Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nintedanib Teva Pharma 100 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nintedanib Teva Pharma 100 mg soft capsules
Each soft capsule contains 100 mg nintedanib (as esilate).

Excipients with known effect
Each capsule contains 3.84 mg of soya lecithin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule (capsule).

Nintedanib Teva Pharma 100 mg soft capsules
Pale pink, opaque, oblong soft capsule of approximately 16 mm in length, marked with TV8205.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

Nintedanib Teva Pharma must not be taken on the same day of docetaxel chemotherapy administration (= day 1). If a dose of Nintedanib Teva Pharma is missed, administration should resume at the next scheduled time at the recommended dose. The individual daily doses of Nintedanib Teva Pharma should not be increased beyond the recommended dose to make up for missed doses. The recommended maximum daily dose of 400 mg should not be exceeded.

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

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

Dose adjustments
As initial measure for the management of adverse reactions (see Tables 1 and 2) treatment with Nintedanib Teva Pharma should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline).
Nintedanib Teva Pharma 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 Nintedanib Teva Pharma 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 ≥ 2 x ULN and alkaline phosphatase (ALKP) < 2 x ULN (see Table 2) treatment with Nintedanib Teva Pharma should be interrupted. Unless there is an alternative cause established, Nintedanib Teva Pharma should be permanently discontinued (see also section 4.4).

Table 1: Recommended dose adjustments for Nintedanib Teva Pharma in case of diarrhoea, vomiting and other non-haematological or haematological adverse reactions

CTCAE* Adverse reaction	Dose adjustment
Diarrhoea ≥ grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment ***OR*** Diarrhoea ≥ grade 3 despite anti-diarrhoeal treatment	After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.
Vomiting ≥ grade 2 ***AND/OR*** Nausea ≥ grade 3 despite anti-emetic treatment	
Other non-haematological or haematological adverse reaction of ≥ grade 3	

* CTCAE: Common Terminology Criteria for Adverse Events

Table 2: Recommended dose adjustments for Nintedanib Teva Pharma in case of AST and/or ALT and bilirubin elevations

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

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase
ALKP: Alkaline phosphatase; ULN: Upper limit normal

Special populations

Paediatric population
The safety and efficacy of nintedanib in children aged 0-18 years have not been established.

Elderly patients (≥ 65 years)
No overall differences in safety and efficacy were observed for elderly patients.
In the pivotal trial 1199.13, 85 patients (12.9 % of the patients with adenocarcinoma histology) were ≥ 70 years of age (median age: 72 years, range: 70 - 80 years) (see section 5.1).
No adjustment of the initial dosing is required in elderly patients (see section 5.2).

Race and body weight
Based on population pharmacokinetic (PK) analyses, no a priori dose adjustments of nintedanib are necessary (see section 5.2). Safety data for Black and African American patients are limited.

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). No adjustment of the starting dose is needed for patients with mild hepatic impairment (Child Pugh A) based on clinical data. Limited safety data available from 9 patients with moderate hepatic impairment (Child Pugh B) are insufficient to characterize this population. The safety, efficacy and pharmacokinetics of nintedanib have not been investigated in patients with severe hepatic impairment (Child Pugh C).
Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Nintedanib Teva Pharma is not recommended (see sections 4.4 and 5.2).

Method of administration
Nintedanib Teva Pharma capsules must be taken orally, preferably with food, swallowed whole with water, and must not be chewed. The capsule should not be opened or crushed (see section 6.6).

4.3 Contraindications

Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Gastrointestinal disorders
Diarrhoea was the most frequently reported gastro-intestinal adverse reaction and appeared in close temporal relationship with the administration of docetaxel (see section 4.8). In the clinical trial LUME-Lung 1 (see section 5.1), the majority of patients had mild to moderate diarrhoea.
Serious cases of diarrhoea leading to dehydration and electrolyte disturbances have been reported with nintedanib in the post-marketing period. Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, for example loperamide, and may require interruption, dose reduction or discontinuation of therapy with Nintedanib Teva Pharma (see section 4.2).

Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse reactions (see section 4.8). Interruption, dose reduction or discontinuation of therapy with nintedanib (see section 4.2) may be required despite appropriate supportive care. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration.

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. Interruption, dose reduction or discontinuation of therapy with [nintedanib may be required (see section 4.2).

Neutropenia and sepsis
A higher frequency of neutropenia of CTCAE grade ≥ 3 was observed in patients treated with nintedanib in combination with docetaxel as compared to treatment with docetaxel alone.
Subsequent complications such as sepsis or febrile neutropenia have been observed (including fatal cases).

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

Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see sections 4.2 and 5.2). Limited safety data are available in 9 patients with hepatocellular carcinoma and moderate hepatic impairment classified as Child Pugh B. Although no unexpected safety findings were reported in these patients, the data are insufficient to support a recommendation for treatment of patients with moderate hepatic impairment. The efficacy of nintedanib has not been investigated in patients with moderate hepatic impairment (Child Pugh B).
The safety, efficacy and pharmacokinetics of nintedanib have not been studied in patients with severe hepatic impairment (Child Pugh C). Treatment with nintedanib is not recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Cases of drug-induced liver injury have been observed with nintedanib treatment, including severe liver injury with fatal outcome. Elevation 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 before initiation of the combination treatment with nintedanib 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 nintedanib is continued as monotherapy after discontinuation of docetaxel.
If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with Nintedanib Teva Pharma may be required (see section 4.2). 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; total bilirubin ≥ 2 x ULN and ALKP < 2 x ULN) treatment with Nintedanib Teva Pharma should be interrupted. Unless there is an alternative cause established, Nintedanib Teva Pharma should be permanently discontinued (see section 4.2).

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 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 use (see section 4.8). Patients should be monitored during nintedanib 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

VEGFR inhibition might be associated with an increased risk of bleeding. In the clinical trial (LUME-Lung 1; see section 5.1) with nintedanib, the frequency of bleeding in both treatment arms was comparable (see section 4.8). Mild to moderate epistaxis represented the most frequent bleeding event. The majority of fatal bleeding events were tumour-associated. There were no imbalances of respiratory or fatal bleedings and no intracerebral bleeding was reported.

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

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 medicinal products that could cause bleeding (for clinical trials' data, see also 'Therapeutic anticoagulation' below). In case of bleeding, dose adjustment, interruption or discontinuation should be considered based on clinical judgement (see section 4.2). Post-marketing bleeding events include but are not limited to gastrointestinal, respiratory and central nervous system organs, with the most frequent being respiratory.

Therapeutic anticoagulation

There are no data available from clinical trials for patients with inherited predisposition to bleeding or for patients receiving a full dose of anticoagulative treatment prior to start of treatment with nintedanib (for post-marketing experience, see 'Haemorrhage' above). 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 nintedanib 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, international normalised ratio (INR), and clinical bleeding episodes.

Brain metastasis

Stable brain metastasis

No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for ≥ 4 weeks before start of treatment with nintedanib 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 nintedanib.

Venous thromboembolism

Patients treated with nintedanib have an increased risk of venous thromboembolism including pulmonary embolism and deep vein thrombosis. Patients should be closely monitored for thromboembolic events. Caution should be used especially in patients with additional risk factors for thromboembolic events. Nintedanib should be discontinued in patients with life-threatening venous thromboembolic reactions.

Arterial thromboembolic events

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

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, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal perforations and ischaemic colitis

The frequency of gastrointestinal perforation was comparable between the treatment arms in the clinical trial. However, based on the mechanism of action patients treated with nintedanib may have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations and ischaemic colitis, some of which were fatal, have been reported in the post-marketing period under nintedanib. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. Nintedanib should therefore only be initiated at least 4 weeks after major surgery. Therapy with nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation. In patients who develop ischaemic colitis nintedanib should be discontinued, and exceptionally, nintedanib can be reintroduced after complete resolution of ischaemic colitis and careful assessment of patient's condition and other risk factors.

Nephrotic range proteinuria

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

Posterior reversible encephalopathy syndrome (PRES)

Some cases of posterior reversible encephalopathy syndrome (PRES) have been reported post- marketing.
PRES is a neurological disorder (confirmed with magnetic resonance imaging) which can present with headache, hypertension, visual disturbances, seizure, lethargy, confusion and other visual and neurologic disturbances, and can be fatal. PRES has been reported with other VEGF inhibitors.

If PRES is suspected, nintedanib treatment must be discontinued. Reinitiating nintedanib therapy in patients previously experiencing PRES is not known and should be left to the physician's recommendation.

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 LUME-Lung 1 trial. No dedicated trials investigating the effect of nintedanib on wound healing were performed. Treatment with nintedanib should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing.

Effect on QT interval
No QT prolongation was observed for nintedanib in the clinical trial program (see section 5.1). As several other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administering nintedanib 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.
P-glycoprotein (P-gp)
Nintedanib is a substrate of P-gp (see section 5.2). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on Cmax 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 Cmax upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with nintedanib, 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 adverse reactions may require interruption, dose reduction, or discontinuation of therapy with nintedanib (see section 4.2).

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Co-administration with nintedanib should be carefully considered.

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

Co-administration with other medicinal products
Co-administration of nintedanib with docetaxel (75 mg/m^2) did not alter the pharmacokinetics of either medicinal product to a relevant extent.

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy

There is no information on the use of nintedanib in pregnant women, but preclinical studies in animals have shown reproductive toxicity of this active substance (see section 5.3). As nintedanib may cause foetal harm also in humans, it should not be used during pregnancy unless the clinical condition requires treatment. Pregnancy testing should be conducted at least prior to treatment with Nintedanib Teva Pharma. Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Nintedanib Teva Pharma.

If the patient becomes pregnant while receiving nintedanib, she should be apprised of the potential hazard to the foetus. Termination of the treatment with nintedanib should be considered.

Breast-feeding

There is no information on the excretion of nintedanib and its metabolites in human milk. Preclinical studies showed that small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) were secreted into milk of lactating rats. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with Nintedanib Teva Pharma.

Fertility

Based on preclinical investigations there is no evidence for impairment of male fertility (see section 5.3).
There are no human or animal data on potential effects of nintedanib on female fertility available.

4.7 Effects on ability to drive and use machines

Nintedanib 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.

4.8 Undesirable effects

Summary of the safety profile

The safety data provided in the sections below are based on the global, double-blind randomised pivotal phase 3 trial 1199.13 (LUME-Lung 1) comparing treatment with nintedanib plus docetaxel against placebo plus docetaxel in patients with locally advanced, or metastatic, or recurrent NSCLC after first-line chemotherapy and based on data observed during the post-marketing period. The most frequently reported adverse drug reactions (ADRs) 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). For the management of selected adverse reactions, see section 4.4. Information about selected adverse reactions observed from the LUME-Lung 1 trial are described below.

Tabulated list of adverse reactions

Table 3 summarizes the frequencies of adverse drug reactions that were reported in the pivotal trial LUME-Lung 1 for patients with NSCLC of adenocarcinoma tumour histology (n = 320) or from the post-marketing period. The following terms are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping adverse reactions are presented in order of decreased seriousness.

Table 3: Summary of ADRs per frequency category

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1,000 < 1/100)	Not known
Infections and infestations		Febrile neutropenia, Abscesses, Sepsis		
Blood and lymphatic system disorders	Neutropenia (includes febrile neutropenia)	Thrombocytopenia		
Metabolism and nutrition disorders	Decreased appetite, Electrolyte imbalance	Dehydration, Weight decreased		
Nervous system	Peripheral	Headache1)		Posterior reversible encephalopathy syndrome

disorders	neuropathy			
Cardiac disorders			Myocardial infarction (see section 4.4)	
Vascular disorders	Bleeding1) (see section 4.4)	Venous thromboembolism3), Hypertension		Aneurysms and artery dissections
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Abdominal pain		Perforation1) Pancreatitis2)	Colitis
Hepatobiliary disorders	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Blood alkaline phosphatase (ALKP) increased	Hyperbilirubinaemia, Gamma-glutamyltransferase (GGT) increased	Drug-induced liver injury	
Skin and subcutaneous tissue disorders	Mucositis (including stomatitis), Rash, Alopecia1)	Pruritus		
Renal and urinary disorders		Proteinuria1)	Renal failure (see section 4.4)	

1) In clinical trials the frequency was not increased in patients treated with nintedanib plus docetaxel as compared to placebo plus docetaxel.
2) 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.
3) Cases of pulmonary embolism have been reported.

Description of selected adverse reactions

Diarrhoea
Diarrhoea occurred in 43.4 % (≥ grade 3: 6.3 %) of adenocarcinoma patients in the nintedanib arm. The majority of adverse reactions appeared in close temporal relationship with the administration of docetaxel. Most patients recovered from diarrhoea following treatment interruption, anti-diarrhoeal therapy and nintedanib dose reduction.

For recommended measures and dosing adjustments in case of diarrhoea, see sections 4.4 and 4.2, respectively.

Liver enzyme elevations and hyperbilirubinaemia
Liver-related adverse reactions occurred in 42.8 % of nintedanib-treated patients. Approximately one third of these patients had liver-related adverse reactions of ≥ grade 3 severity. In patients with increased liver parameters, the use of the established stepwise dose reduction scheme was the appropriate measure and discontinuation of treatment was only necessary in 2.2 % of patients. In the majority of patients, elevations of liver parameters were reversible.

For information about special populations, recommended measures and dosing adjustments in case of liver enzyme and bilirubin elevations, see sections 4.4 and 4.2, respectively.

Neutropenia, febrile neutropenia and sepsis
Sepsis and febrile neutropenia have been reported as subsequent complications of neutropenia. The rates of sepsis (1.3 %) and febrile neutropenia (7.5 %) were increased under treatment with nintedanib as compared to the placebo arm. It is important

that the patient's blood counts are monitored during therapy, in particular during the combination treatment with docetaxel (see section 4.4).

Bleeding
In the post-marketing period non-serious and serious bleeding events, some of which fatal, have been reported, including patients with or without anticoagulant therapy or other medicinal products that could cause bleeding. Post-marketing bleeding events include but are not limited to gastrointestinal, respiratory and central nervous system organs, with the most frequent being respiratory (see also section 4.4).

Perforation
As expected via its mechanism of action perforation might occur in patients treated with nintedanib. However, the frequency of patients with gastrointestinal perforation was low.

Peripheral neuropathy
Peripheral neuropathy is also known to occur with docetaxel treatment. Peripheral neuropathy was reported in 16.5 % of patients in the placebo arm and in 19.1 % of patients in the nintedanib arm.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

There is no specific antidote or treatment for nintedanib overdose. The highest single dose of nintedanib administered in phase I studies was 450 mg once daily. In addition, 2 patients 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 case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX09

Mechanism of action
Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and ß) 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.

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 ≥ 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.

Clinical efficacy and safety

Efficacy in the pivotal phase 3 trial LUME-Lung 1

The efficacy and safety of nintedanib was investigated in 1314 adult patients with locally advanced, metastatic or recurrent NSCLC after one prior line of chemotherapy. `Locally recurrent´ was defined as local re-occurrence of the tumour without metastases at trial entry. The trial included 658 patients (50.1 %) with adenocarcinoma, 555 patients (42.2 %) with squamous cell carcinoma, and 101 patients (7.7 %) with other tumour histologies.

Patients were randomised (1:1) to receive nintedanib 200 mg orally twice daily in combination with 75 mg/m2 of intravenous docetaxel every 21 days (n = 655) or placebo orally twice daily in combination with 75 mg/m2 of docetaxel every 21 days (n = 659). Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 versus 1), bevacizumab pretreatment (yes versus no), brain metastasis (yes versus no) and tumour histology (squamous versus non-squamous tumour histology).

Patient characteristics were balanced between treatment arms within the overall population and within subgroups according to histology. 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. Five point eight percent (5.8 %) of the patients had stable brain metastasis at trial 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 trial 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 trial with locally recurrent disease stage as had been evaluated at baseline.

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.

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 (hazard ratio (HR) 0.79; 95 % confidence interval (CI): 0.68 - 0.92; p = 0.0019) as determined by the Independent Review Committee. 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 (Table 4).

As shown in Table 4, 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 trial endpoints such as disease control and change in tumour size showed significant improvements.

Table 4: Efficacy results for trial LUME-Lung 1 for patients with adenocarcinoma tumour histology

	Nintedanib + Docetaxel	Placebo + Docetaxel
Progression free survival (PFS)* - primary analysis		
Patients, n	277	285
Number of Deaths or Progressions, n (%)	152 (54.9)	180 (63.2)
Median PFS [months]	4.0	2.8
HR (95 % CI)	0.77 (0.62; 0.96)	
Stratified Log-Rank Test p-value**	0.0193	
Progression free survival (PFS)* - follow-up analysis**		
Patients, n	322	336
Number of Deaths or Progressions, n (%)	255 (79.2)	267 (79.5)
Median PFS [months]	4.2	2.8
HR (95 % CI)	0.84 (0.71; 1.00)	
Stratified Log-Rank Test p-value**	0.0485	
Disease control [%]	60.2	44.0
Odds ratio (95 % CI)+	1.93 (1.42; 2.64)	
p-value+	< 0.0001	
Objective response [%]	4.7	3.6
Odds ratio (95 % CI)+	1.32 (0.61; 2.93)	
p-value+	0.4770	
Tumour shrinkage [%]°	-7.76	-0.97
p-value°	0.0002	
Overall Survival (OS)* **		
Patients, n	322	336
Number of Deaths, n (%)	259 (80.4)	276 (82.1)
Median OS [months]	12.6	10.3
HR (95 % CI)	0.83 (0.70; 0.99)	
Stratified Log-Rank Test p-value*	0.0359	

HR: hazard ratio; CI: confidence interval

***** Primary PFS analysis performed when 713th PFS events had been observed based on IRC-assessment in the overall ITT population (332 events in adenocarcinoma patients).

****** Stratified by baseline ECOG PS (0 versus 1), brain metastases at baseline (yes versus no) and prior treatment with bevacizumab (yes versus no).

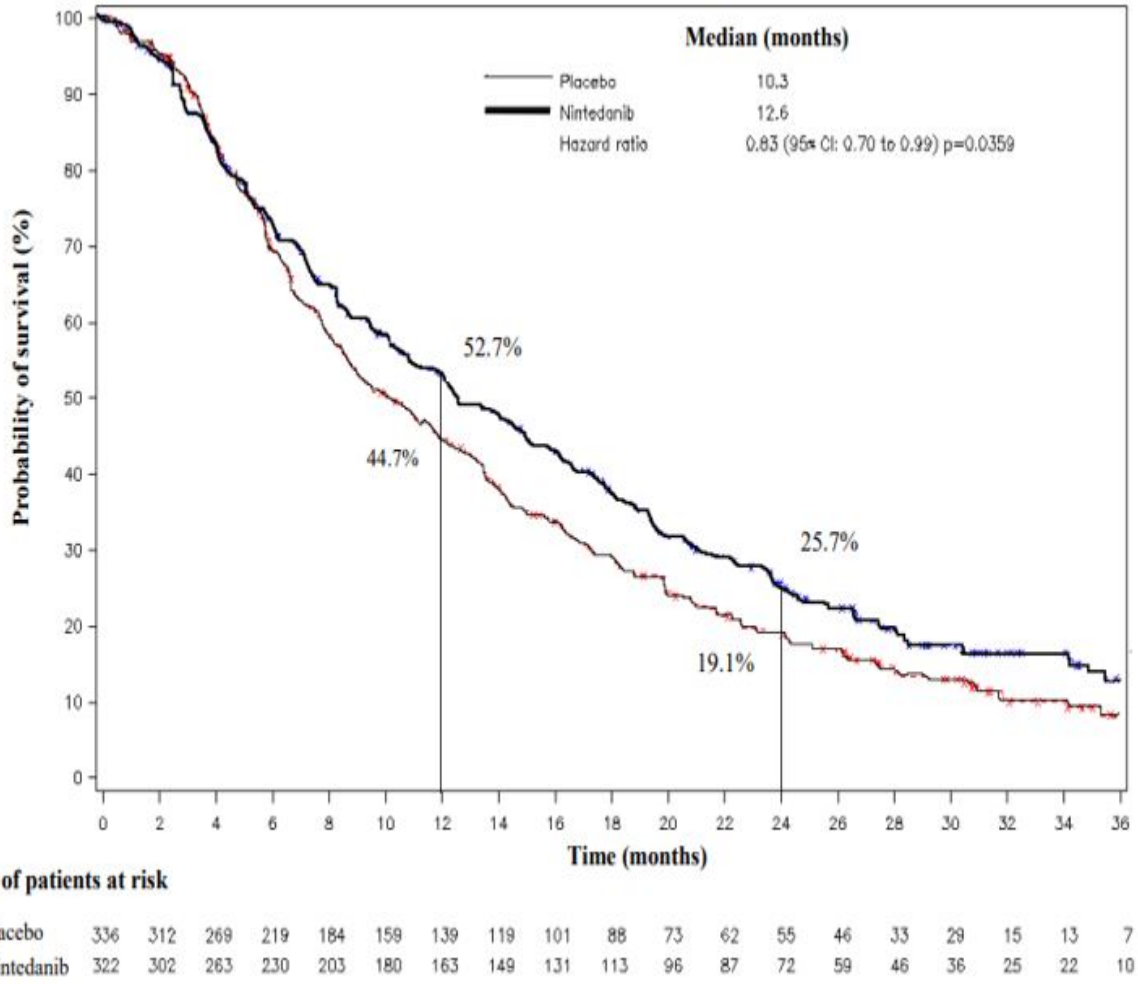
*** OS analysis and follow-up PFS-analysis performed when 1121 death cases had been observed in the overall ITT population (535 events in adenocarcinoma patients).

+ Odds ratio and p-value were obtained from a logistic regression model adjusted for baseline ECOG Performance Score (0 versus 1).

° Adjusted mean of best-% change from baseline and p-value generated from an ANOVA model adjusting for baseline ECOG PS (0 versus 1), brain metastases at baseline (yes versus no) and prior treatment with bevacizumab (yes versus no).

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 versus 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 trial with a particularly poor treatment prognosis, namely, patients who progressed during or shortly after first-line therapy prior to trial entry. This population included those adenocarcinoma patients identified at baseline as having progressed and entered the trial 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 trial ≥ 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.

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 trial comparing nintedanib monotherapy against sunitinib monotherapy in patients with renal cell carcinoma. In this trial 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 population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing nintedanib in all subsets of the paediatric population in non-small cell lung cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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. Nintedanib exposure increased dose-proportionally in the dose range of 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 tmax fasted: 2.00 hours; fed: 3.98 h).

In an in vitro study, mixing nintedanib capsules with a small amount of apple sauce or chocolate pudding for up to 15 minutes did not have any impact on the pharmaceutical quality. Swelling and deformation of the capsules due to the water uptake of the gelatin capsule shell was observed with longer exposure time to the soft food. Therefore, taking the capsules with soft food would not be expected to alter the clinical effect when taken immediately.

Distribution
Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (Vss: 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.

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 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). 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 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 [14C] 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 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 Cmax and 1.38-fold for AUCτ. Nintedanib trough concentrations remained stable for more than one year.

Other information on drug-drug interactions

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 in preclinical studies 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 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.

Pharmacokinetic/pharmacodynamic relationship(s)
In exploratory pharmacokinetic 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.

Population pharmocokinetic analysis in special populations
The pharmacokinetic properties of nintedanib were similar in healthy volunteers, cancer patients, and patients of the target population. Exposure to nintedanib was not influenced by gender (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), liver metastases, ECOG performance score, alcohol consumption, and P-gp genotype.

Population PK analyses indicated moderate effects on exposure to nintedanib depending on age, body weight, and race (see below). Based on the high inter-individual variability of exposure observed in the clinical LUME-Lung-1 trial these effects are not considered clinically relevant. However, close monitoring is recommended in patients with several of these risk factors (see section 4.4).

Age
Exposure to nintedanib increased linearly with age. AUCτ,ss decreased by 16 % for a 45-year old patient (5th percentile) and increased by 13 % for a 76-year old patient (95th percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population were older than 75 years.

Body weight
An inverse correlation between body weight and exposure to nintedanib was observed. AUCτ,ss increased by 25 % for a 50 kg patient (5th percentile) and decreased by 19 % for a 100 kg patient (95th percentile) relative to a patient with the median weight of 71.5 kg.

Race
The population mean exposure to nintedanib was 33 - 50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patients while it was 16 - 22 % lower in Koreans compared to Caucasians (body weight corrected). Based on the high inter-individual variability of exposure these effects are not considered clinically relevant. Data from black individuals was very limited but in the same range as for Caucasians.

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

Concomitant treatment with oral hormonal contraceptives
In a dedicated pharmacokinetic study, female patients with SSc-ILD received a single dose of a combination of 30 µg ethinylestradiol and 150 µg levonorgestrel before and after twice daily dosing of 150 mg nintedanib for at least 10 days. The adjusted geometric mean ratios (90% confidence interval (CI)) were 117% (108% – 127%; Cmax) and 101% (93% – 111%; AUC0–tz) for ethinylestradiol and 101% (90% – 113%; Cmax) and 96% (91% – 102%; AUC0–tz) for levonorgestrel, respectively (n=15), indicating that co-administration of nintedanib has no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel.

5.3 Preclinical safety data

General toxicology
Single dose toxicity studies in rats and mice indicated a low acute toxic potential of nintedanib. In repeat dose toxicology studies in rats, adverse effects (e.g. thickening of epiphyseal plates, lesions of the incisors) were mostly related to the

mechanism of action (i.e. VEGFR-2 inhibition) of nintedanib. These changes are known from other VEGFR-2 inhibitors and can be considered class effects.

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

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

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

In rats, embryofoetal lethality and teratogenic effects were observed at exposure levels below human exposure, at the maximum recommended human dose (MRHD) of 200 mg b.i.d. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryofoetal lethality was observed at an exposure approximately 8 times higher than at the MRHD. Teratogenic effects on the aortic arches in combination with the heart and the urogenital system were noted at an exposure 4 times higher than at the MRHD and on the embryofoetal development of the axial skeleton at an exposure 3 times higher than at the MRHD

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5 % of the administered dose).
Genotoxicity studies indicated no mutagenic potential for nintedanib.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Medium-chain triglycerides
Lauroyl macrogolglycerides
Lecithin, soya bean (E322)

Capsule shell:
Gelatin
Glycerol(E422)
Titanium Dioxide (E171)
Iron oxide red (E172)
Lecithin, soya bean (E322)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PCTFE/PVC//Alu perforated unit-dose blisters containing 30 x 1, 60 x 1 or 120 x 1 capsules.
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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

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10 DATE OF REVISION OF THE TEXT