromboembolic events

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 idiopathic pulmonary fibrosis (IPF) when treated with nintedanib monotherapy.

Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Arterial thromboembolic events were infrequently reported: in 0.7% of patients in the placebo and 2.5% in the nintedanib treated group.

While adverse events reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%).

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



### Venous thromboembolism

Patients treated with **CYENDIV<sup>®</sup>** have an increased risk of venous thromboembolism including deep vein thrombosis. Patients should be closely monitored for thromboembolic events. **CYENDIV<sup>®</sup>** should be discontinued in patients with life-threatening venous thromboembolic reactions.

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

### Gastrointestinal perforations

The frequency of gastrointestinal perforation was comparable between the treatment arms in the LUME-Lung 1 study. **Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. CYENDIV<sup>®</sup> should therefore only be initiated at least 4 weeks after major, incl. abdominal, surgery. Therapy with CYENDIV<sup>®</sup> should be permanently discontinued in patients who develop gastrointestinal perforation.**

In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients. **Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery, or a recent history of a hollow organ perforation, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. CYENDIV<sup>®</sup> should therefore only be initiated at least 4 weeks after major, incl. abdominal, surgery. Therapy with CYENDIV<sup>®</sup> should be permanently discontinued in patients who develop gastrointestinal perforation.**

### Wound healing complication

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

### Soya lecithin

**CYENDIV<sup>®</sup>** contains soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.

### 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  $\geq 50$  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.

## **INTERACTIONS**

### P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see section *Pharmacokinetics*). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on  $C_{max}$  in a dedicated drug-drug interaction study.

In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3 % based on AUC and to 60.3 % based on  $C_{max}$  upon co-administration with rifampicin compared to administration of nintedanib alone.

If co-administered with **CYENDIV<sup>®</sup>**, 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 **CYENDIV<sup>®</sup>** (see section *Dosing and administration*).

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

### Food

**CYENDIV<sup>®</sup>** is recommended to be taken with food (see section *Pharmacokinetics*).

### Cytochrome (CYP)-enzymes

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

### Co-administration with other drugs

Co-administration of nintedanib with docetaxel (75 mg/m<sup>2</sup>) did not alter the pharmacokinetics of either drug to a relevant extent.

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

## **FERTILITY, PREGNANCY AND LACTATION**

### Fertility

Based on preclinical investigations, there is no evidence for impairment of male fertility (see section *Toxicology*). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 200 mg twice daily (see section *Toxicology*).

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

### Contraception

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

### Pregnancy

There is no information on the use of **CYENDIV**<sup>®</sup> in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this drug (see section **Toxicology** ). As nintedanib may cause foetal harm also in humans, it must not be recommended during pregnancy and pregnancy testing should be conducted at least prior to treatment with **CYENDIV**<sup>®</sup>.

Female patients should be advised to notify their doctor or pharmacist if becoming pregnant during therapy with **CYENDIV**<sup>®</sup>.

If the patient becomes pregnant while receiving **CYENDIV**<sup>®</sup> the patient should be apprised of the potential hazard to the foetus. Termination of the treatment should be considered.

### Breastfeeding / lactation

There is no information on the excretion of nintedanib and its metabolites in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites ( $\leq 0.5$  % of the administered dose) were secreted into milk of lactating rats.

A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with **CYENDIV**<sup>®</sup>.

For fertility, pregnancy and lactation information for docetaxel please refer to the corresponding product information for docetaxel.

## **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 **CYENDIV**<sup>®</sup>.

## **SIDE EFFECTS**

### Summary of the safety profile

The safety data provided in the following 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 and based on data observed during the post-marketing period. **The most frequently reported adverse reactions specific for nintedanib were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting.** Table 3 provides a summary of the adverse reactions by System Organ Class

(SOC).

Nintedanib has been studied in clinical trials of 1529 patients suffering from Idiopathic Pulmonary Fibrosis (IPF).

The safety data provided in the following are based on the two Phase 3, randomised, double-blind, placebo-controlled studies in 1061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2) and based on data observed during the post-marketing period.

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

For the management of selected adverse reactions please also refer to section *Special Warnings and Precautions*.

Table 3 Summary of Adverse Reactions in trial LUME- Lung 1 (NSCLC patients of adenocarcinoma histology)

<b>System Organ Class - MedDRA terminology –</b>	<b>CCDS verbatim term MedDRA (version 15.1) PTs</b>	<b>Frequency category according to EU SmPC Guideline</b>
Infections and infestations	Sepsis	Common
	Abscess	Common
	Febrile neutropenia	Common
Blood and lymphatic system	Neutropenia**	Very common
	Thrombocytopenia	Common
Metabolism and nutrition	Dehydration	Common
	Electrolyte imbalance	Very common
	Decreased appetite	Very common
	Weight decreased	Common
Vascular disorders	Hypertension	Common
	Venous thromboembolism	Common
	Bleeding	Very common
Gastrointestinal Disorder	Diarrhea	Very common
	Vomiting	Very common
	Abdominal pain	Very common
	Perforation	Uncommon
	Nausea	Very common
	Stomatitis	Very common
	Pancreatitis	Uncommon
Hepatobiliary disorders	Drug-induced liver injury	Uncommon
	Alanine aminotransferase increased	Very common
	Aspartate aminotransferase increased	Very common
	Blood alkaline Phosphatase increased	Very common
	Gamma-Glutamyltransferase increased	Common
Skin and subcutaneous tissue	Hyperbilirubinemia	Common
	Mucositis***	Very common
	Rash	Very common
Nervous system disorders	Pruritus	Common
	Peripheral neuropathy	Very common

- 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.
- 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.

Table 4 Summary of Adverse Reactions in randomised Phase III trials (IPF)

System Organ Class - MedDRA terminology –	CCDS verbatim term MedDRA (version 16.1) PTs	Frequency category according to EU SmPC Guideline
Blood and lymphatic system	Thrombocytopenia	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Common
	Weight decreased	Common
Vascular disorders	Hypertension	Uncommon
	Bleeding <sup>1</sup>	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Abdominal pain	Very common
	Vomiting	Common
	Pancreatitis	Uncommon
Hepatobiliary disorders	Drug-induced liver injury	Uncommon
	Hepatic enzyme increased	Very common
	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common
	Gamma- glutamyltransferase increased	Common
	Blood alkaline Phosphatase increased	Uncommon
	Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue	Rash	Common
	Pruritus	Uncommon
<sup>1</sup> Exceptionally LLT		

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

2) Non-serious and serious bleeding events , some of which were fatal have been observed in the post-marketing period in line with clinical trial experience

### **SAFETY MONITORING**

**Reporting all serious adverse reactions after approval of the Nintedanib capsules is important. It allows continued monitoring of the benefit/risk balance of the product. Indian patients being treated with this drug should be monitored closely for any untoward occurrence and overall safety of the patients.**

**Healthcare professionals are requested to monitor and report all serious adverse reactions and report the same to Pharmacovigilance Programme of India (PvPI) Email**



## **OVERDOSE**

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

In the INPULSIS trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (*nasopharyngitis*) occurred and resolved during the period of incorrect dosing, with no onset of other reported events.

In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

## **PHARMACOLOGICAL PROPERTIES**

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitors.  
ATC code: L01XE31

### Mechanism of action

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR  $\alpha$  and  $\beta$ ) 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 (Flt)-3, lymphocyte-specific tyrosine-protein kinase (Lck) and proto-oncogene tyrosine-protein kinase Src (Src) are inhibited.

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR)  $\alpha$  and  $\beta$ , 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

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. In particular, treatment of tumour xenografts with nintedanib

led to a rapid reduction in tumour micro vessel density, pericytes vessel coverage and tumour perfusion.

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  $\geq 200$  mg. Logistic regression revealed a statistically significant association of the anti-angiogenic effect to nintedanib exposure. DCE-MRI effects were seen 24-48 h 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 stabilization.

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<sub>50</sub> 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- $\beta$ 2-induced fibroblasts to myofibroblast transformation. In addition, the anti-inflammatory activity of nintedanib is thought to limit fibrotic stimulation by reduction of profibrotic mediators like IL-1 $\beta$  and IL-6. The contribution of the anti-angiogenic activity of nintedanib to its mechanism of action in fibrotic lung diseases is currently not clarified. In in vivo studies, nintedanib was shown to have potent anti-fibrotic and anti-inflammatory activity.

## CLINICAL TRIALS

### Efficacy in the pivotal phase 3 trial LUME-Lung 1

The efficacy and safety of Nintedanib 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 randomized (1:1) to receive nintedanib 200 mg orally twice daily in combination with 75 mg/m<sup>2</sup> of i.v. docetaxel every 21 days (n = 655) or placebo orally twice daily in combination with 75 mg/m<sup>2</sup> of docetaxel every 21 days (n = 659). Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 vs. 1), bevacizumab pretreatment (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 5**, 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. Overall survival 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 5 Efficacy results for study LUME-Lung 1 for all patients and for patients with adenocarcinoma tumour histology

	All patients		Adenocarcinoma tumour histology	
	Nintedanib b (n = 565)	Placebo (n = 569)	Nintedanib (n = 277)	Placebo (n = 285)
<b>Progression free survival*</b>				
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) <sup>+</sup>	1.56 (1.23, 1.98)		1.98 (1.41, 2.77)	
p-value <sup>+</sup>	0.0002		<0.0001	
Objective response [%]	3.4	1.9	4.3	3.5
Odds ratio (95% CI) <sup>+</sup>	1.77 (0.85, 3.89)		1.25 (0.53, 3.01)	
p-value <sup>+</sup>	0.1283		0.6122	
Adjusted mean of best % change of tumour size from baseline [%]	-3.93	1.15	-7.38	-0.28
p-value <sup>o</sup>	0.0002		0.0002	
<b>Overall Survival***</b>				
Number of OS events, n (%)	(n= 655) 564 (86.1)	(n= 659) 557 (84.5)	(n= 322) 259 (80.4)	(n= 336) 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 713<sup>th</sup> PFS events in the overall population.

\*\* 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 it is 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).

o Adjusted mean of best % change from baseline and p-value generated from an ANOVA model adjusting for baseline ECOG PS (0 vs. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no). In the all patients population it is additionally adjusted by tumour histology (squamous vs. non-squamous). One patient (135301) has a baseline ECOG PS of 2.

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



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 1<sup>st</sup> 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  $\geq$  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.

The clinical efficacy of nintedanib has been studied in patients with IPF in two phase 3, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 and INPULSIS-2). Patients were randomized in a 3:2 ratio to treatment with Nintedanib Capsules 150 mg or placebo twice daily for 52 weeks.

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

Annual rate of decline in FVC

The annual rate of decline of FVC (in mL) was significantly reduced in patients receiving nintedanib compared to patients receiving placebo. The treatment effect was consistent in both trials. See Table 6 for individual and pooled study results.



Table 6 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	<b>Nintedanib capsules 150 mg twice daily</b>	Placebo	<b>Nintedanib Capsules 150 mg twice daily</b>	Placebo	<b>Nintedanib Capsules 150 mg twice daily</b>
Number of analysed patients	204	309	219	329	423	638
Rate <sup>1</sup> (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 <sup>1</sup>		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

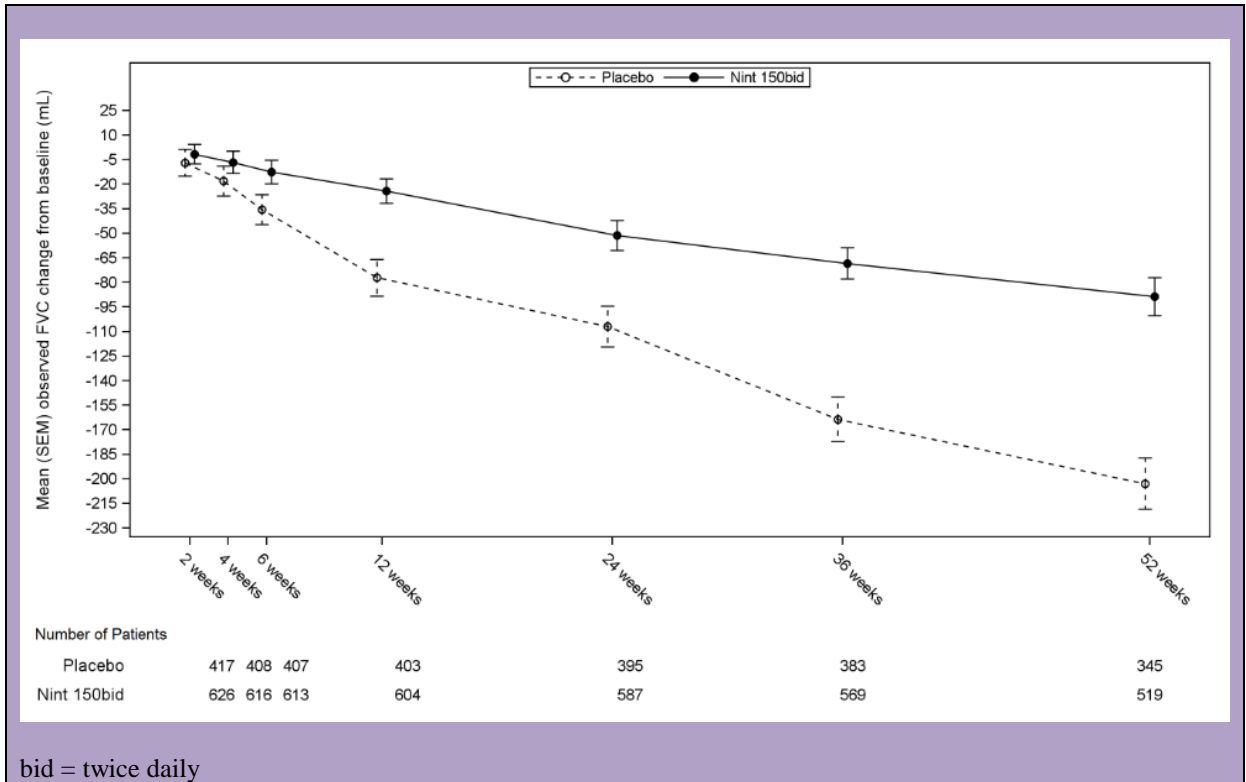
<sup>1</sup> Estimated based on a random coefficient regression model.

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



FVC responder analysis

In both INPULSIS trials, the proportion of FVC responders, defined as patients with an absolute decline in FVC % predicted no greater than 5% (a threshold indicative of the increasing risk of mortality in IPF), was significantly higher in the nintedanib group as compared to placebo. Similar results were observed in analyses using a conservative threshold of 10%. See Table 7 for individual and pooled study results.

Table 7 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	<b>Nintedanib Capsules</b> 150 mg twice daily	Placebo	<b>Nintedanib Capsules</b> 150 mg twice daily	Placebo	<b>Nintedanib Capsules</b> 150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
<b>5% threshold</b>						
Number (%) of FVC responders <sup>1</sup>	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 <sup>2</sup>		0.0010		0.0011		<0.0001
<b>10% threshold</b>						
Number (%) of FVC responders <sup>1</sup>	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 <sup>2</sup>		0.0007		0.1833		0.0007
<sup>1</sup> 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. <sup>2</sup> Based on a logistic regression						

Time to progression ( $\geq 10\%$  absolute decline of FVC % predicted or death)

In both INPULSIS trials, the risk of progression was statistically significantly reduced for patients treated with nintedanib compared with placebo. In the pooled analysis, the HR was 0.60 indicating a 40% reduction in the risk of progression for patients treated with nintedanib compared with placebo, see Table 8.

Table 8: Frequency of patients with  $\geq 10\%$  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	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 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 <sup>1</sup>						
p-value <sup>2</sup>		0.0001		0.0054		<0.0001
Hazard ratio <sup>3</sup>		0.53		0.67		0.60
95% CI		(0.39, 0.72)		(0.51, 0.89)		(0.49, 0.74)
<sup>1</sup> Based on data collected up to 372 days (52 weeks + 7 day margin).						
<sup>2</sup> Based on a Log-rank test.						
<sup>3</sup> Based on a Cox's regression model.						

#### Change from baseline in SGRQ total score at week 52

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

In INPULSIS-1, the increase from baseline in SGRQ total score at week 52 was comparable between nintedanib and placebo (difference between treatment groups: -0.05; 95% CI: -2.50, 2.40; p=0.9657). In the pooled analysis of the INPULSIS trials, the estimated mean change from baseline to week 52 in SGRQ total score was smaller in the nintedanib group (3.53) than in the placebo group (4.96), with a difference between the treatment groups of -1.43 (95% CI: -3.09, 0.23; p = 0.0923). Overall, the effect of nintedanib on health-related quality of life as measured by the SGRQ total score is modest, indicating less worsening compared to placebo.

#### Time to first acute IPF exacerbation

In the INPULSIS-2 trial, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving nintedanib compared to placebo, in the INPULSIS-1 trial there was no difference in between the treatment groups. In the pooled analysis of the INPULSIS trials, a numerically lower risk of first acute exacerbation was observed in patients receiving nintedanib compared to placebo. See Table 9 for individual and pooled study results.

Table 9 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	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 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 <sup>1</sup>						
p-value <sup>2</sup>		0.6728		0.0050		0.0823
Hazard ratio <sup>3</sup>		1.15		0.38		0.64
95% CI		(0.54, 2.42)		(0.19, 0.77)		(0.39, 1.05)

<sup>1</sup> Based on data collected up to 372 days (52 weeks + 7 day margin).

<sup>2</sup> Based on a Log-rank test.

<sup>3</sup> 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

In the pre-specified pooled analysis of survival data of the INPULSIS trials, overall mortality over 52 weeks was lower in the nintedanib group (5.5%) compared with the placebo group (7.8%). The analysis of time to death resulted in a HR of 0.70 (95% CI 0.43, 1.12; p = 0.1399). The results of all survival endpoints (such as on-treatment mortality and respiratory mortality) showed a consistent numerical difference in favour of nintedanib (see Table 10).

Table 10: 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	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 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 <sup>1</sup>						

p-value <sup>2</sup>		0.2880		0.2995		0.1399
Hazard ratio <sup>3</sup>		0.63		0.74		0.70
95% CI		(0.29, 1.36)		(0.40, 1.35)		(0.43, 1.12)

<sup>1</sup> Based on data collected up to 372 days (52 weeks + 7 day margin).

<sup>2</sup> Based on a Log-rank test.

<sup>3</sup> Based on a Cox's regression model.

#### Supportive evidence from the phase II trial (1199.30) Nintedanib Capsules 150 mg twice daily results:

Additional evidence of efficacy is provided by the randomised, double-blind, placebo-controlled, dose finding phase II trial including a nintedanib 150 mg bid dose group. The primary endpoint, rate of decline in FVC over 52 weeks was lower in the nintedanib arm (-0.060 L/year, N=84) than the placebo arm (-0.190 L/year, N=83). The estimated difference between the treatment groups was 0.131 L/year (95% CI 0.027, 0.235). The difference between the treatment groups reached nominal statistical significance (p = 0.0136).

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

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

Additional data from the phase IV INJOURNEY trial with CYENDIV<sup>®</sup> 150 mg twice daily and add-on pirfenidone:

Concomitant treatment with nintedanib and pirfenidone has been investigated in an exploratory open-label, randomised trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomised patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to week 12. Gastrointestinal adverse events were frequent and in line with the established safety profile of each component. Diarrhoea, nausea and vomiting were the most frequent adverse events reported in 20 (37.7%) versus 16 (31.4%), in 22 (41.5%) versus 6 (11.8%) and in 15 (28.3%) versus 6 (11.8%) patients, treated with pirfenidone added to nintedanib versus nintedanib alone, respectively.

Mean (SE) absolute changes from baseline in FVC at week 12 were -13.3 (17.4) mL in patients treated with nintedanib with add-on pirfenidone (n=48) compared to -40.9 (31.4) mL in patients treated with nintedanib alone (n=44).

#### Quality of Life

Treatment with nintedanib did not significantly change the time to deterioration of the pre-specified symptoms cough, dyspnoea and pain, but resulted in a significant deterioration in the diarrhoea symptom scale. Nevertheless, the overall treatment benefit of nintedanib was observed without adversely affecting self-reported quality of life. .

#### 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.



However, 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.

### **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  $AUC_{\tau}$ . Nintedanib trough concentrations remained stable for more than one year.

#### Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 hours;). The absolute bioavailability of a 100 mg dose was 4.69 % (90 % CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

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

#### Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution ( $V_{ss}$  : 1050 L, 45.0 % gCV) was observed.

The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8 %. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869.

#### Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human ADME study. *In vitro*, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage.

In preclinical *in vivo* experiments, BIBF 1202 did not show efficacy despite its activity at target receptors of the substance.

#### Elimination

Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV)

[58]. Urinary excretion of the unchanged active substance within 48 hours was about 0.05 % of dose (31.5 % gCV) after oral and about 1.4 % of the dose (24.2 % gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6 % gCV). The major route of elimination of drug related radioactivity after oral administration of [<sup>14</sup>C] nintedanib was via faecal/biliary excretion (93.4 % of dose, 2.61 % gCV). The contribution of renal excretion to the total clearance was low (0.649 % of dose, 26.3 % gCV). The overall recovery was considered complete (above 90 %) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50 %).

#### Exposure-response relationship

In exploratory pharmacokinetic (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

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 section ***Special warnings and precautions***).

#### Intrinsic and Extrinsic Factors; Special Populations

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

#### Age

Exposure to nintedanib increased linearly with age.  $AUC_{\tau,ss}$  decreased by 16 % for a 45-year old patient (5<sup>th</sup> percentile) and increased by 13 % for a 76-year old patient (95<sup>th</sup> percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population was older than 75 years. Studies in paediatric populations have not been performed.

#### Body weight

An inverse correlation between body weight and exposure to nintedanib was observed.  $AUC_{\tau,ss}$  increased by 25 % for a 50 kg patient (5<sup>th</sup> percentile) and decreased by 19 % for a 100 kg patient (95<sup>th</sup> percentile) relative to a patient with the median weight of 71.5 kg.

## Race

The population mean exposure to nintedanib was 33 - 50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patients while it was 16 - 22 % lower in Koreans compared to Caucasians (body weight corrected).

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

## Hepatic impairment

In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib based on C<sub>max</sub> and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 - 3.7 for C<sub>max</sub> 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<sub>max</sub> (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

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 up-titration 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% - 151%) and 96% (70% - 131%) for C<sub>max</sub> and AUC<sub>0-tz</sub> of nintedanib, respectively (n=12). In group 2, the adjusted geometric mean ratios (90% CI) were 97% (86% - 110%) and 95% (86% - 106%) for C<sub>max,ss</sub> and AUC<sub>τ,ss</sub> of pirfenidone, respectively (n=12). Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when administered in combination

## Drug-Drug Interaction Potential

### Metabolism

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

### Transport

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

## **TOXICOLOGY**

### General toxicology

Single dose toxicity studies in rats and mice indicated a low acute toxic potential of

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

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

There was no evidence of liver enzyme increases in rats, dogs, and Cynomolgus monkeys.

Mild liver enzyme increases which were not due to serious adverse effects such as diarrhoea were only observed in Rhesus monkeys.

## Reproduction toxicity

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

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (MRHD) 200 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, embryofetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats.

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk ( $\leq 0.5$  % 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.

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

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

In rabbits, embryofetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk ( $\leq 0.5$  % of the administered dose).

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

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**Storage-**

**Store at 2<sup>0</sup> to 8<sup>0</sup>C**

**Do not Freeze**

**Store in the original package in order to protect from moisture**

**Store in a safe place out of the reach of children.**

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