

**Nintedanib (OFEV®)****Criteria for Use****March 2015**

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

*The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.*

*The Product Information should be consulted for detailed prescribing information.*

*See the VA National PBM-MAP-VPE Monograph on this drug at [www.pbm.va.gov](http://www.pbm.va.gov) or <http://vawww.pbm.va.gov> for further information.*

**Exclusion Criteria** *If the answer to ANY item below is met, then the patient should NOT receive nintedanib*

- The diagnosis of idiopathic pulmonary fibrosis has not been confirmed (see **Inclusion Criteria and Issues for Consideration**)<sup>1,2</sup>
- Patient is a current smoker
- Presence of liver function test abnormalities (may be a temporary or permanent exclusion depending upon severity and pattern; see **Monitoring** and **Issues for Consideration**)
- Patient has Child Pugh Class B or C hepatic impairment
- Patient is currently receiving treatment with pirfenidone (ESBRIET®)
- There is documented ongoing nonadherence to prior medications or medical treatment

**Inclusion Criteria** *The answers to one of the following must be fulfilled in order to meet criteria.*

- Treatment is initiated and followed by VA Pulmonologist experienced in the diagnosis and management of interstitial lung disease
- The diagnosis of idiopathic pulmonary fibrosis meets ATS/ERS/JRS/ALAT diagnostic requirements and has been confirmed through formal interdisciplinary discussion (Interstitial Lung Disease Consensus Committee, or similar)<sup>1,2</sup>
- Pregnancy should be excluded prior to receiving nintedanib and the patient provided contraceptive counseling on potential risk vs. benefit of taking nintedanib if patient were to become pregnant.

**Dosage and Administration**

- The recommended dosage of nintedanib is 150mg twice daily with food.
- Dose modifications may be required for adverse effects, liver function abnormalities or drug interactions (see **Monitoring**)

## Monitoring

- **Pulmonary specialty follow-up should occur at least biannually for assessment of drug response** (see **Issues for Consideration**)
- **Adherence:** Treatment adherence is required for maximal benefit; patients should be monitored to insure adherence
- **Liver chemistries:**
  - Obtain AST, ALT, ALKP, and GGT at baseline, monthly for 3 months, and thereafter as clinically indicated.
- **Dose modifications for liver chemistry abnormalities:**
  - For AST or ALT >3 but ≤5x upper limit of normal (ULN), without symptoms or hyperbilirubinemia, after starting nintedanib therapy:
    - ◇ Discontinue confounding medications, exclude other causes, and monitor the patient closely.
    - ◇ Reduce nintedanib to 100mg twice daily, or place on temporary hold.
    - ◇ Repeat liver chemistry tests as clinically indicated.
    - ◇ Resume at 100mg twice daily or at full-dosage, as applicable, when liver chemistry tests have normalized
  - Nintedanib should be permanently discontinued
    - ◇ If AST or ALT >3 but ≤5x ULN and accompanied by symptoms or hyperbilirubinemia
    - ◇ For AST or ALT >5x ULN, regardless of symptoms or hyperbilirubinemia
- **Dose modifications for adverse reactions:**
  - Diarrhea may 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.
  - Mild or moderate nausea 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.

## Drug Discontinuation

- Temporarily discontinue nintedanib in response to elevated liver function tests (as defined in **Monitoring**) or adverse reactions of moderate severity
- Permanently discontinue nintedanib in response to
  - Liver function test abnormalities as defined in **Monitoring**
  - Severe adverse drug reactions
  - Significant nonadherence to therapy
  - Smoking
- Consider discontinuation of nintedanib in response to a perceived treatment failure based upon serial pulmonary function trends (see **Issues for Consideration**)

## Issues for Consideration

- **ATS/ERS/JRS/ALAT Consensus Guidelines (2011) require the following for diagnosis of IPF:**
  - Exclusion of other known causes of interstitial lung disease [domestic and occupational environmental exposures, connective tissue disease, and drug toxicity]

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- Presence of a pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography [HRCT] and
  - Specific combinations of HRCT and surgical lung biopsy patterns in patients subjected to surgical lung biopsy.

Diagnostic accuracy of IPF is improved through formal multidisciplinary interaction (Pulmonary, Radiology, and Pathology joint consultation/conferencing) and the Consensus Committee strongly recommended that approach in the evaluation of suspected IPF.

- **ATS/ERS/JRS/ALAT Consensus Guidelines (2011)** recommend that FVC and DL<sub>CO</sub> measurements be performed during routine monitoring of IPF and that such monitoring occur at 3 to 6 month intervals. More frequent repetition of FVC and DL<sub>CO</sub> should be performed in the presence of progressive dyspnea or other features of a more rapidly progressive course.
  - **ATS/ERS/JRS/ALAT Consensus Guidelines (2011)** indicate that a change in absolute forced vital capacity (FVC) of 10% [with or without a concomitant change in carbon monoxide diffusing capacity(DL<sub>CO</sub>)] or a change in absolute DL<sub>CO</sub> of 15% (with or without a concomitant change in FVC) is a surrogate marker of mortality and is evidence of disease progression. Nintedanib has been shown to decrease (not stop) progression of IPF; the extent of disease progression at which nintedanib inefficacy can be assumed has not been established.
  - Due to a mechanism of action which includes VEGFR inhibition, nintedanib may increase risk of gastrointestinal perforation, bleeding, and thrombosis. In clinical trials, the incidence of gastrointestinal perforation was 0.3% in patients given nintedanib (vs. 0% given placebo). These trials also reported bleeding events in 10% of nintedanib-treated patients (vs. 7%), arterial thromboembolic events in 2.5% of nintedanib-treated patients (vs. 0.8%), and myocardial infarction in 1.5% of patients given nintedanib (vs. 0.4%). These events occurred in spite of trial enrollment criteria which excluded patients with a predisposition to bleeding or thrombosis, patients on full-dose anticoagulation or intensive antiplatelet therapy, and patients with active cardiac disease. Caution should be exercised when administering nintedanib to these at-risk populations.
  - Nintedanib is PREGNANCY CATEGORY D and can cause fetal harm when administered to a pregnant woman. 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. If nintedanib is used during any portion of a pregnancy the patient should be advised of the potential hazard to a fetus.
  - 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.
  - There have been no dedicated pharmacokinetic studies of nintedanib in patients with hepatic impairment; in addition, clinical studies excluded patients with AST, ALT, and total bilirubin > 1.5x ULN. Patients with mild hepatic impairment prior to initiation of nintedanib should be closely monitored for adverse reactions and the need for dose modification or drug discontinuation.
  - AUC<sub>0-inf</sub> and C<sub>max</sub> of nintedanib in smokers reflect a 21% reduced exposure which may alter the drug's efficacy.
  - There is no evidence to support or recommend the combined use of nintedanib and pirfenidone. Also, in a multiple dose study, administration of nintedanib with pirfenidone significantly reduced nintedanib exposure (nintedanib AUC and C<sub>max</sub> were decreased 68.3 and 59.2%, respectively).
  - Randomized controlled trials of nintedanib did not enroll patients with severe IPF; there is little data to indicate to what extent nintedanib is effective in patients with severe IPF (FVC < 50%).
  - There is inadequate evidence to support the efficacy associated with long term administration of reduced-dose nintedanib (100mg twice daily).
  - There are inadequate data to strongly recommend for or against provision of nintedanib to patients placed on a lung transplant wait list. In 2011, the median time from wait list enrollment to lung transplant for US
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IPF patients was 2.1 months and up to 79% of patients received a transplant within one year of wait list placement.<sup>4,5</sup> This typically shortened period of nintedanib administration could reduce potential for significant drug benefit. Alternatively, the mortality rate among US IPF patients listed for lung transplant remains high (11% reported in 2011) and there are no guarantees that status as a transplant candidate will not change or that a lung donor will be identified for every potential recipient. Whether nintedanib should be provided to a patient on a lung transplant wait list should follow a case-specific assessment of the risks and benefits associated with such therapy.

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## References

1. 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.
2. Gulati M. Diagnostic Assessment of Patients with Interstitial Lung Disease. *Prim Care Respir* 2011; 20: 120-127
3. 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.
4. Kistler KD, Nalysnyk L, Rotella P et al. Lung Transplantation in Idiopathic Pulmonary Fibrosis: A Systematic Review of the Literature. *BMC Pulm Med* 2014; 14: 139-50.
5. Chen H, Shiboski SC, Golden JA et al. Impact of the Lung Allocation Score on Lung Transplantation for Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med* 2009; 180: 468-74.

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