Drug Monograph

Drug/Drug Class: **Ofev™ (nintedanib) capsule/ IPF Agent**

Prepared for: MO HealthNet
Prepared by: Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Ofev™ is available in a 100 mg and a 150 mg capsule containing 100 mg and 150 mg of nintedanib respectively. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877
Summary of Findings:	Efficacy of Ofev™ for the treatment of idiopathic pulmonary fibrosis was demonstrated in two phase 3, randomized, double-blind, placebo-controlled trials (n=1066). Ofev™ significantly reduced the annual rate of FVC decline and improved the number of patients with FVC response compared with placebo in both the INPULSIS-1 and INPULSIS-2 trials. Ofev™ also significantly reduced acute exacerbations, delayed time to first acute exacerbation, and improved quality of life in INPULSIS-2 but not in INPULSIS-1.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ No PA Required

© 2015 Xerox Heritage, LLC All Rights Reserved.

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[3]

Idiopathic Pulmonary Fibrosis (IPF) is a serious disease in which a cause cannot be found. IPF causes tissue deep in lungs to become thick and stiff, or scarred, over time. IPF usually affects middle-aged and older adults. In some people, fibrosis happens quickly. In others, the process is much slower. In some people, the disease stays the same for years. Many people only live about 3 to 5 years after diagnosis. The most common cause of death related to IPF is respiratory failure.

Dosage Form(s) [1]

Ofev™ is available in a 100 mg and a 150 mg capsule containing 100 mg and 150 mg of nintedanib respectively.

Manufacturer [1]

Boehringer Ingelheim Pharmaceuticals, Inc. , Ridgefield, CT 06877

Indication(s) [1]

Ofev™ is indicated for the treatment of idiopathic pulmonary fibrosis.

Clinical Efficacy [1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Ofev™ is a small molecule kinase inhibitor shown to inhibit the vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), fibroblast growth factor receptors (FGFR1, FGFR2, and FGFR3), and platelet-derived growth factor receptors (PDGFR) alpha and beta. By binding to these receptors, Ofev™ blocks intracellular signaling and prevents proliferation, migration, and transformation of fibroblasts implicated in idiopathic pulmonary fibrosis pathogenesis. Ofev™ is also shown to inhibit Fms-like tyrosine kinase-3 (FLT3) and other non-receptor tyrosine kinases (ie, Lck, Lyn, and Src), but the role of these receptors in the treatment of idiopathic pulmonary fibrosis is unknown.

Pharmacokinetics

	Ofev
Protein binding	97.8%, primarily albumin
Volume of distribution	1050 L
Metabolism	Liver, via esterases to BIBF 1202 (25%) and via CYP3A4 (5%)
Half-life	9.5 hours

Ofev™ significantly reduced the decline in FVC compared with placebo in the INPULSIS-1 and INPULSIS-2 clinical trials.

© 2015 Xerox Heritage, LLC All Rights Reserved.

STUDY DESIGN	Two identical, multicenter, randomized, double-blind, placebo-controlled, 52-week phase 3 clinical trials (n=1066).
INCLUSION CRITERIA	Patients 40 years or older diagnosed with idiopathic pulmonary fibrosis within the previous 5 years.
EXCLUSION CRITERIA	Patients receiving therapy for idiopathic pulmonary fibrosis other than stable doses of prednisone (up to 15 mg) or equivalent.
TREATMENT REGIMEN	Patients were randomized to receive Ofev™ nintedanib 150 mg twice daily or placebo for 52 weeks.
RESULTS	Ofev™ significantly reduced the annual rate of FVC decline compared with placebo in both the INPULSIS-1 (-114.7 vs -239.9 mL) and INPULSIS-2 (-113.6 vs -207.3 mL) trials. FVC response, defined as a 5% or less decline in FVC, was significantly higher in the Ofev™ groups compared with placebo groups in INPULSIS-1 (52.8% vs 38.2%) and INPULSIS-2 (53.2% vs 39.3%). Ofev™ significantly reduced acute exacerbations (3.6% vs 9.6%), delayed time to first acute exacerbation, and improved quality of life in INPULSIS-2 but not in INPULSIS-1.
SAFETY	Diarrhea was the most common adverse event but was typically mild to moderate in severity. Approximately 5% of patients in the Ofev™ groups experienced elevated liver enzymes compared with < 1% in the placebo groups. Myocardial infarction occurred in 1.6% and 1.5% in each of the Ofev™ groups and 0.5% in each of the placebo groups.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Use caution in patients with cardiovascular risk factors, including coronary artery disease, as arterial thromboembolic events have been reported; interruption of treatment may be necessary if signs or symptoms of acute myocardial ischemia develop.
- Diarrhea, usually mild to moderate, has been commonly reported; treat symptoms and reduce dosage or discontinue if symptoms persist.
- Nausea and vomiting, usually mild to moderate, have been commonly reported; treat symptoms and reduce dosage or discontinue if symptoms persist.
- Use caution in patients with recent abdominal surgery as gastrointestinal perforation has been reported; discontinue if condition occurs; use in patients at risk of perforation only if the anticipated benefit outweighs the potential risk.
- Increased risk of bleeding; use in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.
- Liver enzymes (ALT, AST, alkaline phosphatase, gamma glutamic transpeptidase, and

© 2015 Xerox Heritage, LLC All Rights Reserved.

bilirubin) may become elevated; monitoring recommended and dosage adjustment or interruption may be necessary.
- Hepatic impairment, moderate or severe; use is not recommended.
- Concomitant use with P-glycoprotein and CYP3A4 inducers should be avoided.
- Smoking should be avoided.
- Embryofetal toxicity can occur; adequate contraception should be used during treatment and for at least 3 months following discontinuation.

Adverse Effects [1]

Most common, ≥ 5%	Ofev™ (n=723)	Placebo (n=508)
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain	15%	6%
Liver enzyme elevation	14%	3%
Vomiting	12%	3%
Decreased appetite	11%	5%
Weight decreased	10%	3%
Headache	8%	5%
Hypertension	5%	4%

Drug Interactions [1]

- Anticoagulants
- P-glycoprotein and CYP3A4 inducers: rifampin, phenytoin, carbamazepine
- P-glycoprotein and CYP3A4 inhibitors: ketoconazole

Dosage and Administration [1]

The recommended dosage is 150 mg orally every 12 hours with food. Dosage adjustment may be necessary for elevated liver enzymes or other adverse reactions.

© 2015 Xerox Heritage, LLC All Rights Reserved.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Nintedanib	Ofev	Boehringer Ingelheim	100 mg capsules	1 capsule twice daily	$8080
			150 mg capsules	1 capsule twice daily	$8080
Pirfenidone	Esbriet	InterMune	267 mg capsules	3 capsules three times daily	$7878

*Missouri Maximum Allowable Cost

Conclusion

Ofev™ is a small molecule kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis. It was granted Breakthrough Designation, fast track approval, priority review, and orphan product designation for the treatment of a rare disease. Efficacy of Ofev™ was demonstrated in two phase 3, randomized, double-blind, placebo-controlled trials (n=1066). It significantly reduced the annual rate of FVC decline and improved the number of patients with FVC response compared with placebo in both the INPULSIS-1 and INPULSIS-2 trials. Ofev™ also significantly reduced acute exacerbations, delayed time to first acute exacerbation, and improved quality of life in INPULSIS-2 but not in INPULSIS-1. Gastrointestinal adverse effects were commonly noted in the clinical trials.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

© 2015 Xerox Heritage, LLC All Rights Reserved.

References

1. Product Information: Ofev™, nintedanib capsules. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, 10/2014
2. Richeldi L, du Bois RM, Raghu G et al: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370(22):2071-2082.
3. What is Pulmonary Fibrosis. Retrieved March 4, 2015 from http://www.nhlbi.nih.gov

Prepared by: Luke Boehmer, PharmD

Date: March 4, 2015

© 2015 Xerox Heritage, LLC All Rights Reserved.