Drug Use Research & Management Program
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New Drug Evaluation: Nintedanib capsules, oral

Month/Year of Review: July 2015
Generic Name: Nintedanib
PDL Class: Idiopathic Pulmonary Fibrosis Agents

End Date of Literature Search: January 2015
Brand Name (Manufacturer): Ofev™ (Boehringer Ingelheim Pharmaceuticals)
Dossier Received: Yes

Research Questions:

- Is there evidence of efficacy for nintedanib in the treatment of idiopathic pulmonary fibrosis (IPF) as demonstrated by clinical improvement in outcomes such mortality, functional status (e.g., exercise tolerance), quality of life or symptoms (e.g., acute exacerbations)? If so, is there direct comparative evidence with other treatments for IPF?
- Is there evidence of acceptable adverse effects for nintedanib in comparison to other treatments for IPF?
- Are there subgroups of patients that may receive greater benefit or harm from nintedanib therapy?

Conclusions:

- There is insufficient evidence comparing nintedanib to other treatment for IPF. Current evidence is based on two placebo-controlled studies (INPULSIS-1 and INPULSIS-2).
- There is insufficient evidence that nintedanib reduces mortality in patients with IPF.[1]
- There is moderate strength of evidence from the INPULSIS trials (n=1066) that nintedanib slows disease progression based on surrogate outcomes as demonstrated by changes in forced vital capacity (FVC). Adjusted annual rate of change in FVC were significantly superior in the nintedanib groups compared to placebo in both studies.[1] INPULSIS-1 reported a significant benefit in FVC decline ≤10% with a number needed to treat (NNT) of 7. Results were not significant for this outcome in INPULSIS-2.
- There is low strength of evidence that nintedanib improved quality of life based results of the INPULSIS-2 study that showed less deterioration in scores of patients taking nintedanib compared to placebo, 2.80 points vs. 5.48 points, p=0.02.[1] Clinical benefit on quality of life resulting from a difference of 2.69 points between groups is unknown. There was no significant difference in quality of life scores in INPULSIS-1.[1]
- There is low strength of evidence that incidence of acute exacerbations were significantly improved in the nintedanib group compared to placebo in INPULSIS-2. In INPULSIS-1 no significant difference between groups was demonstrated.[1]
- Common adverse reactions experienced by patients in the nintedanib group were diarrhea, nausea, abdominal pain and vomiting. Diarrhea occurred in over 60% of the patients and was the most common adverse reaction leading to discontinuations in INPULSIS-1 and INPULSIS-2, 4.5% and 4.3%, respectively.[1,2] Elevated liver enzymes 3-4-times the upper limit of normal occur at higher incidence with nintedanib than placebo, and may require dosage reduction or interruption.

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Date: July 2015

Recommendations:

- Make nintedanib non-preferred and restrict use to appropriate populations that meet prior authorization clinical criteria (see **Appendix 2**).

Background:

Idiopathic pulmonary fibrosis is a type of fibrosing interstitial pneumonia originally thought to be due to chronic inflammation. More recently abnormal wound healing has been implicated in the pathogenesis. In most IPF cases the etiology is unknown; however a link to cigarette smoking and environmental factors has been described. Familial pulmonary fibrosis accounts for less than 5% of IPF cases and genetic factors have been seen in sporadic cases of IPF.[4] IPF is chronic, progressive and unpredictable with a median survival rate of 2-3 years after diagnosis. Estimates of prevalence range from 2-29 cases per 100,000 in the population at large.[4] IPF is usually diagnosed between the ages of 40-70 years and is slightly more common in men than women. The diagnosis of IPF requires a detailed patient history to rule out other interstitial lung diseases. Most patients can be diagnosed based upon a specific interstitial pneumonia pattern seen on high-resolution computerized tomography (HRCT) of the chest. Patients may also be diagnosed by a specific combination of HRCT and surgical lung biopsy pattern.[4] Common symptoms of IPF are: chronic exertional dyspnea, cough, bibasilar inspiratory crackles and finger clubbing.[4] Staging of IPF is not currently used in practice to direct clinical decision making and there are no corresponding changes in percent-predicted FCV associated with different stages.[4] Indicators of disease progression are worsening respiratory symptoms, declining pulmonary function tests and acute respiratory decline.

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of IPF therapy.[5] Other clinically meaningful outcomes include acute exacerbation of IPF (usually measured by worsening dyspnea), all-cause non-elective hospitalizations and quality of life.[6] However, endpoints commonly studied in clinical trials include FVC and diffusion capacity for carbon monoxide (DLco) as a surrogate endpoint for lung function; 6-minute-walk test (6MWT) as a surrogate endpoint for functional status; HRCT imaging features; and biomarkers.[6,7] There is no consensus on the most appropriate surrogate outcomes to be used in IPF trials and there are no validated surrogate endpoints.[6] Further, it is uncertain what magnitude of difference for FVC or 6MWT constitutes a clinically meaningful change for patients with IPF.[5] Progression-free survival, usually assessed by combining decline in FVC and death, is a composite endpoint used in some IPF trials. The World Health Organization – Quality of Life Questionnaire (WHO-QoL) and St. George's Hospital Respiratory Questionnaire (SGRQ), which measure distress due to respiratory symptoms, are also used to measure the impact of IPF on patients' quality of life.

Multiple features have been identified with increased mortality in IPF patients (Table 1).[5] Predictors of disease progression and mortality have been demonstrated with FVC changes. Decreased survival rates have been associated with declining FVC rates of 5-10% or more, and a sign of disease progression is indicated by a decrease in FVC of ≥10%.[4,6,9] Limited evidence suggests that small decreases in FVC (5-10%) is associated with poor outcomes. A decline in the 6MWT has also been correlated with increased mortality in patients with IPF.[9] Retrospective cohort studies have suggested a decline of 30 meters (m) in the 6MWT to be a clinically meaningful threshold.[6] Standards in conducting the 6MWT are lacking, making interpretation of this test result difficult, though it is thought to be a robust indicator of functional exercise capacity.[6,11]

The joint American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) evidence-based guideline on the diagnosis and management of IPF was updated in 2011.[4] Treatment recommendations and corresponding evidence designation, using the GRADE methodology, is presented in table 2. Wide ranges of medical therapies for IPF have been explored but none have clearly demonstrated a clinical benefit in IPF. A Cochrane review found no randomized controlled trials (RCTs) to assess the benefits of corticosteroid monotherapy in patients with IPF.[12] Observational cohort studies have failed to find a mortality benefit in patients treated with corticosteroids.[12] Treatment with azathioprine and prednisone has been studied in patients with IPF without demonstrating definitive benefits and is not currently recommended. Cyclophosphamide treatment in IPF has failed to show mortality benefits and is also not recommended. The use of everolimus failed to show improved efficacy in patients with IPF

and may cause harm. A study of anticoagulant use in patients with IPF was discontinued early due to excess deaths in the warfarin group with a low probability of benefit from treatment.[14] Bosentan was studied in patients with IPF in the BUILD-1 and BUILD-3 trials but was not shown to improve outcomes and is therefore not recommended.[15,16] Ambrisentan, macitentan, sildenafil, interferon-gamma, etanercept and imatinib have been studied in IPF patients without benefit. The ATS/ERS/JRS/ALAT guideline weakly recommends against the use of pirfenidone but suggests it could be considered an option for patients who realize the expected benefits are small and there are risks of adverse reactions (ASCEND results not included in guideline).[4] The use of pirfenidone in IPF is weakly recommended by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[17] French practical guidelines and National Institute for Health and Care Excellence (NICE) recommend pirfenidone in patients with mild to moderate IPF (FVC ≥50%).[18,19] The only treatment shown to improve survival in IPF patients is lung transplantation.[4] Pirfenidone and nintedanib are currently the only drugs approved by the FDA for IPF, with the evidence for their use presented below.

Table 1. ATS/ERS/JRS/ALAT Statement on Selected Features Associated with Increased Risk of Mortality in IPF.[8]

Baseline Factors	**Longitudinal Factors**
Level of dyspnea DLco <40% predicted Desaturation ≤88% during 6MWT Extent of honeycombing on HRCT Pulmonary hypertension	Decrease in FVC ≥10% absolute value Decrease in DLco by ≥15% absolute value Worsening of fibrosis on HRCT
Definitions of abbreviations: 6MWT= 6-minute walk-test; DLco = diffusion capacity for carbon monoxide; HRCT = high-resolution computer tomography.	

Raghu G, Collard H, Egan J, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guideline for Diagnosis and Management. Am J Respir Crit Care Med 2011;183:788-824.

Table 2. ATS/ERS/JRS/ALAT Treatment Recommendations.[4]

	Treatment	**Evidence Grade**
Recommendation AGAINST the use of treatment in IPF is STRONG	Corticosteroid Monotherapy	Very low
	Colchicine	Very low
	Cyclosporine A	Very low
	Combined corticosteroid and immune-modulator therapy	Low
	Interferon γ 1b	High
	Bosentan	Moderate
	Etanercept	Moderate
Recommendation AGAINST the use of treatment in IPF is weak	Combined acetylcysteine and azathioprine and prednisone	Low
	Acetylcysteine monotherapy	Low
	Anticoagulation	Very low
	Pirfenidone	Low
Recommendation for therapy in IPF patients is STRONG	Long-term oxygen therapy	Very low
Recommendation for procedure in IPF patients is STRONG	Lung transplantation	Very low
Recommendation AGAINST procedure in patients with respiratory failure due to IPF is WEAK	Mechanical ventilation	Low
Recommendation for procedure in IPF patients is WEAK	Pulmonary rehabilitation	Low
Recommendation for therapy in IPF patients with acute exacerbations is WEAK	Corticosteroids	Very low
Recommendation AGAINST the treatment of associated IPF conditions is WEAK	Pulmonary hypertension	Very low
Recommendation for therapy in IPF patients is WEAK	Asymptomatic gastroesophageal reflux	Very low

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Nintedanib was studied in two double blind, placebo-controlled, phase 3, randomized trials in 717 patients and lasting 52 weeks. Both studies, INPULSIS-1 and INPULSIS-2, were conducted in the same manner with the same methodology.[1] Patients were randomized to nintedanib 150 mg orally twice daily or placebo for 52 weeks. The dose could be decreased to 100 mg twice daily if needed for the management of adverse events. The primary endpoint was the annual rate of decline in FVC. Secondary endpoints were absolute change from baseline in FVC, FVC response (decline in the percentage of predicted FVC not more than 5 percentage points and decline not more than 10 percentage points at week 52), time to the first acute exacerbation and change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ). The SGRQ measures a total score of 0 to 100, with higher scores correlated with worse health-related quality of life. Randomized controlled trial in IPF patients have demonstrated between group differences in SGRQ total scores ranging from -3.3 to -6.[18] In patients with chronic obstructive pulmonary disease, the minimal important difference is 4 points.[19] However, the minimal important difference in patients with IPF has not been determined.

Patients in INPULSIS-1 had mild to moderate IPF, were predominately men and were a mean age of 67 years.[1] A majority of participants were former smokers (70%). In INPULSIS-1, the adjusted annual rate of change in FVC was less with nintedanib compared to placebo, -114.7 mL/year vs. -239.9 mL/year, respectively ($p<0.001$). The absolute percent predicted change in FVC favored nintedanib, with an absolute difference from placebo of 3.2% (95% CI 2.1 to 4.3; $P<0.001$). The number of patients that had less than 10% decline in FVC at 52 weeks was significantly higher in the nintedanib group compared to placebo with a NNT of 7. Incidence (percent) of first investigator reported acute exacerbation was not significantly different between nintedanib and placebo groups (HR 1.15, 95% CI, 0.54 to 2.42; p=0.67). In addition, there was no significant difference in quality of life as seen in SGRQ scores between the groups at 52 weeks.

The patient demographics in INPULSIS-2 were similar to patients enrolled in INPULSIS-1.[1] Nintedanib was statistically superior to placebo based on the surrogate endpoint of adjusted annual rate of change in FVC (absolute difference 93.7 mL/year, 95% CI 44.8 to 142.7; $p<0.001$). The difference in the adjusted absolute mean change from baseline in percent predicted FVC was 3.1%, favoring nintedanib treatment ($p<0.001$). Nintedanib and placebo groups were not significantly different in the number of patients with ≤10 % decline in FVC at 52 weeks. Results showed nintedanib to be superior to placebo in cumulative incidence (percent) of first investigator reported acute exacerbation (HR 0.38, 95% CI, 0.19 to 0.77; p=0.005). Nintedanib was associated with a significant improvement in SGRQ score compared to placebo with an absolute difference -2.69 (95% CI -4.95 to 0.43; p=0.02). However, it is unknown if such a small difference is clinically significant.[18,19]

Prespecified pooled data of INPULSIS-1 and INPULSIS-2 showed a statistically significant benefit of nintedanib over placebo for the surrogate endpoint of annual rate of FVC change, with a difference of -109.9 mL (95% CI 75.9 to 144.0 mL).[1] Absolute mean change from baseline in FVC, from pooled data, showed a significant advantage with nintedanib therapy over placebo (difference 110.6 mL, 95% CI 83.2 to 137.9 mL; $p<0.001$). A significant FVC response (patients with an absolute decline in % predicted FVC of no more than 5% or no more than 10% at week 52) favored the nintedanib groups compared to placebo in pooled analysis data. Time to first acute exacerbation was not significantly different in the pooled nintedanib group compared to placebo (HR 0.64, 95% CI 0.39 to 1.05; p=0.08). In a prespecified pooled analysis, death from any cause, death due to respiratory cause, and death that occurred between randomization and 28 days after the last dose of the study drug were not significantly different between groups.

Conclusions of clinical efficacy for nintedanib are limited to only two, small phase 3 studies using a surrogate primary endpoint for analysis. The INPULSIS studies were fair-good quality with high levels of overall attrition that could potentially influence results. Wide confidence intervals seen with the primary endpoint suggest an imprecise prediction in the true treatment effect. The clinically meaningful endpoints of time to first acute exacerbation and quality of life improvements were only significant in IMPULSIS-2. The clinical importance of increased myocardial infarctions seen with nintedanib will need further investigation.

Clinical Safety:

The most common adverse reactions occurring ≥5% are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased and hypertension (Table 2).[2] Diarrhea was the most common adverse event leading to discontinuations; fourteen patients randomized to nintedanib in both studies versus no patients in the placebo group in INPULSIS-1 and 1 patient in the placebo group in INPULSIS-2. Serious adverse events were similar between groups in both trials. Elevated liver enzymes, at 3-4 times the upper limit of normal, were more common in patients taking nintedanib compared to placebo. Myocardial infarction was reported in more often in pirfenidone treated patients compared to placebo, 1.5% vs. 0.4%, respectively.

Table 3. Adverse Reactions Occurring in ≥5% of Pirfenidone-treated Patients More commonly Than Placebo[2]

Adverse Reaction	Pirfenidone 150 mg (n=723)	Placebo (n=508)
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 decreased	10%	3%
Hypertension	5%	4%

Pharmacology and Pharmacokinetic Properties:[2]

Parameter	
Mechanism of Action	Works by inhibiting receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases (nRTKs), which are involved in the pathogenesis of IPF.
Oral Bioavailability	4.7%
Distribution and Protein Binding	Bi-phasic disposition kinetics and high protein binding (97.8%).
Elimination	Urinary excretion 0.05%
Half-Life	9.5 hours
Metabolism	Hydrolytic cleavage by esterases and subsequent glucuronidation by UGT enzymes. CYP-dependent metabolism accounted for 5% of the total.

Abbreviations: CYP – cytochrome P450.

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Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Hospitalizations
3) Disease Progression (FVC, VC)
4) Exercise tolerance (6MWD)
5) Quality of life
6) Acute exacerbations and symptoms

Primary Study Endpoint:
1) Adjusted annual rate of change in FVC

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Richeldi, et al. (INPULSIS-1)[1] PC, DB, RCT, Phase 3 52 weeks	1. Nintedanib 150 mg twice daily (N) 2. Placebo (P)	Demographics: Men: 81% Age: 67 years FVC: 2,801 mL Predicted DLco: 48% Key Inclusion Criteria: • Age >40 years; • IPF dx previous 5 years; • FVC ≥50% of predicted value; • DLco 30-79% of predicted value • HRCT of the chest previous 12 months; • Prednisone ≤15 mg/day, or equivalent, allowed if dose stable x8 weeks before screening. Key Exclusion Criteria: • Treatments for IPF other than prednisone or	ITT: 1.309 2.204 PP: 1.229 2. 163 Attrition: 1. 105 (34%) 2. 41 (20%)	Primary Endpoint: Adjusted Annual Rate of Change in FVC: N: -114.7 mL/year P: -239.9 mL/year Difference 125.3 mL/year (95% CI 77.7 to 172.8) P<0.001 Secondary Endpoints: Mean Change in SGRQ Score from baseline at week 52: N: +4.34 points P: +4.39 points Absolute difference -0.05 (95% CI -2.50 to 2.40; p=0.97) Mean Change from Baseline % predicted FVC: N: -2.8 % P: -6.0 % Difference 3.2% (95% CI 2.1 to 4.3; p<0.001) FVC decline ≤10 percentage points: N: 218 (70.6%)	NA NA	Diarrhea: N: 190 (61.5%) P: 38 (18.6%) p-value not reported Serious Adverse Events: N: 96 (31.1%) P: 55 (27.0%) p-value not reported Elevated Liver Enzymes*: N: 15 (4.9%) P: 1 (0.5%) p-value not reported Adverse Events Leading to Discontinuations: N: 65 (21.0%) P: 22 (10.8%) p-value not reported * ALT/AST 3-4x ULN.		**Quality Rating**: Fair - Good **Internal Validity (Risk of Bias)**: Selection: Interactive telephone and web-based response system. Performance: Double-blind design and treatment was masked with identical packaging. Detection: Outcome assessors were blinded. Attrition: Attrition was high overall (27%). Modified ITT analysis was used. **Applicability**: Patient: Population representative of patients with IPF. A majority (70%) of patients were former smokers. 27% required dose reduction to 100 mg BID compared to 5% w/ placebo. Intervention: new drug. Comparator: Placebo-controlled; no active control Outcomes: Annual rate of decline in FVC is an FDA accepted surrogate endpoint. Data on long-term health outcomes are lacking. Setting: Patients recruited from 205 outpatient sites in 24 countries. **Analysis**: Absolute changes in FVC from baseline were small in both groups, suggesting enrolled patients had less progressive IPF.

		equivalent; • Anticoagulant or high-dose antiplatelet therapy; • abnormal labs; • Cardiac disease; • Lung transplant candidates.		P: 116 (56.9%) Odds Ratio 1.91 (95% CI 1.32 to 2.79; p<0.001)	14/7			
2. Richeldi, et al. (INPULSIS-2)[1] PC, DB, RCT, Phase 3 52 weeks	1. Nintedanib 150 mg twice daily (N) 2. Placebo (P)	Demographics: Men: 78% Age: 67 years FVC: 2,646 mL Predicted DLco: 46.7% Key Inclusion Criteria: See INPULSIS-1 Key Exclusion Criteria: See INPULSIS-2	ITT: 1. 329 2. 219 PP: 1. 246 2. 169 Attrition: 1. 83 (25%) 2. 50 (23%)	Primary Endpoint: Adjusted Annual Rate of Change in FVC: N: -113.6 mL/year P: -207.3 mL/year Absolute difference 93.7 mL/year (95% CI 44.8 to 142.7; p<0.001) Secondary Endpoints: Mean Change in SGRQ Score from baseline at week 52: N: +2.80 points P: +5.48 points Difference -2.69 (95% CI -4.95 to 0.43; p=0.02) Mean Change from Baseline % predicted FVC: N: -3.1% P: -6.2% Difference 3.1% (95% CI 1.9 to 4.3; p<0.001) FVC decline ≤10 percentage points: N: 229 (69.6%) P: 140 (63.9%) OR 1.29 (95% CI 0.89 to 1.86; p=0.18)	NA NA NA NS	Diarrhea: N: 208 (63.2%) P: 40 (18.3%) p-value not reported Serious Adverse Events: N: 98 (29.8%) P: 72 (32.9%) p-value not reported Elevated Liver Enzymes*: N: 17 (5.2%) P: 2 (0.9%) p-value not reported Adverse Events Leading to Discontinuations: N: 58 (17.6%) P: 33 (15.1%) p-value not reported * ALT/AST 3-4x ULN.		**Quality Rating**: Fair - Good **Internal Validity (Risk of Bias)**: Selection: Interactive telephone and web-based response system. Performance: Double-blind design and treatment was masked with identical packaging. Detection: Outcome assessors were blinded. Attrition: Attrition overall was high (24%). Modified ITT analysis was used. **Applicability**: Patient: A majority of participants were former smokers (65%). 29% required dose reduction to 100 mg BID compared to 3% w/ placebo. Intervention: new drug. Comparator: Placebo-controlled; no active control Outcomes: Annual rate of decline in FVC is an FDA accepted surrogate endpoint. Data on long-term health outcomes are lacking. Setting: Patients recruited from 205 outpatient sites in 24 countries. **Analysis**: Population representative of patients with IPF. Absolute changes in FVC from baseline were small in both groups, suggesting enrolled patients had less progressive IPF.

Abbreviations [alphabetical order]: ALT/AST = alanine aminotransferase/aspartate aminotransferase; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; DLco = carbon monoxide diffusing capacity; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; ITT = intention to treat; mITT = modified intention to treat; mL= milliliters; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PP = per protocol; ULN = upper limit of normal.

References:

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Author: Kathy Sentena Date: July 2015

Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OFEV safely and effectively. See full prescribing information for OFEV.

OFEV® (nintedanib) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

OFEV is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food. (2.2)
- Consider temporary dose reduction to 100 mg, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 6)
- Prior to treatment, conduct liver function tests. (2.1, 5.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg and 100 mg (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with OFEV. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
- Gastrointestinal disorders: Diarrhea, nausea, and vomiting have occurred with OFEV. Treat patients at first signs with adequate hydration and antidiarrheal medicine (e.g., loperamide) or anti-emetics. Discontinue OFEV if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment. (5.2)
- Embryofetal toxicity: Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.3)
- Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. (5.4)
- Bleeding events have been reported. Use OFEV in patients with known bleeding risk only if anticipated benefit outweighs the potential risk. (5.5)
- Gastrointestinal perforation has been reported. Use OFEV with caution when treating patients with recent abdominal surgery. Discontinue OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Coadministration of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for tolerability of OFEV. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (8.3)
- Hepatic impairment: Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment. OFEV is not recommended for use in patients with moderate or severe hepatic impairment. (8.6, 12.3)
- Renal impairment: The safety and efficacy of OFEV have not been studied in patients with severe renal impairment and end-stage renal disease. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV. (8.8)

Appendix 2: Suggested Prior Authorization Criteria

Idiopathic Pulmonary Fibrosis (IPF) Agents

Goal: Restrict use of IPF agent to populations in which the drug has demonstrated efficacy.

Length of Authorization: Up to 1 year

Requires PA:

- Non-preferred drugs

Preferred Alternatives:

- None at this time

Approval Criteria		
1. Is this request for continuation of therapy (patient has already been on IPF drug)	Yes: Go to Renewal Criteria	No: Go to #2
2. Does the patient have a diagnosis of idiopathic pulmonary fibrosis (ICD-9 516.31)?	Yes: Go to #3	No: Pass to RPH; Deny for medical appropriateness.
3. Is the treatment prescribed by a pulmonologist?	Yes: Go to #4	No: Pass to RPH; Deny for medical appropriateness.
4. Does the patient have a forced vital capacity (FVC) >50%?	Yes: Go to #5	No: Pass to RPH; Deny for medical appropriateness.
5. Is the patient a current smoker?	Yes: Pass to RPH; Deny for medical appropriateness. Efficacy of approved drugs for IPF may be altered in smokers due to decreased exposure (see prescribing information).	No: Go to #6
6. Are pirfenidone and nintedanib concurrently prescribed in this patient?	Yes: Pass to RPH; Deny for medical appropriateness. Safety and efficacy of concomitant therapy has not been established.	No: Approve for up to 12 months.
Renewal Criteria		
Is there evidence of disease progression (defined as ≥10% decline in percent-predicted FVC) within the previous 12 months?	Yes: Pass to RPH; Deny for medical appropriateness.	No: Approve for up to 12 months.

P&T/DUR Review: *7/15 (KS)*
Implementation: ***TBD***