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

**PRESENTATION**
Ninteda 100mg Capsule available in blister pack of 6x10's & 3x10's
Ninteda 150mg Capsule available in blister pack of 3x10's & 6x10's

**Dosage:**
As directed by the physician.

**INSTRUCTIONS:**
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک :
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات :
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔ (درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.

**Manufactured by:**
**Kaizen Pharmaceuticals (Pvt.) Ltd.**
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

**ART No. 1627**



# Ninteda

(Nintedanib)

نِنٹیڈا

(نِنٹیڈ انب)

**100mg & 150mg Capsules**

۱۰۰ ملی گرام کیپسولز اور ۱۵۰ ملی گرام کیپسولز

**COMPOSITION:**
**Ninteda Capsule 100mg**
Each soft gelatin capsule contains:
Nintedanib Ethanesulfonate 120.40mg Eq. to Nintedanib..... 100mg

**Ninteda Capsule 150mg**
Each soft gelatin capsule contains:
Nintedanib Ethanesulfonate 180.60mg Eq. to Nintedanib..... 150mg

**CLINICAL PHARMACOLOGY**
**PHARMACODYNAMICS**
**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.

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

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**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%).

**SPECIAL POPULATION**
**Elderly patients (≥ 65 years)**
No overall differences in safety and efficacy were observed for elderly patients. No a-priori dose adjustment is required in elderly patients. Patients ≥ 75 years may be more likely to require dose reduction to manage adverse effects.

**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).

**Hepatic impairment**
In adult patients with mild hepatic impairment (Child Pugh A), the recommended dose of Nintedanib is 100 mg twice daily approximately 12 hours apart. In patients with mild hepatic impairment (Child Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered. The safety and efficacy of Nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Nintedanib is not recommended.

**Paediatric population**
Nintedanib should not be used in children

**THERAPEUTIC INDICATIONS**
Nintedanib soft capsules are indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).
Nintedanib soft capsules are also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
Nintedanib soft capsules are indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

**DOSAGE & ADMINISTRATION**
Treatment should be initiated by physicians experienced in the management of diseases for which Nintedanib soft capsules is approved.

**Posology**
**Adults**
The recommended dose is 150 mg Nintedanib twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose.
If a dose is missed, administration should resume at the next scheduled time at the recommended dose. If a dose is missed the patient should not take an additional dose. The recommended maximum daily dose of 300 mg should not be exceeded.

**Dose adjustments**
In addition to symptomatic treatment if applicable, the management of adverse reactions to Nintedanib could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment may be resumed at the full dose (150 mg twice daily in adult patients) or a reduced dose (100 mg twice daily in adult patients). If an adult patient does not tolerate 100 mg twice daily, treatment with Nintedanib should be discontinued.
If diarrhea, 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 in adult patients) or at the full dose (150 mg twice daily in adult patients). In case of persisting severe diarrhea, 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 > 3× 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 in adult patients) which subsequently may be increased to the full dose (150 mg twice daily in adult patients).

**METHOD OF ADMINISTRATION**
For oral administration only.

**ADVERSE REACTIONS**
Most frequently reported adverse reactions associated with the use of Nintedanib included diarrhea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased.

**CONTRAINDICATIONS**
**Pregnancy**
Hypersensitivity to Nintedanib, or to any of the excipients.

**PRECAUTIONS**
**Gastrointestinal disorders**
**Diarrhea**
In most patients, the adverse reaction was of mild to moderate intensity and occurred within the first 3 months of treatment.
Serious cases of diarrhea leading to dehydration and electrolyte disturbances have been reported. Patients should be treated at first signs with adequate hydration and anti-diarrheal medicinal products, e.g., loperamide, and may require dose reduction or treatment interruption. Nintedanib treatment may be resumed at a reduced dose or at the full dose. In case of persisting severe diarrhea despite symptomatic treatment, therapy with Nintedanib should be discontinued.

**Nausea and vomiting**
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 or at the full dose. 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). Adult 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), see section 4.8) and bilirubin were reversible upon dose reduction or interruption in the majority of cases. If transaminase (AST or ALT) elevations > 3× 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 or reintroduced at a reduced dose which subsequently may be

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increased to the full dose (see section 4.2 Dose adjustments). 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.
Adult patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations of liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations (see section 5.2). Close monitoring is recommended in patients with these risk factors.

**Renal function**
Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with 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.

**Hemorrhage**
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 in adult patients, 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 ischemic 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 ischemic colitis**
In the clinical trials in adult patients, 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 ischemic 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 ischemic colitis. Exceptionally, Nintedanib can be reintroduced after complete resolution of ischemic colitis and careful assessment of patient's condition and other risk factors.

**Nephrotic range proteinuria and thrombotic microangiopathy**
Very few cases of nephrotic range proteinuria with or without renal function impairment have been reported post-marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of the symptoms has been



observed after Nintedanib was discontinued, with residual proteinuria in some cases. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.
VEGF pathway inhibitors have been associated with thrombotic microangiopathy (TMA), including very few case reports for Nintedanib. If laboratory or clinical findings associated with TMA occur in a patient receiving Nintedanib, treatment with Nintedanib should be discontinued and thorough evaluation for TMA should be completed.

**Hypertension**
Administration of 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 ≤ 2 L/min/$m^2$, 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 Nintedanib 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 (Section 5.1). 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.

**DRUG INTERACTIONS**
**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, 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