Pharmacy Policy Bulletin

Title: Cystic Fibrosis Agents (Kalydeco®, Orkambi®, Symdeko®)

Policy #: Rx.01.117

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for ivacaftor (Kalydeco®), lumacaftor/ivacaftor (Orkambi®), and **tezacaftor/ivacaftor** (**Symdeko®)** as provided under the mem prescription drug benefit.

Description:

Cystic fibrosis (CF) is an inherited disease that affects mucus and sweat produced by secretory glands. The cystic fibrosis conductance regulator (CFTR) is a chloride channel present at the surface of epithelial cells in multiple organs. Mutations in this gene alter its ability to regulate the transport of chloride, sodium, and bicarbonate, leading to thick secretions in the lungs, pancreas, and other organs. Thickening of mucus can provide an environment for bacteria to grow, leading to repeated infections. Mucus blockage prevents pancreatic digestive enzymes from reaching the small intestine, reducing fat and protein absorption, which can lead to malnourishment. CF also causes sweat to become salty, which can lead to dehydration and fatigue when sweat leaves the body.

Approximately 30,000 people in the United States, and 70,000 worldwide, are living with cystic fibrosis (CF). Over 2000 mutations in the CFTR gene have been identified. The most common of which is the F508del mutation, affecting approximately 90% of those with CF. Approximately 50% of those with CF are homozygous for F508Del mutation. Other mutations in the CTFR gene include, but are not limited to: G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N and S549R,etc.

Ivacaftor (Kalydeco®)

Ivacaftor (Kalydeco®) is indicated for the treatment of CF in patients age 12 months and older who have one of the following mutations in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data*

E56K	G178R	S549R	K1060T	G1244E	2789+5G→A
P67L	E193K	G551D	A106T	S1251N	3272-26A→G
R74W	L206W	G551S	G1069R	S1255P	3849+10kbC→T
D110E	R347H	D579G	R1070Q	D1270N	
D110H	R352Q	S945L	R1070W	G1349D	
R117C	A455E	S977F	F1074L	711+3A→G	
R117H	S549N	F1052V	D1152H	E831X	

Ivacaftor is a potentiator of the CFTR protein, which promotes increased chloride transport by potentiating the gating (channel-open probability) of the CFTR protein, and improves the regulation of salt and water absorption and secretion in various tissues.

Lumacaftor/ivacaftor (Orkambi®)

Lumacaftor/ivacaftor (Orkambi®) is indicated for the treatment of CF in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene*.

The F508del mutation causes protein misfolding resulting in impaired processing and gating of the CFTR protein. Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and gating activity. Ivacaftor adds the benefit of potentiating gating of the CFTR protein.

*If genotype unknown, an FDA-cleared CF mutation test should be performed to detect the presence of a CFTR mutation.

Tezacaftor/ivacaftor (Symdeko®)

Tezacaftor/ivacaftor (Symdeko®) is indicated for the treatment of CF in patients age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene*.

Tezacaftor facilitates the cellular processing and trafficking of normal and select mutant forms of CFTR (including F508del-CFTR) to increase the amount of mature CFTR protein delivered to the cell surface. Ivacaftor is a potentiator of the CFTR protein, which facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface

*If genotype unknown, an FDA-cleared CF mutation test should be performed to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing. .

Policy:

Ivacaftor (Kalydeco®) is approved when ALL of the following are met:

1. Diagnosis of cystic fibrosis (CF); AND
2. Member is 12 months of age or older; AND
3. Prescribed by pulmonologist; AND
4. Presence of one of the following mutations in the CFTR gene:

E56K	G178R	S549R	K1060T	G1244E	2789+5G→A
P67L	E193K	G551D	A106T	S1251N	3272-26A→G
R74W	L206W	G551S	G1069R	S1255P	3849+10kbC→T
D110E	R347H	D579G	R1070Q	D1270N	
D110H	R352Q	S945L	R1070W	G1349D	
R117C	A455E	S977F	F1074L	711+3A→G	
R117H	S549N	F1052V	D1152H	E831X	

(if the patient's genotype is unknown, an FDA-cleared test must be used to detect the presence of CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test); AND

D. Member is NOT homozygous for the F508del mutation in the CFTR gene.

Lumacaftor/ivacaftor (Orkambi®) is approved when ALL of the following are met:

1. Diagnosis of cystic fibrosis; AND
2. Member is 2 years of age or older; AND
3. Prescribed by pulmonologist; AND
4. Homozygous for the F508del mutation in the CFTR gene (if the patient's genotype is unknown, an FDA-cleared CR mutation test must be performed to determine the presence of the F508del mutation on both alleles of the CFTR gene)

Tezacaftor/ivacaftor (Symdeko®) is approved when ALL of the following are met:

1. Diagnosis of cystic fibrosis; AND

2. Member is 12 years of age or older; AND

3. Prescribed by pulmonologist; AND

4. Documentation of one of the following:

a. Member is homozygous for the F508del mutation; OR

b. Member has at least one tezacaftor/ivacaftor responsive mutation in the CFTR gene

E56K	R117C	A455E	S945L	R1070W	3272-26A→ G
P67L	E193K	F508del	S977F	F1074L	3849+10kbC→ T
R74W	L206W	D579G	F1052V	D1152H	
D110E	R347H	711+3A→ G	K1060T	D1270N	
D110H	R352Q	E831X	A1067T	2789+5G→ A	

(If the patient's genotype is unknown, an FDA-cleared test must be used to detect the presence of CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test).

Black Box Warning:

N/A

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

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Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Drug Name	Generic Name
Kalydeco®	Ivacaftor
Orkambi®	Lumacaftor/ivacaftor
Symdeko®	tezacaftor/ivacaftor

Cross References:

N/A

Policy Version Number:	14.00
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