Drug Monograph

Drug/Drug Class:	**Kalydeco® (ivacaftor) Tablet/ cystic fibrosis transmembrane conductance regulator (CFTR) potentiator**
Prepared for:	MO HealthNet
Prepared by:	ACS, A Xerox Company

☒ **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:	Each tablet of Kalydeco® contains 150 mg of ivacaftor. Vertex Pharmaceuticals Incorporated 130 Waverly Street Cambridge, MA 02139
Summary of Findings:	Ivacaftor potentiates the G551D-CFTR protein and has demonstrated efficacy for the treatment of CF in patients 6 years of age and older who have a G551D-CFTR mutation. Patients taking Kalydeco® demonstrated significant improvements in the risk for pulmonary exacerbations, CF symptoms, and weight gain.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☒ No PA Required ☐ Appropriate Indications ☐ Under Solicitation

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

Cystic Fibrosis affects approximately 30,000 people in the United States, and is the most common fatal genetic disease in the Caucasian population. CF is caused by mutations in the gene that encodes the CFTR protein. This protein regulates chloride and water transport in various tissues such as the lung, sweat glands, pancreas, and gastrointestinal tract. Clinical symptoms of cystic fibrosis are abnormally thick, sticky mucus in the lungs and gastrointestinal tract which leads to respiratory infections and digestive problems.

Dosage Form(s)[1]

Each tablet of Kalydeco® contains 150 mg of ivacaftor.

Manufacturer

Vertex Pharmaceuticals Incorporated 130 Waverly Street Cambridge, MA 02139

Indication(s)[1]

Kalydeco® is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator and is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *G551D* mutation.

Clinical Efficacy[1-6] (mechanism of action/pharmacology, comparative efficacy)

Ivacaftor is a potentiator of the CFTR protein. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein.

PHARMACOKINETICS (1)

	Ivacaftor
Protein binding	99%
Volume of distribution	353 L
Metabolism	Extensive hepatic via CYP3A4 to 2 major metabolites (1 active, 1 inactive).

Excretion	Feces (87.8%) Urine
Half-life	12 hours

The approval of ivacaftor was primarily based upon two randomized, double-blind, placebo-controlled clinical trials involving 213 patients with CF and a G551D mutation in the CFTR gene. The primary efficacy endpoint in both studies was improvement in lung function. Results indicated that patients treated with ivacaftor experienced significant improvements in FEV1 from baseline ($p < 0.0001$) through week 24 and the changes persisted for 48 weeks. In addition, ivacaftor patients demonstrated significant improvements in the risk for pulmonary exacerbations, CF symptoms, and weight gain compared with placebo.

STUDY DESIGN	Two randomized, double-blind, placebo-controlled clinical trials (n=213).
INCLUSION CRITERIA	Clinically stable CF patients 6 years of age and older with a G551D mutation in the CFTR gene. Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age, 26 years) with a baseline FEV1 between 40% to 90% predicted (mean, 64%; range, 32% to 98%). Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age, 9 years) with a baseline FEV1 between 40% to 105% predicted (mean, 84%; range, 44% to 134%).
EXCLUSION CRITERIA	Patients who had persistent Burkholderia cenocepacia, B dolosa, or Mycobacterium abscessus isolated from sputum at screening; patients with abnormal liver function tests: 3 or more liver function tests (ALT, AST, AP, GGT, or total bilirubin) >= 3 times the ULN.
TREATMENT REGIMEN	Patients in both trials were randomized 1:1 to receive either ivacaftor 150 mg or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (eg, tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted. The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV1 through 24 weeks of treatment. Other efficacy variables included absolute change in sweat chloride from baseline to week 24, time to first pulmonary exacerbation through week 48 (Trial 1 only), absolute change in weight from baseline to week 48, and improvement in relevant CF respiratory symptoms such as cough, sputum production, and difficulty breathing. A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified pulmonary signs or symptoms.
RESULTS	In both studies, treatment with ivacaftor resulted in a significant improvement in FEV1. The treatment difference between ivacaftor and placebo for the mean absolute change in percent predicted FEV1 from baseline through week 24 was 10.6 percentage points ($p < 0.0001$) in Trial 1 and 12.5 percentage points ($p < 0.0001$) in Trial 2, and the changes persisted through 48 weeks. Improvements in percent predicted FEV1 were observed regardless of age, disease severity, sex, and geographic region. Patients treated with ivacaftor demonstrated

	statistically significant improvements in the risk for pulmonary exacerbations, CF symptoms (in Trial 1 only), and weight gain.
SAFETY	Fewer people in the ivacaftor treatment group discontinued treatment due to adverse effects than in the placebo groups. Adverse events commonly observed with ivacaftor included headache, upper respiratory tract infection, oropharyngeal pain, nasal congestion, abdominal pain, and diarrhea.

Contraindications[1]

- None

Warnings and Precautions[1]

- Elevated transaminases (ALT, AST): Assess prior to initiating, every 3 months during the first year of therapy, and annually thereafter; monitor patients with elevated transaminase levels until abnormalities resolve; interrupt dose for an ALT or AST greater than 5 times the ULN; after resolution consider risks/benefits of resuming therapy.
- Concomitant use with strong CYP3A inducers not recommended (eg, rifampin, St. John's Wort); may cause decreased exposure and diminished efficacy.

Adverse Effects[1]

Most common, >= 8%,	**Ivacaftor (n=109)**	**Placebo (n=104)**
▪ Headache	24%	16%
▪ Oropharyngeal pain	22%	18%
▪ Upper respiratory tract infection	22%	14%
▪ Nasal congestion	20%	15%
▪ Abdominal pain	16%	13%
▪ Nasopharyngitis	15%	12%
▪ Diarrhea	13%	10%
▪ Rash	13%	7%
▪ Nausea	12%	11%
▪ Dizziness	9%	1%

Drug Interactions[1]

- CYP3A and/or P-glycoprotein substrates: cyclosporine, digoxin, midazolam, tacrolimus
- CYP3A inducers, strong: carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort
- CYP3A inhibitors, moderate: fluconazole, grapefruit juice, Seville oranges
- CYP3A inhibitors, strong: clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole

Dosage and Administration[1]

Adults and pediatric patients 6 years of age and older: 150 mg orally every 12 hours with fat-containing food. Reduce dose for moderate and severe hepatic impairment or when co-administered with moderate or strong CYP3A inhibitors.

Cost Comparisons (at commonly used dosages)

COST (AWP)*

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Ivacaftor	Kalydeco	Vertex	150 mg tablets	1 tablet every 12 hours	$ 29,400.00

*The Average Wholesale Price (AWP) as published by Thomson Reuters is in most cases the manufacturer's suggested AWP and does not necessarily reflect the actual AWP charged by a wholesaler. Thomson Reuters bases the AWP data it published on AWP reported by manufacturers or AWP is calculated based on a markup specified by the manufacturer. This markup is typically based on the Wholesale Acquisition Cost (WAC) or Direct Price (DIRP), as provided by the manufacturer, but may be based on other pricing provided by the manufacturer. Please refer to the AWP Policy available at http://www.micromedex.com/products/redbook/awp/ for more information on the published AWP information.

Conclusion

Ivacaftor potentiates the G551D-CFTR protein and has demonstrated efficacy for the treatment of cystic fibrosis in patients 6 years of age and older who have a G551D-CFTR mutation. Ivacaftor increases chloride transport on the surface of epithelial cells in multiple organs and is the first drug approved to treat the underlying cause of CF and is designated as an orphan drug. In addition, an extension study is underway to evaluate the long-term safety and durability of ivacaftor. Currently the manufacturer is evaluating a combination of ivacaftor and a second drug that may help patients with the more common delta F508-CFTR mutation, which is present in more than 90% of CF patients.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1. Product Information: Kalydeco™, ivacaftor tablets. Vertex Pharmaceuticals, Inc., Cambridge, MA, 01/2012.
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3. Ramsey BW, Davies J, McElvaney NG et al: VX08-770-102 Study Group: A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011; 365(18):1663-1672.
4. Antoniu SA: Cystic fibrosis transmembrane regulator potentiators as promising cystic fibrosis therapies. Expert Opin Investig Drugs 2011; 20(3):423-425.
5. Accurso FJ, Rowe SM, Clancy JP et al: Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med 2010; 363(21):1991-2003.
6. Van Goor F, Hadida S, Grootenhuis PD et al: Rescue of CF airway epithelial cell function in

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