MTF Formulary Management
Pulmonary-1s: Idiopathic Pulmonary Fibrosis (IPF) Drugs
Pulmonary Miscellaneous Subclass

Defense Health Agency Pharmacy Operations Division

Bottom Line

- **Pirfenidone (Esbriet) is now designated as Uniform Formulary and step-preferred, while nintedanib (Ofev) is non step-preferred; all new users of Ofev must try Esbriet first.**
- **Manual prior authorization applies to Esbriet and Ofev; see section below.**
- **There are limited pharmacotherapeutic options for treating IPF. Both Esbriet and Ofev offer novel mechanisms of action and have sufficient data to show a reduction in the inexorable rate of decline of lung function that is the hallmark of this disease.**

Uniform Formulary Decision: The Director, DHA, approved the recommendations from the May 2017 DoD P&T Committee meeting on July 27, 2017. Implementation will occur by August 30, 2017.

Uniform Formulary (UF) Agents		Nonformulary (NF) Agents
BCF drugs — MTFs must have on formulary	**MTFs may have on formulary***	**MTFs must not have on formulary**
None*	**Step-Preferred:** ** • pirfenidone (Esbriet) **Non Step-Preferred:** • nintedanib (Ofev)**	• None
***** Note that prednisone, which is also used to treat IPF, is on the BCF. ****Step-preferred – Esbriet must be tried first before Ofev in all new users.**		

Formulary Management Issues and Prior Authorization

- The IPF drugs have not been previously reviewed for formulary placement.
- Manual prior authorization (PA) applies to both Esbriet and Ofev, which was implemented in February 2016. The manual PAs currently in place reflect an evidence-based approach to management and encourage appropriate patient selection.
- New users of IPF agents are now required to try Esbriet prior to Ofev ("step therapy"). The initial prescription requires active management by a pulmonologist, non-smoking status, and a documented diagnosis of IPF. Concurrent usage of both Esbriet and Ofev is not allowed, due to the lack of evidence for concomitant therapy. No changes were made to the PA for Esbriet.
- Ofev can be used in the following clinical situations where Esbriet may not be appropriate: in patients where Esbriet therapy has failed (shown by a progression in the rate of decline of IPF), intolerable adverse effects, or when a patient is concomitantly taking CYP450 1A2 inhibitors (e.g., fluvoxamine).
- For both IPF drugs, PA expires after one year; continued therapy will be approved if there has been a document of positive response to therapy.

Clinical Summary

- Idiopathic pulmonary fibrosis (IPF) is difficult to diagnose and treatment options are limited. Prognosis of patients diagnosed with IPF is quite grim, with many averaging only 3 to 5 years survival after diagnosis.
- No drugs have shown a significant effect on slowing the decline of lung function associated with IPF. Ofev and Esbriet are the newest agents for treating IPF. Many older products are no longer considered standard of care (e.g., triple therapy with prednisone, azathioprine, and N-acetylcysteine) due to data showing not only minimal benefit, but occasionally significant harm.
- Recent evidence-based guidance conditionally supports use of Esbriet and Ofev, and encourages a multidisciplinary approach for correct diagnosis and optimal treatment decisions.
- While there are no head-to-head trials comparing Esbriet with Ofev, the results of efficacy endpoints for both drugs were similar in the populations studied that led to FDA approval. Overall, there is a modest but measurable effect on slowing decline in lung function compared to placebo. It is uncertain if this benefit persists past approximately 1 year.

- Study populations in the major trials for Esbriet and Ofev have typically focused on those with mild to moderate disease as defined by forced vital capacity (FVC), measured as part of enrollment criteria.
- Pirfenidone (Esbriet) approval was delayed since there was concern about the significance of pulmonary function benefit in one of the two initial studies presented to the FDA. However, a third study showed significant slowing in the rate of decline of lung function. Similarly, nintedanib (Ofev) showed a reduction in the rate of decline in lung function in two Phase III studies. Ultimately, the FDA approved both drugs in October 2014.
- The FDA found that nintedanib had convincing benefit in FVC, supported by numerical trends in favor of mortality, and other secondary efficacy measures. Pirfenidone improved FVC in two of three studies, and showed numerical trends in favor of mortality, and other secondary efficacy measures.
- The available evidence suggests that Esbriet and Ofev have similar efficacy when compared to placebo. There is no evidence to support switching among the products, and there is no data from a clinical perspective to definitively aid in selecting patients for one agent over another.
- Esbriet is administered as three 267 mg capsules three times daily with food for a total of 2,403 mg per day. A new formulation of 801 mg tablets administered three times daily is now available. Ofev is given 150 mg twice daily, 12 hours apart and with food.

Safety & Tolerability

- Both Esbriet and Ofev appear safe and well tolerated over the studied treatment periods. Pirfenidone has been in use longer than nintedanib worldwide.
- The most common adverse events include gastrointestinal side effects for both drugs, more prominently for Ofev. Pirfenidone uniquely has a rash/photosensitivity issue that can occur soon after starting and has a pregnancy category D rating, although the typical disease demographic is usually not relevant for this concern.
- Both drugs may require dosage reduction or discontinuation resulting from adverse events. Pirfenidone adverse events are most commonly due to rash and photosensitivity, while nintedanib is affected by diarrhea issues.
- Each agent has unique drug-drug interactions. Nintedanib is affected by inhibitors and inducers of CYP450 3A4, 5, and 7, while pirfenidone is affected by inhibitors and inducers of CYP450 1A2.

References

- DoD P&T Committee minutes: http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee/Meeting-Minutes
- Current/future drug classes under review by the DoD P&T Committee: http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee
- TRICARE Formulary Search Tool: http://www.express-scripts.com/tricareformulary
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents and Executive Summaries available at: http://www.health.mil/DoDPTResources
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

Pulmonary-1/Pulmonary Miscellaneous
Idiopathic Pulmonary Fibrosis (IPF)
Price Comparison at MTF

Drug	MTF Cost/Month (May 2017)
Basic Core Formulary	
prednisone	$ **Most Cost Effective**
Uniform Formulary Step Preferred	
pirfenidone (Esbriet)	$$$ **Less Cost-Effective**
Uniform Formulary Step Non-Preferred	
nintedanib (Ofev)	$$$$ **Least Cost-Effective**

Legend:
- $ = "Most Cost-Effective" represents Rxs with the lowest cost and best clinical efficacy
- $$ = "Less Cost-Effective" represents higher cost Rxs with similar clinical efficacy
- $$$ = "Less Cost-Effective" represents next higher cost Rxs with similar clinical efficacy
- $$$$ = "Least Cost-Effective" represents Rxs with the highest cost with similar clinical efficacy