NINTESUN
(Nintedanib soft gelatin capsules 100 mg and 150 mg)

1. NAME OF THE MEDICINAL PRODUCT

NINTESUN 100 (Nintedanib Soft Gelatin Capsule 100 mg)
NINTESUN 150 (Nintedanib Soft Gelatin Capsule 150 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nintedanib soft gelatin capsules 100mg contains Nintedanib Esylate equivalent to 100 mg
Nintedanib soft gelatin capsule 150mg contains Nintedanib Esylate equivalent to 150 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NINTESUN 100: Oblong peach soft gelatin capsules imprinted with "S105" in black ink and filled with yellow colored oily suspension

NINTESUN 150: Oblong brown soft gelatin capsules imprinted with "S106" in black ink and filled with yellow colored oily suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

NINTESUN is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

NINTESUN is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of conditions for which nintedanib is indicated.

Posology
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 effects 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) or a reduced dose (100 mg twice daily). If a patient does not tolerate 100 mg twice daily, treatment 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).

Special populations

Elderly patients (≥ 65 years)

No overall differences in safety and efficacy has been reported for elderly patients. No *a-priori* dose adjustment is required on the basis of a patient's age. Patients ≥75 years may be more likely to require dose reduction to manage adverse effects.

Renal impairment

Less than 1 % of a single dose of nintedanib is reported to be excreted via the kidney. 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 reported to be studied in patients with severe renal impairment (<30 ml/min CrCL).

Hepatic Impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B). In 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 reported 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

Treatment of paediatric patients with nintedanib for fibrosing Interstitial Lung Diseases (ILDs) is not registered.

Method of administration

Nintedanib is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed.

The capsules may be taken with a small amount (teaspoonful) of cold or room temperature soft food, such as apple sauce or chocolate pudding, and must be swallowed unchewed immediately, to ensure the capsule stays intact.

The capsule should not be opened or crushed. If contact with the content of the capsule occurs, hands should be washed immediately and thoroughly.

4.3 Contraindications

- Pregnancy
- Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients listed in this product.

4.4 Special warnings and precautions for use

Gastrointestinal disorders

Diarrhoea

The most frequent gastro-intestinal event reported with nintedanib is diarrhoea. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment.

Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require dose reduction or treatment interruption. Nintedanib treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with 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.

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.

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

Hepatic Function
The safety and efficacy of nintedanib has not been reported to be 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 events may be increased in patients with mild hepatic impairment (Child Pugh A). Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of nintedanib.

Cases of drug-induced liver injury have been reported with nintedanib treatment. Non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome have been reported. The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be observed upon initiation of treatment with nintedanib, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Elevations of liver enzymes (ALT, AST, 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 (<65kg), Asian and female patients have been reported to 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.

Close monitoring is recommended in patients with these risk factors.

Haemorrhage
Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding.

Cases of haemorrhage have been reported in post-marketing period (including patients with or without anticoagulant therapy or other drugs that could cause bleeding). Therefore these patients should only be treated with nintedanib if the anticipated benefit outweighs the potential risk. In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been reported.

Arterial thromboembolic events
Use caution 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
No increased risk of venous thromboembolism have been reported 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
Due to the mechanism of action of nintedanib, patients might have an increased risk of gastrointestinal perforation. 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.

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 reported after nintedanib was discontinued. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.

Wound healing complication
No increased frequency of impaired wound healing has been reported. Based on the mechanism of action nintedanib may impair wound healing. No dedicated studies reported 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
The benefit/risk of the co-administration of nintedanib with pirfenidone has not been established.

Effect on QT interval
No evidence of QT prolongation have been reported for nintedanib. As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered 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.

4.5 Interaction with other medicinal products and other forms of interaction

P-glycoprotein (P-gp)
Nintedanib is a substrate of P-gp. Co-administration with the potent P-gp inhibitor ketoconazole has been reported to increase exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on Cmax.

Exposure to nintedanib has been reported to decrease 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 Pgp 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, have been reported did not inhibit or induce CYP enzymes. 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 bosentan did not alter the pharmacokinetics of nintedanib.

Co-administration of nintedanib with oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no information on the use of nintedanib in pregnant women, but reproductive toxicity of this active substance has been reported in animals. As nintedanib may cause foetal harm also in humans, it must not be applied 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 the patient should be apprised of the potential hazard to the foetus.

Lactation
There is no information reported on the excretion of nintedanib and its metabolites in human milk.
Small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) have been reported to be secreted into milk of lactating rats. A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with nintedanib.

Women of childbearing potential / Contraception
Nintedanib may cause foetal harm in humans. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with nintedanib and to use highly effective contraceptive methods at the initiation of, during and at least 3 months after the last dose of nintedanib. Nintedanib does not relevantly affect the plasma exposure of ethinylestradiol and levonorgestrel. 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.

Fertility
There is no evidence for impairment of male fertility also, there is no evidence that female fertility in animal is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 150 mg twice daily.

4.7 Effects on ability to drive and use machines

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

For the management of selected adverse reactions see section 4.4.

Tabulated list of adverse reactions
The below table provides a summary of the adverse reactions reported with nintedanib by MedDRA System Organ Class (SOC) and frequency category.

Table: Summary of ADRs per frequency category

MedDRA System Organ Class terminology	***Nintedanib adverse reactions***	***Frequency category***		
		Idiopathic Pulmonary Fibrosis	***Other chronic fibrosing ILDs with a progressive phenotype***	***SSc-ILD***
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon	Uncommon	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Common	Very common	Common
	Weight decreased	Common	Common	Common
Vascular disorders	Hypertension	Uncommon	Common	Common
	Bleeding[1, 2]	Common	Common	Common
	Aneurysms and artery dissections	Not known	Not known	Not known
Gastrointestinal disorders	Diarrhoea	Very common	Very common	Very common
	Nausea	Very common	Very common	Very common
	Abdominal pain	Very common	Very common	Very common
	Vomiting	Common	Very common	Very common
	Pancreatitis	Uncommon	Uncommon	Not known
Hepatobiliary disorders	Drug-induced liver injury	Uncommon	Common	Uncommon
	Hepatic enzyme increased	Very common	Very common	Very common
	Alanine aminotransferase increased	Common	Very common	Common
	Aspartate aminotransferase increased	Common	Common	Common
	Gamma-glutamyltransferase increased	Common	Common	Common

	Blood alkaline Phosphatase increased	Uncommon	Common	Common
	Hyperbilirubinaemia	Uncommon	Uncommon	Not known
Skin and subcutaneous tissue disorders	Rash	Common	Common	Uncommon
	Pruritus	Uncommon	Uncommon	Uncommon
	Alopecia	Uncommon	Uncommon	Not known
Nervous system disorders	Headache	Common	Common	Common
Renal and urinary disorder	Proteinuria	Uncommon	Uncommon	Not known

1) Term represents a group of events that describe a broader medical concept rather than a single condition or MedDRA preferred term.
2) Non-serious and serious bleeding events, some of which were fatal, have been reported in the post-marketing period

Description of selected adverse reactions

Diarrhoea

Diarrhoea was reported in 62.4% of patients treated with nintedanib. The event was reported to be of severe intensity in 3.3% of nintedanib treated patients. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. Diarrhoea led to permanent treatment discontinuation in 4.4% of patients; otherwise the events were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption.

Hepatic enzyme increased

Liver enzyme elevations were reported in 13.6% of nintedanib treated patients. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease. For further information about special populations, recommended measures and dosing adjustments in reported case of diarrhoea and hepatic enzyme increased, refer additionally to sections 4.4 and 4.2, respectively.

4.9 Overdose

There is no specific antidote or treatment for nintedanib overdose. An overdose of maximum 600 mg twice daily up to eight days has been reported in two patients. 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. One patient has been reported to be inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) reported and resolved during the period of incorrect dosing, with no onset of other reported events. In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein-tyrosine kinase inhibitor.
ATC code: L01EX09.

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 vascular endothelial growth factor receptor (VEGFR) 1-3. In addition, nintedanib inhibits Lck, Lyn, Src, and CSF1R kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in interstitial lung diseases.

Pharmacodynamic effects

Nintedanib has been reported to inhibit processes assumed to be involved in the initiation of the fibrotic pathogenesis, the release of pro-fibrotic mediators from peripheral blood monocytic cells and macrophage polarisation to alternatively activated macrophages. Nintedanib has been reported to inhibit fundamental processes in organ fibrosis, proliferation and

migration of fibroblasts and transformation to the active myofibroblast phenotype and secretion of extracellular matrix. Nintedanib has been reported to have anti-inflammatory effects and anti-fibrotic effects in the lung, skin, heart, kidney, and liver. Nintedanib also exerted vascular activity. It reduced dermal microvascular endothelial cell apoptosis and attenuated pulmonary vascular remodelling by reducing the proliferation of vascular smooth muscle cells, the thickness of pulmonary vessel walls and percentage of occluded pulmonary vessels.

5.2 Pharmacokinetic properties

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Absorption

Nintedanib has been reported to reach 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 has been reported as 4.69 % (90 % CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability have been reported to be decreased by transporter effects and substantial first-pass metabolism.

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

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

Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (V_{ss}: 1,050 L, 45.0 % gCV) have been reported.

Protein binding of nintedanib in human plasma has been reported to be high, with a bound fraction of 97.8 %. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869.

Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by 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 has not been reported in human plasma. *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, 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 has been reported to be high (CL: 1,390 mL/min, 28.8 % gCV). Urinary excretion of unchanged active substance within 48 h has been reported to be 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 [^{14}C] nintedanib has been reported to be via faecal/biliary excretion (93.4 % of dose, 2.61 % gCV). The contribution of renal excretion to the total clearance was reported to be low (0.649 % of dose, 26.3 % gCV). The overall recovery has been reported to be considered complete (above 90 %) within 4 days after dosing. The terminal half-life of nintedanib has been reported to be between 10 and 15 h (gCV % approximately 50%).

Linearity/non-linearity

The pharmacokinetics (PK) of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). Accumulation upon multiple administrations has been reported to be 1.04-fold for C_{max} and 1.38-fold for AUC_{τ}. Nintedanib trough concentrations remained stable for more than one year.

Transport

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

Exposure-response relationship

Exposure–response analyses of patients with IPF, other chronic fibrosing ILDs with a progressive phenotype and SSc-ILD indicated an E_{max}-like relationship between exposure and the annual rate of decline in FVC with an EC_{50} of around 3 ng/mL (relative standard error: around 55%). For comparison, median reported nintedanib trough concentrations for 150 mg bid nintedanib were about 10 ng/mL.

With respect to safety, there seemed to be a weak relationship between nintedanib plasma exposure and ALT and/or AST elevations. Actual administered dose might be the better predictor for the risk of developing diarrhea of any intensity, even if plasma exposure as risk determining factor could not be ruled out.

Pharmacokinetics in special patient groups

The PK properties of nintedanib have been reported to be similar in healthy volunteers, patients with IPF, patients with other chronic fibrosing ILDs with a progressive phenotype, patients with SSc-ILD, and cancer patients. Exposure to nintedanib has been reported to not be influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), liver metastases, ECOG performance score, alcohol consumption, or P-gp genotype.

Moderate effects on exposure to nintedanib depending on age, body weight, and race has been reported (see below). These effects have not been reported to be clinically relevant.

Age

Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ was reported to decrease 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. An increase in nintedanib exposure of approximately 20 - 25% has been reported in patients ≥ 75 years compared with patients under 65 years.

Body weight

An inverse correlation between body weight and exposure to nintedanib has been reported. $AUC_{\tau,ss}$ was reported to be 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.

Race

The population mean exposure to nintedanib has been reported to be 33-50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patient while it has been reported to be 16- 22 % lower in Koreans compared to Caucasians (body weight corrected). Very limited data from Black individuals has been reported but in the same range as for Caucasians.

Hepatic impairment

Exposure to nintedanib based on C_{max} and AUC has been reported to be 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for C_{max} and 1.2 – 3.8 for AUC, respectively). In moderate hepatic impairment (Child Pugh B), exposure was reported to be 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 reported.

Concomitant treatment with pirfenidone

No evidence of a relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone has been reported when administered in combination.

Concomitant treatment with bosentan
Co-administration of nintedanib with bosentan has not reported to alter the pharmacokinetics of nintedanib.

Concomitant treatment with oral hormonal contraceptives
Co-administration of nintedanib has been reported to have no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium-chain Triglycerides (Miglyol 812 N), Lecithin (Topcithin SB), Lauroyl polyoxyl-6 glycerides (Labrafil M 2130 CS), Gelatin Type B (160 Bloom), Glycerin (99.7%,Optim), Titanium Dioxide, Ferric Oxide (Yellow), Ferric Oxide (Red), Purified water, Isopropyl Alcohol, Opacode Black S-1-17823.

Opacode Black S-1-17823 is a ready-made printing liquid containing Shellac glaze, Isopropyl alcohol, Iron Oxide Black, N-butyl alcohol, Propylene Glycol and Ammonium Hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.5 Nature and contents of container

NINTESUN 100 and NINTESUN 150 is available as 10 Capsules Blister of Cold form laminate and Aluminum foil. Such 1 blister is packed in Show box along with Pack Insert

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Sun Pharmaceutical Industries Ltd.
Halol-Baroda Highway,
Halol - 389350, Dist. Panchmahal,
Gujarat, INDIA

Date of Revision:
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