

Nintedanib (OFEV®) National Drug Monograph March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹

Description/ Mechanism of Action	Nintedanib inhibits multiple receptor tyrosine kinases, the following of which have been implicated in the pathogenesis of idiopathic pulmonary fibrosis: fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR).
Indication(s) under Review in this document	Nintedanib is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).
Dosage Form(s) Under Review	Capsules containing 100 or 150mg nintedanib
REMS	No REMS
Pregnancy Rating	Pregnancy Category D

Executive Summary^{2,3}

Efficacy	<ul style="list-style-type: none"> US approval of nintedanib was based upon one Phase II and two Phase III multicenter, randomized, double-blind, placebo-controlled trials conducted in patients with mild-to-moderate IPF. In the Phase II trial, TOMORROW, patients were randomized to receive nintedanib 150mg twice daily or placebo for 52 weeks and the annual rate of forced vital capacity (FVC) decline was assessed as the primary efficacy endpoint. There was a trend toward reduction of FVC decline (0.06L with nintedanib versus 0.19L with placebo, $p = 0.06$). St. George's Respiratory Questionnaire (SGRQ) scores were significantly reduced in patients receiving nintedanib, suggesting a health-related quality of life benefit, and the incidence of acute exacerbations/100 patient years was reduced by 85%. There was no effect on 52 week survival or death from any cause. Patients enrolled in INPULSIS-1 and INPULSIS-2 were randomized to receive nintedanib 150mg twice daily for 52 weeks and annual rate of FVC decline was determined as the primary endpoint in each trial. In INPULSIS-1, nintedanib, compared with placebo, reduced annual FVC decline by 52.2% ($p < 0.001$) but did not alter SGRQ scores or positively influence time to first acute exacerbation or risk of acute exacerbation. Patients in INPULSIS-2 had a 45% reduction in annual FVC decline ($p < 0.001$), and also exhibited lowered SGRQ scores ($p = 0.02$), increased time to first acute exacerbation ($p = 0.005$), and reduced risk of acute exacerbation ($p = 0.007$). All-cause mortality, deaths due to respiratory cause, on treatment deaths, and time to death were not significantly affected by nintedanib administration in INPULSIS-1 and INPULSIS-2.
Safety	<ul style="list-style-type: none"> Pooled safety data for nintedanib is available from the TOMORROW and INPULSIS 1 & 2 trials. At the recommended dosage of 150mg twice daily, 21% of patients discontinued nintedanib due to adverse reactions and 16% of patients required permanent dose reductions due to adverse reactions. The most common adverse reactions were gastrointestinal: diarrhea (62%), nausea (14%), abdominal pain (15%), and vomiting (12%). There was a 14% incidence of liver enzyme elevation. Arterial thromboembolic events occurred in 2.5% of patients compared to an incidence of 0.8% in those receiving placebo. There is an increased risk of bleeding and gastrointestinal perforation related to the VEGFR inhibitory effects of nintedanib.

Potential Impact	<ul style="list-style-type: none"> Nintedanib is a FDA approved treatment for IPF, available as an oral capsule for twice daily administration. Compared to placebo, nintedanib reduces disease progression in patients with IPF, as evidenced by reductions in annual FVC decline. While nintedanib has been shown to improve health-related quality of life and favorably influence the pattern of acute exacerbations in patients with IPF, no mortality benefit has been demonstrated with its use. Gastrointestinal adverse reactions result in the need to dose-reduce or discontinue nintedanib in a significant percentage of patients. There were no effective pharmacological therapies for IPF prior to the simultaneous FDA approval (October, 2014) of nintedanib and another agent, pirfenidone.
------------------	---

Background

Purpose for review The purpose of the review is to evaluate the efficacy and safety of nintedanib in the treatment of IPF.

Other therapeutic options	Non-formulary Alternative	Other Considerations
	Pirfenidone	Supplemental oxygen, pulmonary rehabilitation and other supportive measures; lung transplant

Efficacy (FDA Approved Indications)^{1, 2, 3}

Literature Search Summary

A literature search was performed on PubMed/Medline (1995 to December 2014) using the search terms nintedanib and idiopathic pulmonary fibrosis. The search was limited to studies performed in humans and published in the English language. The pivotal phase 2 and 3 clinical trials published in peer-reviewed journals are included.

Review of Efficacy

The FDA approval of nintedanib was based on data from a placebo-controlled Phase 2 study (TOMORROW) which was followed by two large Phase 3 trials reported together, known as INPULSIS -1 and INPULSIS-2 (Table 1).

TOMORROW was a multinational, multicenter, randomized, double-blind, Phase 2 study evaluating the efficacy and safety of 4 nintedanib doses (50mg once daily, 50mg twice daily, 100mg twice daily, and 150mg twice daily) which enrolled 428 patients with mild to moderate IPF. The primary endpoint was the annual rate of decline in forced vital capacity at 52 weeks (FVC, a measure of how well the lungs work based on the volume of air one can exhale with force after inhaling as deeply as possible).

INPULSIS -1 and INPULSIS-2 were 52 week, multinational, multicenter, randomized, double-blind, Phase 3 studies, replicate in design, which respectively enrolled 513 and 548 patients with mild to moderate IPF. The primary endpoint for both INPULSIS trials was the annual rate of decline in FVC. The authors presented a pooled data analysis of INPULSIS - 1 and INPULSIS -2 results.

Data from the TOMORROW and INPULSIS 1 & 2 trials are included in the prescribing information for nintedanib.

Table 1. Summary of Phase 2 and 3 Randomized Controlled Clinical Trials supporting the FDA indication for nintedanib (NIN)^{1, 2, 3} (95% confidence intervals)

Study	Population (Inclusionary Criteria)	Regimen	Primary Outcome Measure Annual rate of FVC decline [% reduction]
TOMORROW	Patients \geq 40 years old with diagnosis IPF ^a ; FVC \geq 50% of predicted value; DL _{CO} ^b 30 to 79% of predicted value; PaO ₂ ^c \geq 50mm Hg, depending upon altitude	NIN 150mg BID x 52 weeks ^d	0.06L decline w/ NIN (-0.14, 0.02L) <i>versus</i> 0.19L w/ placebo (-0.26, -0.12) [68.4% reduction; NS (p= 0.06) with the closed testing procedure for multiplicity correction; p = 0.01 when subjected to hierarchical testing]
INPULSIS - 1	Patients \geq 40 years old with diagnosis IPF ^e within past 5 years; FVC \geq 50% of predicted value; DL _{CO} ^b 30 to 79% of predicted value; chest HRCT ^f w/in previous 12 months	NIN 150mg BID x 52 weeks	0.1147L decline w/ NIN <i>versus</i> 0.2399L w/ placebo, a 0.1253L difference (0.0777, .1728L) [52.2% reduction; p < 0.001]
INPULSIS - 2	See INPULSIS - 1	NIN 150mg BID x 52 weeks	0.1136L decline w/ NIN <i>versus</i> 0.2073L w/ placebo, a 0.0937L difference (0.0448, .1427L) [45.2% reduction; p < 0.001]
INPULSIS 1 & 2 Pooled Data	See INPULSIS-1	NIN 150mg BID x 52 weeks	0.1136L decline w/ NIN <i>versus</i> 0.2235L w/ placebo, a 0.1099L difference (0.0759, .144L) [49.22% reduction; p < 0.001]

^a Diagnosis of probable or definite IPF was confirmed per ATS/ERS Consensus Guidelines (2000)⁴

^b Carbon monoxide diffusing capacity (DL_{CO}) measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries. The normal values for CO diffusing capacity vary widely between laboratories, and both absolute values and their reproducibility are largely influenced by the measurement technique. Therefore, this measurement is most useful if the patient's lung function changes are followed consistently by the same laboratory.

^c Partial pressure of oxygen in arterial blood (PaO₂); normal values range from 75 to 100mm Hg at sea level.

^d Eighty-five patients were randomized to the 150mg BID dosage; other nintedanib dosages are excluded in this summary table

^e Diagnosis of IPF was confirmed per ATS/ERS/JRS/ALAT Consensus Guidelines (2011)⁵

^f High-resolution computed tomography (HRCT)

Overall Quality of Evidence: High (Refer to Appendix A); note TOMORROW and both INPULSIS trials were sponsored by Boehringer Ingelheim, the manufacturer of nintedanib.

FVC and DL_{CO} are considered reliable, valid, and responsive measures of disease status as well as independent predictors of survival in patients with IPF.^{6,7}

TOMORROW: To Improve Pulmonary Fibrosis with BIBF 1120²

- A total of 432 patients were enrolled and randomly assigned to receive nintedanib 50mg once (n = 86) or twice (n = 86) daily, 100mg twice daily (n = 86), 150mg twice daily (n = 85), or placebo (n = 85) for 52 weeks. *This monograph will focus on results obtained with the FDA recommended standard dose of 150mg twice daily.*
- Inclusionary criteria are detailed in Table 1. Key exclusionary criteria included medical conditions that might interfere with testing procedures (ex: myocardial infarction or unstable angina), predisposition to hemorrhage or thrombosis, concomitant anticoagulant medication, continuous oxygen supplementation (\geq 15 hours/day, at randomization), elevated liver function enzymes, likelihood of lung transplantation during the study or life expectancy <2.5 years for a disease other than IPF.
- There were no outlying imbalances in patient demographics and baseline characteristics (Table 2).

- Of the 85 patients randomized to nintedanib 150mg twice daily, only 53 completed the 52 week trial (38% dropout rate). Twenty of 85 patients (23.3%) underwent a nintedanib dose reduction during the trial and 11 of these patients eventually discontinued therapy.
- The primary efficacy outcome is expressed in Table 1. Although there was a 68.4% reduction in FVC decline in patients administered nintedanib 150mg twice daily [0.06L decline (95% CI -0.14 to 0.02L) *versus* 0.19L w/ placebo (95% CI, -0.26 to -0.12), primary analysis via a closed testing procedure indicated that this difference approached, but did not achieve, statistical significance ($p = 0.06$). However, a secondary analysis using a hierarchical test resulted in a p value equal to 0.01. From these two analyses, the authors concluded that the nintedanib 150mg twice daily response data, compared to placebo, showed a trend towards reduction of FVC decline.

Table 2: TOMORROW - demographics and baseline characteristics for subjects administered nintedanib 150mg twice daily or placebo; data expressed as number (%) or mean value \pm SD unless otherwise specified²

Characteristics	Placebo (n = 85)	Nintedanib (n = 85)
Age	64.8 \pm 8.6	65.4 \pm 7.8
Male sex – no. (%)	63 (74.1)	65 (76.5)
Surgical lung biopsy available	19 (22.4)	29 (34.1)
Diagnosis of IPF		
Definite	24 (28.2)	33(38.8)
Possible	57 (67.1)	52 (61.2)
Interval since diagnosis (years)	1.4 \pm 1.5	1.0 \pm 1.2
Lung physiological features		
FVC (% predicted, median value)	77.6	78.1
DL _{CO} (mmol/min/kPa, median value)	3.7	3.5
PaO ₂ (mm Hg, median value)	75	78.3
SpO ₂ (%)	96	96

Oxygen saturation (SpO₂) determined by pulse oximetry with subject breathing room air

- Secondary outcome measures included the St. George's Respiratory Questionnaire (SGRQ), which is used to assess health-related quality of life (QOL) related to chronic airflow limitation. The SGRQ assesses 3 domains – symptoms, activity, and impact – and has been shown to be a valid and reliable QOL measure in patients with asthma, COPD, bronchiectasis, and cystic fibrosis (in which a minimum clinically important difference in score has been defined as 4 points). The TOMORROW authors stated that a minimally important difference in score in IPF has been estimated as being -5 to 8 points.
- Positive secondary outcome findings are summarized in Table 3; over 52 weeks, nintedanib 150mg twice daily, compared to placebo, reduced the number of patients with FVC decrease \geq 10% or more than 200ml, reduced loss of total lung capacity, preserved resting SpO₂, and reduced the incidence of acute exacerbations. SGRQ was also positively impacted, primarily in the domains of symptoms and activity, suggesting a health-related quality of life benefit.
- A reduced dose of nintedanib 100mg twice daily, at 52 weeks, resulted in significant improvement *versus* placebo in some secondary measures, specifically: absolute change in FVC [-0.13L \pm 0.04 (-0.20, -0.06) *vs.* -0.23L \pm 0.04 (-0.30, 10.16); $p < 0.01$], change of FVC as % predicted [-3.15% \pm 1.00 (-5.12, -1.17) *vs.* -6.00% \pm 1.02 (-8.01, -4.00); $p < 0.05$], and absolute change in percentage SpO₂ [0.06% \pm 0.36 (-0.65, 0.78) *vs.* -1.29% \pm 0.37 (-2.03, -0.56); $p < 0.01$] (95% CI).
- Nintedanib 150mg twice daily had no effect on other secondary outcome measure: DLco, 6MWT, 52 week survival, and death from any cause.
- The discontinuation rate due to adverse drug effects was 30.6%. Gastrointestinal symptoms occurred in 74.1% of patients given nintedanib 150mg twice daily; diarrhea, nausea, or vomiting was reported in 55.3%, 23.5%, and 12.9% of patients, respectively. Diarrhea related to nintedanib was persistent (mean duration of 85.4 days) and resulted in treatment discontinuation in 10 patients. Increased levels of hepatic transaminases (alanine or aspartate aminotransferase \geq 3x ULN) occurred in 7 patients taking nintedanib and none taking placebo. There were no cardiac adverse events related to the administration of nintedanib.

Table 3: TOMORROW – Summary of positive secondary endpoint findings for subjects administered nintedanib 150mg twice daily for 52 weeks, compared to placebo. Data expressed as number (%) or mean value \pm SD unless otherwise specified; (95% confidence intervals)²

Secondary Outcome Measure	Placebo n = 83	Nintedanib n = 85
Δ FVC as % predicted	-6 ± 1.02 (-8.01, -4.00)	-1.04 ± 0.99 (-2.98, 0.91) P < 0.001
FVC decrease >10% of baseline or > 200ml (%)	37 (44)	20 (23.8) p = 0.004
Δ Total lung capacity, L	-0.24L ± 0.08 (-0.39, -0.09)	0.12L ± 0.8 (-0.03, 0.27) p < 0.001
Δ SpO ₂ (%)	-1.29 (0.37) (-2.03, -0.56)	-0.18 (0.36) (-0.89, 0.53) p < 0.05
SpO ₂ decrease > 4% (%)	11%	3.6% p = 0.03
SGRQ score	+5.46 ± 1.73 (2.06, 8.86)	-0.66 ± 1.71 (-4.02, 2.71) p = 0.007
Incidence of acute exacerbations/per 100 patient years	15.7	2.4 p = 0.02

INPULSIS-1 and INPULSIS-2: Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients³

- INPULSIS-1 and INPULSIS-2 had respective enrollments of 513 and 548 patients; all were randomly assigned in a 3:2 ratio to receive nintedanib 150mg twice daily or placebo, and assessed after a 52 week period.
- The inclusionary criteria for these replicate trials are detailed in Table 1. There were no outlying imbalances between the two treatment groups in either trial regarding patient demographics or characteristics (Table 4), for time since diagnosis of IPF, for history of surgical lung biopsy, or for percentage of patients on systemic corticosteroid therapy (≤ 15mg prednisone equivalent daily permitted if dose had been stable for at least 8 weeks prior to screening).
- Patients were excluded who had liver function test abnormalities > 1.5 x upper limits of normal, recent MI or unstable angina, were likely to receive a lung transplant during the course of the trial, or who were on full-dose anticoagulants or high-dose antiplatelet therapy. Patients taking therapies for IPF other than the previously mentioned corticosteroid were initially excluded; however, once enrolled, after 6 months of study treatment or at any time in event of an acute exacerbation of IPF, higher-dose corticosteroids, azathioprine, cyclophosphamide, cyclosporine, or N-acetylcysteine could be given at the discretion of the investigator.
- Dose interruption or dose reduction from nintedanib 150 to 100mg daily was permitted for the management of adverse events, with later reinstatement of full dose on event resolution.
- In the individual trials, and in the pooled population, the primary endpoint was successfully met; the adjusted annual rate of change in FVC was significantly lower (49 to 52%) in the groups administered nintedanib compared to those given placebo (Table 1).
- Two key secondary endpoints were identified for the trials: the time to first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ; see discussion on page 4).
- In INPULSIS-1, there was no significant difference in time to first acute exacerbation or risk of acute exacerbation (Table 5); in addition, the proportion of patients with at least one investigator-reported acute exacerbation was similar in the nintedanib and placebo groups. In contrast, in INPULSIS-2, compared to placebo at 52 weeks, nintedanib increased the time to first acute exacerbation, reduced the risk of acute exacerbation, and reduced the proportion of patients with at least one investigator reported acute exacerbation from 9.6 to 3.6%. There were no significant differences in acute exacerbation measures when the pooled nintedanib patients were compared to placebo.

Table 4: INPULSIS-1 and INPULSIS-2 demographics and baseline characteristics for patients administered nintedanib 150mg twice daily or placebo; data expressed as number (%) or mean value ± SD³

Characteristics	INPULSIS-1		INPULSIS-2	
	Placebo (n = 204)	Nintedanib (n = 309)	Placebo (n = 219)	Nintedanib (n = 329)
Age	66.9 ± 8.2	66.9 ± 8.4	67.1 ± 7.5	66.4 ± 7.9
Male sex – no. (%)	163 (79.9)	251 (81.2)	171 (78.1)	256 (77.8)

Smoking status				
Never – no. (%)	51 (25)	71 (23)	71 (32.4)	103 (31.3)
Former – no. (%)	144 (70.6)	217 (70.2)	139 (63.5)	218 (66.3)
Current – no. (%)	9 (4.4)	21 (6.8)	9 (4.1)	8 (2.4)
Lung physiological features				
FVC (ml)	2845 ± 820	2757 ± 735	2619 ± 787	2673 ± 776
FVC (% predicted)	80.5 ± 17.3	79.5 ± 17.0	78.1 ± 19.0	80.0 ± 18.1
FEV ₁ : FVC (%)	80.8 ± 6.1	81.5 ± 5.4	82.4 ± 5.7	81.8 ± 6.3
DL _{CO} (mmol/min/kPa)	4.0 ± 1.1	4.0 ± 1.2	3.7 ± 1.3	3.8 ± 1.2
DL _{CO} (% predicted)	47.5 ± 11.7	47.8 ± 12.3	46.4 ± 14.8	47.0 ± 14.5
SpO ₂ (%)	95.9 ± 1.9	95.9 ± 2.0	95.7 ± 2.1	95.8 ± 2.6
Total SGRQ score	39.8 ± 18.5	39.6 ± 17.6	39.4 ± 18.7	39.5 ± 20.5

- Mean SGRQ scores were significantly lower in nintedanib patients in INPULSIS-2, compared to those receiving placebo, consistent with less deterioration in health-related quality of life (Table 5). Nintedanib did not affect SGRQ scores in INPULSIS-1 patients or in the pooled population.
- Compared to placebo-treated patients, loss of FVC (expressed as ml or as % predicted value) was significantly improved (-50 to -53%) by nintedanib in INPULSIS-1, INPULSIS-2 and in the pooled patients. The proportion of patients with ≤ 5% decline in FVC over 52 weeks was halved in all nintedanib treatment groups; the proportion of patients who had ≤ 10% decline in FVC were in the 69-70% range in all treatment groups but did not reach statistical significance in INPULSIS-2.
- All-cause mortality, deaths due to respiratory cause, on treatment deaths (those that occurred between randomization and 28 days after last trial drug intake), and time to death were unaffected by nintedanib, when compared to placebo, in INPULSIS-1, INPULSIS-2, and in the pooled patient group.
- The most frequent adverse event in the nintedanib groups in INPULSIS-1 and INPULSIS-2 was diarrhea (occurring in 61.5 and 63.2% of patients, respectively) which resulted in treatment discontinuation in approximately 4.5% of patients. A higher proportion of patients in the nintedanib groups than in the placebo groups had elevated liver function tests (in both trials, approximately 5% incidence of ALT and/or AST increased ≥ 3 x ULN).

Table 5: Selected secondary endpoint findings for INPULSIS-1, INPULSIS-2, and the pooled population administered nintedanib 150mg twice daily for 52 weeks, or placebo. Data expressed as number or percentage, unless otherwise specified (95% confidence intervals)³

Secondary Endpoint Assessments	INPULSIS-1		INPULSIS-2		Pooled Data	
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib
Time to first acute exacerbation		HR ^a 1.15 (0.54, 2.42) p = 0.67		HR 0.38 (0.19, 0.77) p = 0.005		HR 0.64 (0.39, 1.05) p = 0.08
Risk of an acute exacerbation (incidence per 100 patient years)	5.6	6.6 RR ^b 1.17 (0.56, 2.46) p = 0.68	10.2	3.9 RR 0.38 (0.19, 0.77) p = 0.007	8.0	5.2 RR 0.65 (0.39, 1.06) p = 0.08
SGRQ score	4.39	4.34 (-2.50, 2.40) p = 0.97	5.48	-2.80 (-4.95, -0.43; p = 0.02)	NA ^c	3.53 (-3.09, 0.23) p = 0.09
Δ FVC (ml)	-205.0 (n = 204)	-95.1ml (n = 307) (71.3, 148.6) p < 0.001	-205.0 (n = 217)	-95.3 (n = 327) (70.9, 148.6) p < 0.001	-205 (n = 421)	-94.5 (n = 634) (83.2, 137.9) p < 0.001
Δ FVC (% of predicted value)	-6.0	-2.8 (2.1, 4.3) p < 0.001	-6.2	-3.1 (1.9, 4.3) p < 0.001	-6.1 (n = 421)	-2.9 (n = 634) (2.4, 4.0) p < 0.001
Proportion of patients with ≤ 5% decline (%)	78/204 (38.2%)	163/307 (52.8%) OR ^d 1.85 (1.28, 2.66)	86/217 (39.3%)	175/327 (53.2%) OR 1.79 (1.26, 2.55)	164/423 (38.8%)	338/638 (53.0%) OR 1.8 (1.4, 2.4)

		p = 0.001		p = 0.001		p < 0.001
Proportion of patients with ≤ 10% decline	116/204 (56.9%)	218/307 (70.6%) OR 0 1.85 (1.28, 2.66) p = 0.001	140/217 (63.9%)	229/327 (69.6%) OR 1.29 (0.89, 1.86) p = 0.18	256/421 (60.5%)	447/634 (70.1%) OR 1.6 (1.2, 2.1) p < 0.001

^a Hazard ratio (HR)

^b Relative risk (RR)

^c Data not available (NA)

^d Odds ratio (OR)

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM intranet site only).

Nintedanib is being investigated for its efficacy, alone or in combination with other agents, for the potential treatment of numerous oncologic indications. As of January, 2015, there were 62 trials are listed in www.clinicaltrials.gov with varying statuses (not yet recruiting, recruiting, completed with/without results). One-quarter of the studies are in patients with non-small cell carcinoma of the lung; the efficacy of nintedanib is also being investigated in other solid tumor cancers [breast, gynecologic (ovarian, cervical, endometrial), small cell of the lung, mesothelioma, glioblastoma, thyroid, colorectal, esophago gastric, hepatocellular, biliary tract, prostate, breast, renal cell, and melanoma] and in several lymphoproliferative disorders (multiple myeloma and acute myelogenous leukemia).

Safety (for more detailed information refer to the product package insert)^{1, 2, 3}

	Comments
Boxed Warning	<ul style="list-style-type: none"> None
Contraindications	<ul style="list-style-type: none"> None
Warnings/Precautions	<ul style="list-style-type: none"> Elevated liver enzymes (ALT, AST, ALKP, and GGT) have occurred with nintedanib; monitoring is recommended during treatment. Diarrhea, nausea and vomiting have been noted with nintedanib; treatment with hydration, antidiarrheal or antiemetic agents may be required. Nintedanib can cause fetal harm and should be avoided during pregnancy. Arterial thromboembolic events have been reported with nintedanib and caution should be exercised when treating patients at higher cardiovascular risk

Safety Considerations

The safety assessment of nintedanib is primarily based on pooled data from 3 randomized, double-blind, placebo-controlled, 52 week trials: one phase II trial (TOMORROW) and 2 phase III trials (INPULSIS 1 and INPULSIS 2) in which a total of 723 patients received nintedanib 150mg twice daily and 508 patients received placebo. The median age of subjects was 67 years (range 42 to 89) and most were male (79%) and Caucasian (60%). The median exposure to nintedanib was 10 months for patients receiving nintedanib and 11 months for those receiving placebo.

- In the TOMORROW and INPULSIS 1&2 trials, diarrhea was the most frequent gastrointestinal event reported, occurring in 62% versus 18% of patients treated with nintedanib and placebo, respectively. In most patients diarrhea was characterized as mild to moderate in intensity and typically occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% and discontinuation of therapy in 5% of patients administered nintedanib (*versus* 0% and <1% of patients receiving placebo, respectively). The protocol of the IMPULSIS trials recommended the following approach for management of nintedanib-induced diarrhea:
 - Diarrhea should be initially treated with adequate hydration and antidiarrheal medication (loperamide 4mg at onset, followed by 2mg after every stool until diarrhea has stopped for 12 hours; maximum loperamide dose 12-16mg per day).
 - If diarrhea persists > 8 days despite optimal care, nintedanib should be discontinued or dose reduced (to 100mg twice daily) until movements are reduced to < 4 extra stools/day.

Nintedanib may then be resumed at a reduced dosage (100mg twice daily), or at full dosage, as applicable, and as tolerated. Nintedanib should be permanently discontinued if diarrhea recurs and persists ≥ 8 consecutive days despite a period of dose reduction and after optimal or prophylactic therapy for diarrhea.

- Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with nintedanib and placebo, respectively. These events were typically identified to be mild or moderate in intensity and may be appropriately addressed with anti-emetic treatment or nintedanib dose reduction (to 100mg twice daily); treatment discontinuation is indicated if nausea or vomiting response to conservative measures is inadequate.
- The incidence of liver enzyme (ALT, AST, ALKP, and GGT) elevations was greater with nintedanib than with placebo in patients participating in clinical trials (14% vs. 3%, respectively); elevations were reversible with nintedanib dose modification or interruption and were not associated with clinical signs or symptoms of bilirubin elevation or liver injury. For liver enzyme elevations > 3 x upper limit of normal (ULN) or < 5 x ULN, without signs of severe liver damage, treatment with nintedanib may be interrupted OR the dose can be reduced from 150mg to 100mg twice daily. When interrupted, treatment may be resumed at a reduced dose (100mg twice daily). Once tolerance of reduced dose nintedanib is confirmed, nintedanib can then be increased to full dosage (150mg twice daily).

Table 6: Incidence of adverse reactions occurring in $\geq 5\%$ of nintedanib-treated patients and more commonly than placebo¹

Adverse Reactions	% of Patients (0 to 52 weeks)	
	Nintedanib 150mg twice daily (n = 723)	Placebo (n = 508)
Gastrointestinal		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain	15%	6%
Vomiting	12%	3%
Liver enzyme elevation	14%	3%
Decreased appetite	11%	5%
Headache	8%	5%
Weight decrease	10%	3%
Hypertension	5%	4%

Adverse Reactions

Common adverse reactions Incidence $\geq 5\%$ and more commonly than placebo are detailed in Table 6 and include: Gastrointestinal (various; diarrhea and nausea being the most frequent), liver enzyme elevation, decreased appetite, headache, weight decrease and hypertension.

Death/Serious adverse reactions Arterial thromboembolic events were reported in 2.5% of patients treated with nintedanib and 0.8% of placebo-treated patients. Myocardial infarction occurred in 1.5% of patients given nintedanib compared to 0.4% administered placebo.

Due to its mechanism of action (VEGFR inhibition), nintedanib may increase risk of bleeding or gastrointestinal perforation. In clinical trials, bleeding events were reported in 10% of patients treated with nintedanib and 7% administered placebo, while the incidence of gastrointestinal perforation was 0.3% in nintedanib patients versus 0% in those given placebo.

In clinical trials, the most common adverse events leading to death in patients treated with nintedanib, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE; including MI), fatal events were reported for 0.6% and 1.8% of nintedanib and placebo-treated patients, respectively.

Discontinuations due to adverse reactions	At the recommended dosage of 150mg twice daily, 21% of patients taking nintedanib compared to 15% on placebo permanently discontinued treatment due to an adverse event. The most common adverse reactions leading to discontinuation were diarrhea (5%), nausea (2%), and decreased appetite (2%). Nintedanib should be discontinued for AST or ALT elevations > 5x ULN OR 3x ULN associated with signs or symptoms of severe liver damage.
Laboratory Abnormalities	Liver enzyme (ALT, AST, ALKP, and GGT) elevations may occur with nintedanib therapy which may necessitate dose modification or treatment discontinuation. Liver function tests should be conducted prior to the initiation of nintedanib, monthly for 3 months, and then every 3 months thereafter and as clinically indicated. If ALT and/or AST are > 3 but ≤ 5x ULN without symptoms or hyperbilirubinemia nintedanib should be reduced from 150mg to 100mg twice daily or interrupted altogether. Once liver chemistries have normalized – therapy can be resumed at 100mg twice daily. Reduced dose nintedanib 100mg twice daily may be subsequently increased once tolerance of the reduced dose has been determined. If liver enzymes are > 3 ULN with signs or symptoms of severe liver damage or > 5x, nintedanib should be permanently discontinued.

Drug-Drug Interactions¹

- Consult the prescribing information prior to use of nintedanib for potential drug interactions.
- Nintedanib is a substrate of p-glycoprotein (P-gp). Metabolism of nintedanib occurs primarily through enzymatic hydrolysis, followed by glucuronidation. CYP pathways play only a minor role in the metabolism of nintedanib but what does occur is predominantly a CYP3A4 effect.
- Co-administration of nintedanib with oral doses of ketoconazole, a P-gp and CYP3A4 inhibitor, increased exposure to nintedanib by 60%; thus, concomitant use of nintedanib with other P-gp and CYP3A4 inhibitors (such as erythromycin) may result in a similar effect.
- Co-administration of nintedanib with oral doses of rifampicin, a P-gp and CYP3A4 inducer, decreased exposure to nintedanib by 50%. Decreased exposure to nintedanib could result from concomitant use of other P-gp and CYP3A4 inducers such as carbamazepine, phenytoin or St. John's wort.
- Due to its activity as a VEGF inhibitor, nintedanib has the potential to interfere with the repair and renewal capacity of endothelial cells in response to trauma and possibly increase risk of bleeding. Patients on nintedanib and on full anticoagulation therapy should be monitored closely for bleeding.
- In a multiple dose study, concomitant administration of nintedanib and pirfenidone did not affect pirfenidone exposure but nintedanib AUC and C_{max} were decreased 68.3 and 59.2%, respectively.
- Smoking reduces patient exposure to nintedanib by 21% compared to that of ex- and never-smokers; this effect does not warrant nintedanib dose adjustment but may alter the drug's efficacy. Patients should be encouraged to stop smoking prior to treatment with nintedanib and to avoid smoking while taking the drug.

Risk Evaluation

As of January 2015	Comments										
Sentinel event advisories	<ul style="list-style-type: none"> • None 										
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> • Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List): <table border="1"> <thead> <tr> <th>NME Drug Name</th> <th>Lexi-Comp</th> <th>First DataBank</th> <th>ISMP</th> <th>Clinical Judgment</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment					
NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment							

	Nintedanib	Erlotinib Imatinib Nilotinib Vandetanib	None	None	Natalizumab Nivolumab
	Ofev	None	None	None	Ofirmev Aleve

Other Considerations

None

Dosing and Administration¹

Refer to the package insert for full dosing information.

The recommended daily dose of nintedanib is 150mg twice daily approximately 12 hours apart taken with food.

Food delays the absorption of nintedanib, doubling t_{max} to 4 hours while increasing nintedanib exposure by 20%.

Liver function tests should be performed prior to treatment and periodically thereafter (**Adverse Reactions**, page 10).

Consider temporary dose reduction to 100mg twice daily, temporary hold, or discontinuation of nintedanib for management of adverse reactions.

Special Populations (Adults)¹

	Comments
Elderly	<ul style="list-style-type: none"> In the phase 2 and phase 3 clinical studies of nintedanib, 60.8% of subjects were ≥ 65 years of age, while 16.3% were ≥ 75 years of age. In phase 3 studies, there were no overall differences in efficacy or safety observed between subjects who were 65 and over and younger subjects.
Pregnancy	<ul style="list-style-type: none"> Pregnancy Category D Nintedanib can cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking nintedanib, or if nintedanib is used during pregnancy, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with nintedanib, use adequate contraception during treatment and for at least 3 months after the last dose of nintedanib.
Lactation	<ul style="list-style-type: none"> Excretion of nintedanib and/or its metabolites into human breast milk is probable. According to the PI, due to the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue nintedanib, taking into account the importance of the drug to the mother.
Renal Impairment	<ul style="list-style-type: none"> Based on a single-dose pharmacokinetic study, nintedanib is subject to $< 1\%$ renal excretion. While adjustment of the starting dose in patients with mild (CrCl 60-90 ml/min) to moderate (CrCl 30-60ml/min) renal impairment is not required, the safety, efficacy and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (< 30ml/min CrCl) and end stage renal disease.
Hepatic Impairment-	<ul style="list-style-type: none"> Nintedanib is predominately eliminated via biliary/fecal excretion. No dedicated pharmacokinetic study has been performed in patients with hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) should be monitored for adverse reactions; consider dose modification or discontinuation as warranted.

- The efficacy and safety of nintedanib in patients with Child Pugh B or C classification hepatic impairment has not been investigated; administration of nintedanib to such patients is not recommended.

Pharmacogenetics/genomics • There are no data identified in the FDA approved labeling <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm> (accessed January 27, 2015)

Projected Place in Therapy ^{2, 3, 8, 9, 10}

- Approximately 100,000 people in the United States have IPF, a chronic, progressive, and fatal lung disease characterized by a progressive loss of the ability of the lungs to function due to interstitial scarring. The cause of IPF is unknown and there is no cure. While some patients may experience periods of stability with the disease, the prognosis in IPF is poor: the estimated median survival is only two to five years after diagnosis (similar to that of non-small cell lung cancer). In FY14, 2150 patients in VA were identified through ICD-9 coding to have the diagnosis of IPF.
- In the TOMORROW and the INPULSIS trials, nintedanib 150mg twice daily reduced FVC decline, improved health-related quality of life, and favorably influenced the pattern of acute exacerbations in patients with IPF. Treatment with nintedanib was generally safe but the high incidence of gastrointestinal adverse reactions may interfere with its use in many patients. No mortality benefit has been demonstrated with nintedanib; however, the ability to positively influence the progression of IPF is a major step forward in its management, as there were no effective pharmacological therapies for IPF prior to the 2014 FDA approvals of nintedanib and another agent, pirfenidone.
- Positive outcomes have resulted when nintedanib has been given to patients with mild- to moderate IPF; however, it is unclear whether and to what extent nintedanib is effective in patients with severe disease (FVC < 50%).
- There is little information to characterize the persistence of nintedanib efficacy beyond one year.
- There is inadequate evidence to support the efficacy associated with long term administration of reduced-dose nintedanib (100mg twice daily).
- The use of nintedanib relative to that of pirfenidone, which has a different mechanism of action than nintedanib, has not yet been determined. There is no evidence to support use of the drugs in combination and a significant drug interaction exists between the two agents.

References

1. Ofev® (nintedanib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October, 2014.
2. Richeldi L, Costabel U, Selman M et al., Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis. *N Engl J Med* 2011; 365: 1079-87 + supplementary appendix.
3. Richeldi L, du Bois RM, Raghu G et al., Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis, *N Engl J Med* 2014; 370: 2071-82 + supplementary appendix.
4. American Thoracic Society, European Respiratory Society. Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment: International Consensus Statement. *Am J Respir Crit Care Med* 2000; 161: 646-64.
5. Raghu G, Collard HR, Egan JJ et al. for the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med* 2011; 183: 788-824.
6. Ley B, Collard HR and King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431-40
7. Wells AU and Ward S (2014) Pulmonary Function Tests in Idiopathic Pulmonary Fibrosis in Meyer KC and Nathan SD (Eds) *Idiopathic Pulmonary Fibrosis: A Comprehensive Clinical Guide*, pp 103-21 (New York), Humana Press.
8. Hunninghake GM. A New Hope for Idiopathic Pulmonary Fibrosis (edit). *N Engl J Med* 2014; 370: 2142-3.
9. Ryu JH, Moua T, Daniels CE et al. Idiopathic Pulmonary Fibrosis: Evolving Concepts. *Mayo Clin Proc* 2014; 89: 1130-42.
10. Wuyts WA, Antoniou KM, Borensztajn K et al. Combination Therapy: the Future of Management for Idiopathic Pulmonary Fibrosis? *Lancet Respir Med* 2014; 2: 933-42.

Prepared: March, 2015 Contact person: Michael Chaffman, Pharm.D. BCPS, National PBM Clinical Pharmacy Program Manager

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designationDescription

High

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).

Moderate

Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.

Low

Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010; 153:194-199.