NINTABID* 100

Nintedanib soft Gelatin Capsules 100 mg

NINTABID* 150

Nintedanib soft Gelatin Capsules 150 mg

COMPOSITION

Nintedanib Soft Gelatin Capsules 100 mg
Each Soft Gelatin Capsule Contains:
Nintedanib Ethanesulfonate.....120.4 mg
Equivalent to Nintedanib.....100 mg
Excipients.....q.s.
Approved Colours Used in Capsule Shells

COMPOSITION

Nintedanib Soft Gelatin Capsules 150 mg
Each Soft Gelatin Capsule Contains:
Nintedanib Ethanesulfonate.....180.6 mg
Equivalent to Nintedanib.....150 mg
Excipients.....q.s.
Approved Colours Used in Capsule Shells

PHARMACEUTICAL FORM

Soft gelatin capsule

CLINICAL PARTICULARS

Therapeutic indication

Nintedanib soft Gelatin Capsules are indicated in treatment of Idiopathic Pulmonary Fibrosis (IPF).

Nintedanib soft Gelatin Capsules are 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 tumor histology after first line chemotherapy.

Posology and method of administration

Recommended Dosage for IPF

The recommended dosage of Nintedanib Capsules is 150 mg twice daily administered approximately 12 hours apart.

Nintedanib capsules should be taken with food and swallowed whole with liquid. Nintedanib capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of Nintedanib is not known.

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

Recommended Dosage for Treatment of Adult Patients with Locally Advanced, Metastatic or Recurrent NSCLC of Adenocarcinoma Tumour Histology

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

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

Nintedanib Capsules must not be taken on the same day of docetaxel chemotherapy administration (= day 1). The recommended maximum daily dose of 400 mg should not be exceeded. Patients may continue therapy with Nintedanib Capsules after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dosage Modification in IPF due to Adverse Drug Reactions

In addition to symptomatic treatment, if applicable, the management of adverse drug reactions of Nintedanib Capsules may require dose reduction or temporary interruption until the specific adverse drug reaction resolves to levels that allow continuation of therapy. Nintedanib Capsules treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with Nintedanib Capsules.

If diarrhoea, nausea and/or vomiting persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe diarrhoea, nausea and/or vomiting despite symptomatic treatment, therapy with Nintedanib should be discontinued.

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN), once transaminases have returned to baseline values, treatment with Nintedanib may be reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (150 mg twice daily).

Dosage Modification for Treatment of Adult Patients with Locally Advanced, Metastatic or Recurrent NSCLC of Adenocarcinoma Tumour Histology

As initial measure for the management of adverse reactions (see Tables 1 and 2) treatment with Nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline). Nintedanib 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 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 should be interrupted. Unless there is an alternative cause established, Nintedanib should be permanently discontinued.

Table 1: Recommended dose adjustments for Nintedanib 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 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 should be permanently discontinued

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

ALKP: Alkaline phosphatase; ULN: Upper limit normal

Contraindications

Pregnancy, Hypersensitivity to Nintedanib, to peanut or soya, or to any of the excipients.

Special warnings and precautions for use

Gastrointestinal Disorders

Diarrhoea was the most frequent gastrointestinal adverse reaction reported in 62% versus 18% of patients treated with Nintedanib and placebo, respectively. In most patients, the adverse reaction was of mild-to-moderate intensity and occurred within the first 3 months of treatment. Patients should be treated at presentation/reporting of first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require treatment interruption or dose reduction if diarrhoea continues. Nintedanib treatment may be resumed at the full dose (150 mg twice daily) or at a reduced dose (100 mg twice daily), which subsequently may be increased to the full dosage. In case of persisting severe diarrhoea despite symptomatic treatment, therapy with Nintedanib should be discontinued.

Nausea and vomiting were frequently reported gastrointestinal adverse reactions. In most patients with nausea and vomiting, the event was of mild to moderate intensity. In clinical trials, nausea led to discontinuation of Nintedanib in up to 2.1% of patients and vomiting led to discontinuation of Nintedanib in up to 1.4% of 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 Nintedanib should be discontinued.

Hepatic function

The safety and efficacy of Nintedanib has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore, treatment with Nintedanib is not recommended in such patients. Based on increased exposure, the risk for adverse reactions may be increased in patients with mild hepatic impairment (Child Pugh A). Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of Nintedanib.

Cases of drug-induced liver injury have been observed with Nintedanib treatment, including severe liver injury with fatal outcome. The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated before treatment initiation and during the first month of treatment with Nintedanib. Patients should then be monitored at regular intervals during the subsequent two months of treatment and periodically thereafter, e.g. at each patient visit or as clinically indicated.

Elevations of liver enzymes (ALT, AST, blood alkaline phosphatase (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 ULN are measured, dose reduction or interruption of the therapy with Nintedanib is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Nintedanib may be resumed at 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. If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Nintedanib should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

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

Haemorrhage

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

Arterial thromboembolic events

Patients with a recent history of myocardial infarction or stroke were excluded from the clinical trials. In the clinical trials, arterial thromboembolic events were infrequently reported (Nintedanib 2.5% versus placebo 0.7% for INPULSIS; Nintedanib 0.9% versus placebo 0.9% for INBUILD; Nintedanib 0.7% versus placebo 0.7% for SENSCIS). In the INPULSIS trials, a higher percentage of patients experienced myocardial infarctions in the Nintedanib group (1.6%) compared to the placebo group (0.5%), while adverse events reflecting ischaemic heart disease were balanced between the Nintedanib and placebo groups. In the INBUILD trial, myocardial infarction was observed with low frequency: Nintedanib 0.9% versus placebo 0.9%. In the SENSCIS trial, myocardial infarction was observed with low frequency in the placebo group (0.7%) and not observed in the Nintedanib

group. Caution should be used when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischemia.

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.

Venous thromboembolism

In the clinical 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 and ischaemic colitis

In the clinical trials, the frequency of patients with perforation was up to 0.3% in both treatment groups. Due to the mechanism of action of Nintedanib, patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations and cases of ischaemic colitis, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. Nintedanib should only be initiated at least 4 weeks after abdominal surgery. Therapy with Nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation or ischaemic colitis. Exceptionally, Nintedanib can be reintroduced after complete resolution of ischaemic colitis and careful assessment of patient's condition and other risk factors.

Hypertension

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

Pulmonary hypertension

Data on the use of Nintedanib in patients with pulmonary hypertension is limited. Patients with significant pulmonary hypertension (cardiac index $\leq$ 2 L/min/m², or parenteral epoprostenol/treprostinil, or significant right heart failure) were excluded from the INBUILD and SENSCIS trials. Nintedanib should not be used in patients with severe pulmonary hypertension. Close monitoring is recommended in patients with mild to moderate pulmonary hypertension.

Wound healing complication

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

Co-administration with pirfenidone

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

Effect on QT interval

No evidence of QT prolongation was observed for Nintedanib in the clinical trial programme. As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when Nintedanib is administered 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.

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 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.

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. 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.

Drugs interactions

P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp. 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, erythromycin or cyclosporine) 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.

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

Cytochrome (CYP)-enzymes

Only a minor extent of the biotransformation of Nintedanib consisted of CYP pathways. Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies. 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 oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent.

Co-administration of Nintedanib with bosentan did not alter the pharmacokinetics of Nintedanib.

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

Use in Special Populations

Pregnancy and Lactation

Pregnancy

There is no information on the use of Nintedanib in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this active substance. As Nintedanib may cause foetal harm also in humans, it must not be used during pregnancy and pregnancy testing must be conducted prior to treatment with Nintedanib and during treatment as appropriate. Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Nintedanib. If the patient becomes pregnant while receiving Nintedanib, treatment must be discontinued and she should be apprised of the potential hazard to the foetus.

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. Breast-feeding should be discontinued during treatment with Nintedanib.

Patients with Renal impairment

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).

Patients with Hepatic impairment

In patients with mild hepatic impairment (Child-Pugh A), the recommended dose of Nintedanib is 100 mg twice daily. In patients with mild hepatic impairment (Child-Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered. Treatment of patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment with Nintedanib is not recommended.

No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child-Pugh A) for those undergoing treatment for non-small cell lung cancer (NSCLC.)

Paediatric population

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

Elderly patients ($\geq$ 65 years)

No overall differences in effectiveness were observed between subjects who were 65 years of age and older and younger subjects; no overall differences in safety were observed between subjects who were 65 years of age and older or 75 years of age and older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

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.

Undesirable effects

In IPF Patients

The most frequent serious adverse reactions reported in IPF patients treated with Nintedanib, more than placebo, were bronchitis (1.2% versus 0.8%) and myocardial infarction (1.5% versus 0.4%). The most common adverse events leading to death in patients treated with Nintedanib, more than placebo, were pneumonia (0.7% versus 0.6%), lung neoplasm malignant (0.3% versus 0%), and myocardial infarction (0.3% versus 0.2%). In the predefined category of major adverse cardiovascular events (MACE), including myocardial infarction, fatal events were reported in 0.6% of Nintedanib treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of Nintedanib-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with Nintedanib was diarrhoea (11%).

Adverse reactions leading to discontinuation were reported in 21% of Nintedanib-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in Nintedanib-treated patients were diarrhoea (5%), nausea (2%), and decreased appetite (2%).

The most common adverse reactions with an incidence $\geq$5% and more frequent in the Nintedanib group than the placebo treatment group are listed in Table 3.

Table 3: Adverse Reactions Occurring in $\geq$5% Nintedanib-treated Patients and more commonly than Placebo

Adverse Reaction	Nintedanib, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal paina	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevationb	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous systemic disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertensionc	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine amino-transferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with nintedanib, more than placebo (1.1% versus 0.6%). Alopecia was also reported in more patients treated with nintedanib than placebo (0.8% versus 0.4%).

Combination with Pirfenidone

Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to Nintedanib versus 27 (53%) patients treated with Nintedanib alone. Diarrhoea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%), and in 15 (28%) versus 7 (14%) patients treated with pirfenidone added to Nintedanib versus Nintedanib alone, respectively. More subjects reported AST or ALT elevations (≥3 x ULN) when using pirfenidone in combination with Nintedanib (n=3 (6%) compared with Nintedanib alone (n=0).

Post marketing Experience

The following adverse drug reactions have been identified during post-approval use of Nintedanib: drug-induced liver injury; non-serious and serious bleeding events, some of which were fatal; pancreatitis; thrombocytopenia; rash; and pruritus. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In non-small cell lung cancer (NSCLC)

The most frequently reported adverse drug reactions (ADRs) specific for Nintedanib were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting. Table 4 provides a summary of the adverse reactions by System Organ Class (SOC).

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 4: 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)	Thrombo-cytopenia		
Metabolism and nutrition disorders	Decreased appetite, Electrolyte imbalance	Dehydration, Weight decreased		
Nervous system disorders	Peripheral neuropathy	Headache[1)]		
Cardiac disorders			Myocardial infarction	
Vascular disorders	Bleeding1)	Venous thrombo-embolism[3)], Hypertension		Aneurysms and artery dissections
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Abdominal pain		Perforation[1)] Pancreatitis[2)]	Colitis
Hepatobiliary disorders	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Blood alkaline phosphatase (ALKP) increased	Hyperbiliru-binaemia, Gamma-glutamyl-transferase (GGT) increased	Drug-induced liver injury	
Skin and subcutaneous tissue disorders	Mucositis (including stomatitis), Rash, Alopecia[1)]	Pruritus		
Renal and urinary disorders			Renal failure	

[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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

Overdose

In the IPF trials, 1 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. Overdose was also reported in 2 patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of Nintedanib. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors

Mechanism of action

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. In addition, nintedanib inhibits Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn), Src (proto-oncogene tyrosine-protein kinase src), and CSF1R (colony stimulating factor 1 receptor) kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases.

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.

Pharmacokinetic properties

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 h after oral administration as soft gelatine capsule under fed conditions (range 0.5 - 8 h). The absolute bioavailability of a 100 mg dose was 4.69% (90% CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. Dose proportionality was shown by increase of Nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

After food intake, Nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (CI: 95.3 - 152.5%) and absorption was delayed (median tmax fasted: 2.00 h; fed: 3.98 h).

Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (Vss: 1,050 L, 45.0% gCV) was observed.

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

Biotransformation

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

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

Elimination

Total plasma clearance after intravenous infusion was high (CL: 1,390 mL/min, 28.8% gCV). Urinary excretion of the unchanged active substance within 48 h was about 0.05% of the dose (31.5% gCV) after oral and about 1.4% of the dose (24.2% gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6% gCV). The major route of elimination of 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%).

Population pharmacokinetic analysis in special populations

The PK properties of Nintedanib were similar in healthy volunteers, patients with IPF, patients with other chronic fibrosing ILDs with a progressive phenotype, patients with SSc-ILD, and cancer patients. Based on results of a population PK (PopPK) analysis in patients with IPF and non-small cell lung cancer (NSCLC) (N=1,191) and descriptive investigations, exposure to Nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), alcohol consumption, or P-gp genotype. PopPK analyses indicated moderate effects on exposure to Nintedanib depending on age, body weight, and race (see below). Based on the high inter-individual variability of exposure observed moderate effects are considered not clinically relevant.

Age

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

Studies in paediatric populations have not been performed.

Body weight

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

Hepatic impairment

In a dedicated single dose phase I study and compared to healthy subjects, exposure to Nintedanib based on C_{max} and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for 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 C_{max} (90% CI 4.4 – 13.2) and 8.7-fold higher (90% CI 5.7 – 13.1) based on AUC, respectively, compared to healthy volunteers. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Nonclinical properties

Animal Toxicology or Pharmacology

General toxicology

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

Diarrhoea and vomiting accompanied by reduced food consumption and loss of body weight were observed in toxicity studies in non-rodents There was no evidence of liver enzyme increases in rats, dogs, and cynomolgus monkeys. Mild liver enzyme increases, which were not due to serious adverse effects such as diarrhoea were only observed in rhesus monkeys.

Reproduction toxicity

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

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

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

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

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

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

Genotoxicity studies indicated no mutagenic potential for nintedanib.

DESCRIPTION

Nintedanib is presented as the ethanesulfonate salt (esylate), with the chemical name 1H-Indole-6-carboxylic acid, 2,3 dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino] phenylmethylene]-2-oxo-, methyl ester, (3Z)-, ethanesulfonate (1:1).

Incompatibilities

Not applicable.

Shelf Life:

Please see manufacturing date and expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

Packaging information:

Blister of 10 Capsule.

Storage and handing instructions:

Store below 25°C, excursion permitted from 15°C to 30°C.

Protect from light and moisture.

Marketed by :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

DATE OF REVISION

October 2021

Note: This prescribing information is applicable for India Market only.