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A REVIEW ON EFFICACY AND SAFETY OF NINTEDANIB IN IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

Tyrosine kinases inhibiter nintedanib reduces rate of decline in forced vital capacity (FVC) in patients with idiopathic pulmonary fibrosis, other chronic fibrosin interstitial lung disease (ILDS) with a progressive phenotype and systemic sclerosis associated ILD, (SSc-ILD) recommended dose of od nintedanib is 150mg twice a dilly(BID). IPF were analyzed to the investigate relationship between nintedanib plasma concentration (exposure) and efficacy for most patients with chronic fibrosin ILDs, the 150 mg nintedanib (BID) dose provides exposure levels associated with a therapeutic effect close to the maximum nintedanib effect independent of disease condition and baseline demographic.

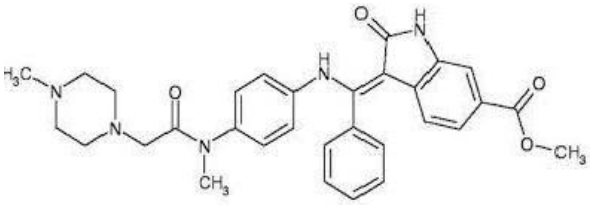
KEYWORDS: (FVC)- Forced vital capacity, (ILDs)- Idiopathic pulmonary fibrosis, other chronic fibrosin interstitial lung disease, (SSc)- systemic sclerosis, (BID)twice a dilly, (IPF) -Idiopathic pulmonary fibrosis, (FGF)- fibroblast growth factor.

INTRODUCTION[1,2]

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial lung disease characterized by a progressive decline in lung function. Although ultimately fatal, the clinical course of IPF is variable and unpredictable; Patients with IPF typically have a reduced diffusing capacity of the lungs for carbon monoxide. And progressive loss of lung function Idiopathic pulmonary fibrosis is believed to arise from an aberrant proliferation of fibrous tissue and tissue remodeling due to the abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts.

Nintedanib is an intracellular inhibitor of tyrosine kinases including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) receptors Nintedanib interferes with processes fundamental to the pathogenesis of IPF, such as fibroblast proliferation, migration and differentiation, the polarization of pro-fibrotic macrophages, and the secretion of extracellular matrix. Nintedanib has been approved for the treatment of IPF in several countries and regions, including the US and Japan.

The latest international clinical practice guideline provides a conditional recommendation for the use of Nintedanib in the treatment of patients with IPF, meaning that it is an appropriate choice for the majority of patients, while recognizing that patients' personal values and preferences should be taken into account when making treatment decisions. The efficacy and safety of Nintedanib 150 mg twice daily (bid) inpatients with IPF were investigated in the two replicate, randomized placebo-controlled, 52-week.



Structure of Nintedanib

IUPAC NAME- methyl (3z)-3-{[4-{methyl [(4-methylpiperazin-1-yl) acetyl] amino} phenyl) amino] (phenyl) methylene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate.

Pro-fibrotic tyrosine kinases such as platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) have been implicated in the pathogenesis of IPF. As key regulators of fibroblast proliferation and migration in the lung, these and other tyrosine kinase receptors play an important role in IPF disease initiation and progression.

Nintedanib is a small-molecule tyrosine kinase inhibitor that competitively blocks the adenosine triphosphate binding

Pocket of both receptor tyrosine kinases and non-receptor tyrosine kinases, such as IPF-implicated PDGFR, FGFR and (proto-oncogene tyrosine-protein kinase) kinase families. Blocking these kinase activities impacts downstream signaling pathways crucial for

normal and disease-associated cellular activity Based upon one phase 2 and two phase 3 registration clinical trials, each demonstrating a significant reduction in the annual rate of forced vital capacity (FVC) decline (consistent with slowed disease progression), oral Nintedanib was approved for the treatment of IPF.

Properties of Nintedanib are shown in table: 1.

Sr.no	Name of Nintedanib properties	Description
1	Molecular formula	C31H33N5O4
2	Melting point (^{o}c)	244 °C
3	Biological half life	10–15 h
4	Water solubility	2.8 mg/mL
5	Pka	7.9 ± 0.2

Properties of Nintedanib table no: 1

It has been shown to slow down decrease in forced vital capacity, and it also improves people's quality of life. Nintedanib does not improve survival in people with IPF. It interferes with processes like fibroblast proliferation, differentiation and laying down extracellular matrix.

Pharmacokinetic parameter of Nintedanib[4,5,6]

Pharmacokinetic parameter of Nintedanib table no: 2.

Sr.no	Parameter	Values
1.	Renal excretion	93%
2.	Metabolism	Esterases
3.	Half life	10-15 h
4.	Plasma protein binding	98%
5.	Bioavailability	4,7%

Only a small percentage of orally taken nintedanib is absorbed in the gut, partially due to a transport proteins (such as P-glycoprotein) moving the substance back into the lumen. Combined with a high first-pass effect, this results in an oral bioavailability of about 4.7% with a 100 mg tablet. The drug reaches peak plasma levels in 2 to 4 hours after oral intake in the form of a soft gelatin capsule.

Nintedanib is mainly inactivated by esterases that cleave the methyl ester, resulting in the free carboxylic acid form, which is then glucuronidated by uridinediphosphate-glucuronosyl transferases and excreted mostly via the bile and faeces.

Safety of Nintedanib[8,9,10]

Major side effects of nintedanib were reported to include liver problems, diarrhea, nausea, vomiting, heart attack, stroke, bleeding problems and tears (perforation) in the stomach or intestinal wall (Safety and Side Effects of OFEV, 2021). The present study thus recorded gastrointestinal and liver dysfunctions as possible adverse events that could be increased by the administration of nintedanib. However, there were no significant differences between the 2 groups in the incidence of mild, moderate and severe gastrointestinal and liver adverse events. In a previous study of patients with IPF, the rates of diarrhea, the most frequent adverse event, were significantly higher in the nintedanib versus non-nintedanib group (61.5% vs. 18.6%), The reason for the divergent findings between the previous and present studies might be attributable to the difference in disease severity and baseline risk of adverse events.

Main finding adverse effect table no: 3.

Main finding adverse effect
1) Total exposure to nintedanib was estimated as **60,107 patient- years**
2) The most common adverse event reported was **diarrhea**
3) Almost all (97 %) of the diarrhea events were **non serious**
4) The average time between starting treatment and first having diarrhea was **60 days**
5) Rarer adverse events reported inundated **increase in liver enzymes** detected in blood tests and **bleeding**

Efficacy of Nintedan[11,12,16]

Efficacy of Nintedanib table no: 4.

Efficacy of Nintedanib
1) Nintedanib reduces disease progression in the majority of the patient
2) After 6 months of nintedanib treatment, 63 % of patents (n= 30/ 48) Had a FVC decline smaller than 5 %.
3) This dose may result in varying plasma exposure level on efficacy.
4) A priori dose adjustment for patient characteristics appears unnecessary.
5) With 150mg twice daily most patients had levels associated with maximum efficacy

CONCUSSION

The present review study of safety and efficacy of nintedanib, the safety profile of nintedanib in patients was seen in clinical trials and described information.

In that review nintedanib pharmacokinetic properties can be studied, and adverse drug reaction also studied.

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