Pirfenidone (ESBRIET®)

Criteria for Use

August 2017

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 or http://vaww.pbm.va.gov for further information.

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

- ☐ The diagnosis of idiopathic pulmonary fibrosis (IPF) has not been confirmed as defined below (see **Inclusion Criteria** and **Issues for Consideration**)[1]
- ☐ 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**)
- ☐ Patient has severe hepatic impairment (Child Pugh Class C)
- ☐ Patient has end-stage renal disease requiring dialysis
- ☐ Patient is currently receiving treatment with nintedanib (OFEV®) [see **Issues for Consideration**]
- ☐ Patient is taking a combination of moderate or strong CYP1A2 inhibitors with other drugs which also inhibit CYP isoenzymes involved in the metabolism of pirfenidone (2C9, 2C19, 2D6, and 2E1) which cannot be altered or discontinued
- ☐ There is documented ongoing nonadherence to prior medications or medical treatment

Inclusion Criteria *The answers to ALL 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 IPF meets ATS/ERS/JRS/ALAT diagnostic requirements and has been confirmed through formal interdisciplinary discussion (Interstitial Lung Disease Consensus Committee, or similar) [see **Issues for Consideration**][1,2]

Dosage and Administration

- Pirfenidone is available in a 267mg capsule and an 801mg tablet.
- The recommended dosage of pirfenidone is 801 mg three times a day with food for a total of 2403 mg/day. Doses should be taken at the same time each day.
- For initiation of treatment or resumption of treatment following a lapse of ≥ 14 days, pirfenidone should be titrated to the full dosage of 801mg three times a day over a 14-day period as follows: Days 1 through 7 → one 267mg capsule three times a day, days 8-14 → two 267mg capsules three times a day, day 15 onward → one 801mg tablet 3 times a day.
- Dose modifications may be required for side effects, liver function abnormalities or drug interactions (see **Monitoring**)
- Pirfenidone administration may result in a photosensitivity reaction or rash; patients should be advised to avoid or minimize exposure to sunlight/artificial UV sources and to utilize SPF≥50 sunblock and occlusive clothing/hats for additional UV protection.

Monitoring

- **Pulmonary specialty follow-up including pulmonary function testing 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 and total bilirubin at baseline, then monthly for 6 months, and every 3 months thereafter
- **Dose modifications for liver chemistry abnormalities:**
  - For AST or ALT >3 but ≤5 × the upper limit of normal (ULN) without symptoms or hyperbilirubinemia after starting pirfenidone therapy:
    - ◊ Discontinue confounding medications, exclude other causes, and monitor the patient closely.
    - ◊ Repeat liver chemistry tests as clinically indicated.
    - ◊ The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent re- titration to the full dosage as tolerated.
  - For AST or ALT >3 but ≤5 × ULN accompanied by symptoms or hyperbilirubinemia: permanently discontinue pirfenidone and do not rechallenge patient
  - For AST or ALT >5 × ULN: permanently discontinue pirfenidone and do not rechallenge patient
- **Dose modifications for drug interactions:**
  - *Strong CYP1A2 inhibitors:* Co-administration of pirfenidone with strong CYP1A1 inhibitors (ex: fluvoxamine, enoxacin) is not recommended; if unavoidable, reduce dose of pirfenidone to 267mg three times daily
  - *Moderate CYP1A2 inhibitors:* Reduce dose of pirfenidone to 534mg three times daily in combination with high-dose moderate CYP1A2 inhibitor (ex: ciprofloxacin 750mg twice daily)
  - Strong or moderate CYP1A2 inhibitors in combination with other drugs which inhibit other CYP isoenzymes involved in the metabolism of pirfenidone would have an unpredictable effect on clearance of the drug; these combinations should be discontinued or avoided during pirfenidone treatment.
  - *Strong CYP1A2 inducers:* Co-administration of pirfenidone with strong CYP1A2 inducers is not recommended due to an expected reduction in pirfenidone exposure and loss of efficacy.
- **Dose modifications for adverse reactions**
  - Temporary pirfenidone dose reductions may be required to allow resolution of symptoms [see **Issues for Consideration**]

Drug Discontinuation

- Temporarily discontinue pirfenidone in response to mildly elevated liver function tests (see **Monitoring**) or adverse reactions of moderate severity (rash, photosensitivity, gastrointestinal, or other)
- Permanently discontinue pirfenidone in response to
  - Severe adverse drug reactions
  - Liver function test abnormalities as defined in **Monitoring**
  - Significant nonadherence to therapy
  - Smoking
- Consider discontinuation of pirfenidone 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 [for example, domestic and occupational environmental exposures, connective tissue disease, and drug toxicity]
  - Presence of a pattern of usual interstitial pneumonia 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 ATS/ERS/JRS/ALAT Consensus Committee strongly recommended that approach in the evaluation of suspected IPF.
- **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_{CO})] or a change in absolute DL_{CO} of 15% (with or without a concomitant change in FVC) is a surrogate marker of mortality and is evidence of disease progression. Pirfenidone has been shown to decrease (not stop) progression of IPF; the extent of disease progression at which pirfenidone inefficacy can be assumed has not been established.
- **ATS/ERS/JRS/ALAT Consensus Guidelines (2011)** recommend that FVC and DL_{CO} 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_{CO} should be performed in the presence of progressive dyspnea or other features of a more rapidly

progressive course.

- Randomized controlled trials of pirfenidone did not enroll patients with severe IPF; there is little data to indicate to what extent pirfenidone is effective in patients with severe IPF (FVC < 50%).
- Data from the Pirfenidone Study in Japan Trial indicate a reduced dose of pirfenidone given in response to an adverse reaction may still effectively reduce FVC decline in IPF.[4]
- $AUC_{0\text{-}inf}$ and C_{max} of pirfenidone are significantly reduced by smoking, resulting in decreased systemic exposure and an expected loss of efficacy
- There is no evidence to support or recommend the combined use of pirfenidone and nintedanib. Also, in a multiple dose study, while concomitant administration of nintedanib and pirfenidone did not affect pirfenidone exposure, nintedanib AUC and C_{max} were respectively decreased 68.3 and 59.2%.[5]
- Pirfenidone is PREGNANCY CATEGORY C; women of childbearing potential should be provided contraceptive counseling on potential risk vs. benefit of taking pirfenidone if the patient were to become pregnant. There are no adequate and well-controlled studies of pirfenidone in pregnant women; pirfenidone should only be used during pregnancy if the benefit to the mother outweighs the potential risk to the fetus.
- It is unknown if pirfenidone is excreted in breast milk; due to the potential for harm to a nursing infant, a decision should be made whether to discontinue nursing or discontinue pirfenidone, taking into account the importance of the drug to the mother.
- There are inadequate data to strongly recommend for or against provision of pirfenidone to patients placed on a lung transplant wait list. In 2011, the median time from wait list enrollment to lung transplant for US IPF patients was 2.1 months and up to 79% of patients received a transplant within one year of wait list placement. This typically shortened period of pirfenidone 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 pirfenidone 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.

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) Taniguchi H, Ebina M, Kondoh Y et al. for the Pirfenidone Study Group in Japan. Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. Eur Respir J 2010; 35: 821-9 + supplementary appendix.
5) Ofev® (nintedanib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October, 2014.
6) 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.
7) 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.

Updated: August 2017. Original version prepared: February, 2015; Updated March 2015.
Contact: Mitchell Nazario, PharmD, VA Pharmacy Benefits Management Services