Nindanix
Nintedanib

COMPOSITIONS

Nindanix 100 Capsule : Each capsule contains Nintedanib Esylate INN equivalent to Nintedanib 100 mg.

Nindanix 150 Capsule: Each capsule contains Nintedanib Esylate INN equivalent to Nintedanib 150 mg.

THERAPEUTIC CLASS: Anti Cancer

CLINICAL PHARMACOLOGY

Mechanism of Action

In NSCLC

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and ß) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling which is crucial for the

proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smoothmuscle cells). In addition, Fms-like tyrosine-protein kinase (Flt)-3, lymphocyte-specific tyrosine-protein kinase (Lck) and proto-oncogene tyrosine-protein kinase Src (Src) are inhibited.

In Idiopathic Pulmonary Fibrosis

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology. In addition, Nintedanib inhibits the following nRTKs: Lck, Lyn and Src kinases. The contribution of FLT3 and nRTK inhibition to IPF efficacy is unknown.

Pharmacodynamics

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.

Cardiac Electrophysiology

In a study in renal cell cancer patients, QT/QTc measurements were recorded and showed that a single oral dose of 200 mg Nintedanib as well as multiple oral doses of 200 mg Nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

Pharmacokinetics

The PK properties of Nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients. The PK of Nintedanib is linear. Dose proportionality was shown by an increase of Nintedanib exposure with increasing doses (dose range 50 to 450 mg once daily and 150 to 300 mg twice daily). Accumulation upon multiple administrations in patients with IPF was 1.76-fold for AUC. Steady-state plasma concentrations were achieved within one week of dosing. Nintedanib through concentrations remained stable for more than one year. The inter-individual variability in the PK of Nintedanib was moderate to high (coefficient of variation of standard PK parameters in the range of 30% to 70%), intra-individual variability low to moderate (coefficients of variation below 40%).

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as a capsule under fed conditions. The absolute bioavailability of a 100 mg dose was 4.7% (90% CI: 3.62 to 6.08) 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 (90% CI: 95.3% to 152.5%) and absorption was delayed (median tmax fasted: 2.00 hours; fed: 3.98 hours), irrespective of the food type.

Distribution

Nintedanib follows bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution which was larger than total body volume (Vss: 1050 L) 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 0.87.

Biotransformation

The prevalent metabolic reaction for Nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biotransformation of Nintedanib consisted of CYP pathways with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected

in plasma in the human ADME study. In vitro, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage. In preclinical in vivo experiments, BIBF 1202 did not show efficacy despite its activity at target receptors of the substance.

Elimination

Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV). Urinary excretion of the unchanged active substance within 48 h was about 0.05 % of the dose (31.5 % gCV) after oral and about 1.4 % of dose (24.2 % gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6 % gCV). The major route of elimination of drug related radioactivity after oral administration of [14C] Nintedanib was via faecal/biliary excretion (93.4 % of dose, 2.61 % gCV). The contribution of renal excretion to the total clearance was low (0.649 % of dose, 26.3 % gCV). The overall recovery was considered complete (above 90 %) within 4 days after dosing. The terminal half-life of Nintedanib was between 10 and 15 h (gCV % approximately 50 %)

The effective half-life of Nintedanib in patients with IPF was 9.5 hours (gCV 31.9%). Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min; gCV 28.8%). Urinary excretion of unchanged drug within 48 hours was about 0.05% of the dose after oral and about 1.4% of the dose after intravenous administration; the renal clearance was 20 mL/min.

INDICATIONS

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

DOSAGE AND ADMINISTRATION

In NSCLC

The recommended dose of Nintedanib is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21-day Docetaxel treatment cycle. It must not be taken on the same day of Docetaxel chemotherapy administration (= day 1).

If a dose of Nintedanib is missed, administration should resume at the next scheduled time at the recommended dose. The individual daily doses of Nintedanib should not be increased beyond the recommended dose to make up for missed doses. The recommended maximum daily dose of 400 mg should not be exceeded.

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

In IPF

Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food.

Recommended dosage in patients with mild hepatic impairment (Child Pugh A): 100 mg twice daily approximately 12 hours apart taken with food.

Consider temporary dose reduction to 100 mg, treatment interruption, or discontinuation for management of adverse reactions.

Prior to treatment initiation, conduct liver function tests and a pregnancy test.

If a dose of Nintedanib is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg.

CONTRAINDICATIONS

None

WARNING AND PRECAUTIONS

Hepatic impairment: Nintedanib is not recommended for use in patients with moderate or severe hepatic impairment. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage is 100 mg twice daily approximately 12 hours apart taken with food. Consider treatment interruption, or discontinuation for management of adverse reactions in these patients.

Elevated liver enzymes and drug-induced liver injury: ALT, AST, and bilirubin elevations have occurred with Nintedanib, including cases of drug induced liver injury. In the post-marketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. Monitor ALT, AST, and bilirubin prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Temporary dosage reductions or discontinuations may be required.

Gastrointestinal disorders: Diarrhea, nausea, and vomiting have occurred with Nintedanib. Treat patients at first signs with adequate hydration and antidiarrheal medicine (e.g., loperamide) or anti-emetics. Discontinue Nintedanib if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment.

Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease.

Bleeding events have been reported. Use Nintedanib in patients with known bleeding risk only if anticipated benefit outweighs the potential risk.

Gastrointestinal perforation has been reported. Use Nintedanib with caution when treating patients with recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue Nintedanib in patients who develop gastrointestinal perforation. Only use Nintedanib in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

SIDE EFFECTS

Very common side effects (may affect more than 1 in 10 people)

- Diarrhoea
- Painful, numb and/or tingling feeling in fingers and toes (peripheral neuropathy)
- Feeling sick (nausea)
- Throwing up (vomiting)
- Pain in the stomach (abdomen)
- Bleeding
- Decrease in the number of white blood cells (neutropenia)
- Inflammation of the mucous membranes lining the digestive tract including sores and ulcers in
- the mouth (mucositis, including stomatitis)
- Rash
- Decreased appetite
- Electrolyte imbalance
- Increased liver enzyme values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase) in the blood as seen from blood tests

Common side effects (may affect up to 1 in 10 people)

- Blood poisoning (sepsis) - please see above
- Decrease in the number of white blood cells accompanied by fever (febrile neutropenia)
- Blood clots in the veins (venous thromboembolism)
- High blood pressure (hypertension)
- Fluid loss (dehydration)
- Abscesses
- Low platelet count (thrombocytopenia)
- Jaundice (hyperbilirubinaemia)
- Increased liver enzyme values (gamma-glutamyltransferase) in the blood as seen from blood
- Tests
- Weight loss
- Itching

Uncommon side effects (may affect up to 1 in 100 people)

- Occurrence of holes in the wall of your gut (gastrointestinal perforation)
- Serious liver problems
- Inflammation of the pancreas (pancreatitis)
- Myocardial infarction
- Renal failure

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on findings from animal studies and its mechanism of action Nintedanib can cause fetal harm when administered to a pregnant woman. There are no data on the use of Nintedanib during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, Nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus.

Lactation

There is no information on the presence of Nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from Nintedanib, advise women that breastfeeding is not recommended during treatment with Nintedanib.

Pediatric Use

The safety and efficacy of Nintedanib in pediatric patients has not been established

Geriatric Use

Of the total number of subjects in phase 2 and 3 clinical studies of Nintedanib, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out

DRUG INTERACTIONS

P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, Ketoconazole, increased exposure to Nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., Erythromycin) with OFEV 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.

Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to Nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., Carbamazepine, Phenytoin, and St. John's wort) with Nintedanib should be avoided as these drugs may decrease exposure to Nintedanib.

Anticoagulants

Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

Pirfenidone

In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with Nintedanib and pirfenidone, the coadministration of Nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of Nintedanib with Pirfenidone.

Co-administration with other medicinal products

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

The potential for interactions of Nintedanib with hormonal contraceptives was not explored

OVERDOSAGE

There is no specific antidote or treatment for Nintedanib overdose. The highest single dose of Nintedanib administered in phase I studies was 450 mg once daily. In addition, 2 patients had an overdose of maximum 600 mg twice daily (b.i.d.) up to eight days. Observed adverse events were consistent with the known safety profile of Nintedanib, i.e. increased liver enzymes and gastrointestinal symptoms. Both patients recovered from these adverse reactions. In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

PHARMACEUTICAL INFORMATION

Storage condition

Store at below 30^{0}C and dry place, away from light and moisture. Keep out of the reach of children.

Packaging

Nindanix 100 Capsule: Each commercial box contains 80 Capsules of Nintedanib Esylate INN equivalent to Nintedanib 100 mg in HDPE Bottle.

Nindanix 150 Capsule: Each commercial box contains 60 Capsules of Nintedanib Esylate INN equivalent to Nintedanib 150 mg in HDPE Bottle.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
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