Pharmacy Policy Bulletin

Title: Cystic Fibrosis Agents (Kalydeco®, Orkambi®, Trikafta®, 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®), elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™),** and **tezacaftor/ivacaftor (Symdeko®)** as provided under the member's 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 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data* as noted in the prescribing information.

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 the F508del mutation on both alleles of the CFTR gene.

Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™)

Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™) is indicated for the treatment of CF in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene*.

Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

*If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation.

Tezacaftor/ivacaftor (Symdeko®)

Tezacaftor/ivacaftor (Symdeko®) is indicated for the treatment of CF in patients age 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence*.

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:

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

A. Diagnosis of cystic fibrosis (CF); AND
B. Member is 4 months of age or older; AND
C. Prescribed by or in consultation with a pulmonologist; AND
D. Presence of one mutation in the CFTR gene that is responsive to ivacaftor as noted in the Prescribing Information

(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)

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

A. Diagnosis of cystic fibrosis; AND
B. Member is 2 years of age or older; AND
C. Prescribed by or in consultation with a pulmonologist; AND
D. 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)

INITIAL CRITERIA: Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™) is approved when ALL of the following are met:

A. Diagnosis of cystic fibrosis (CF); AND
B. Member is 12 years of age or older; AND

C. One of the following:
    1. Member has at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene as detected by an FDA-cleared cystic fibrosis mutation test; OR
    2. Member has at least one mutation in the CFTR gene that is responsive to elexacaftor/tezacaftor/ivacaftor (Trikafta™) as noted in the Prescribing Information; AND
D. Prescribed by or in consultation with a pulmonologist

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

A. Diagnosis of cystic fibrosis; AND
B. Member is 6 years of age or older; AND
C. Prescribed by or in consultation with a pulmonologist; AND
D. Documentation of one of the following:
    1. Member is homozygous for the F508del mutation; OR
    2. Member has at least one tezacaftor/ivacaftor responsive mutation in the CFTR gene as noted in the Prescribing Information

(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).

Initial Authorization: 2 years

REAUTHORIZATION CRITERIA: Ivacaftor (Kalydeco®), Lumacaftor/ivacaftor (Orkambi®), Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™), or Tezacaftor/ivacaftor (Symdeko®) is re-approved when there is positive clinical response to therapy.

Reauthorization: 2 years

Black Box Warning as shown in the drug Prescribing Information:

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:

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.

Aherns R, Rodriguez S, Yen K, Davies JC. VX-770 in subjects 6 to 11 years with cystic fibrosis and the G551D-CFTR mutation [abstract]. Pediatr Pulmonol. 2011;46(suppl 34):283.

Boyle MP, Bell S, Konstan MW, McColley SA, Wisseh S, Spencer-Green G. VX-809, an investigational CFTR corrector, in combination with VX-770, an investigational CFTR potentiator, in subjects with CF and homozygous for the F508del-CFTR mutation [abstract]. Pediatr Pulmonol. 2011;46(suppl 34):287.

Castellani C, Cuppens H, Macek M Jr, Cassiman JJ, Kerem E, Durie P, Tullis E, Assael BM, Bombieri C, Brown A, Casals T, Claustres M, Cutting GR, Dequeker E, Dodge J, Doull I, Farrell P, Ferec C, Girodon E, Johannesson M, Kerem B, Knowles M, Munck A, Pignatti PF, Radojkovic D, Rizzotti P, Schwarz M, Stuhrmann M, Tzetis M, Zielenski J, Elborn JS. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros. 2008 May;7(3):179-96. doi: 10.1016/j.jcf.2008.03.009.

Chen Y, Luo X, Dubey N, et al. Drug-drug interaction between VX-770 and CYP3A modulators [abstract]. J Clin Pharmacol. 2011;51:1348.

Drumm ML, Ziady AG, Davis PB. Genetic variation and clinical heterogeneity in cystic fibrosis. Annu Rev Pathol. 2012;7:267-282.

Flume PA, Borowitz D, Liou T, et al. VX-770 in subjects with CF and homozygous for the F508del-CFTR mutation [abstract]. Pediatr Pulmonol. 2011;46(suppl 34):284-285.

Kalydeco® (Ivacaftor) [package insert]. Boston, MA. Vertex Pharmaceuticals, Inc; December 2020. Available at: https://pi.vrtx.com/files/uspi_ivacaftor.pdf. Accessed on March 31, 2021.

Orkambi® (lumacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; July 2019. Available at: https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf. Accessed on March 31, 2021.

McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of investigational CFTR potentiator, VX-770, in subjects with CF [abstract]. Pediatr Pulmonol. 2011;46(suppl 34):284.

Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.

National Heart, Lung, and Blood Institute. Cystic Fibrosis. Bethesda, MD. Accessed March 31, 2021.

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.

Robinson KA, Saldanha IJ, McKoy NA. Management of infants with cystic fibrosis: a summary of the evidence for the Cystic Fibrosis Foundation working group on care of infants with cystic fibrosis. J Pediatr. 2009;155(suppl 6): S94-S105.

Simon, RH. Cystic fibrosis: Overview of the treatment of lung disease. In: UpToDate. Waltham, MA. Accessed on March 31, 2021.

Symdeko® (tezacaftor/ivacaftor) [package insert]. Boston, MA. Vertex Pharmaceutical Inc.; December 2020. Available at: https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf. Accessed March 31, 2021.

Trikafta™ (elexacaftor/tezacaftor/ivacaftor and ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2020. Available at: https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf. Accessed on March 31, 2021.

Van Goor F, Hadida S, Grootenhuis PD, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S A. 2009;106(44):18825-18830.

Van Goor F, Yu H, Burton B, Huang T, Hoffman B, Negulescu P. VX-770 potentiation of CFTR forms with channel gating defects in vitro [abstract]. Pediatr Pulmonol. 2011;46(suppl 34):215.

Woodworth BA, Zhang S, Skinner D, Sorscher EJ, Rowe SM. Comparison of CFTR and ciliary beat frequency activation by the CFTR modulators VX-770, VRT532, and UCCF-152 in primary sinonasal epithelial cultures [abstract]. Pediatr Pulmonol. 2011;46(suppl 34):251-252.

Yu H, Burton B, van Goor F. VX-770, an investigational CFTR potentiator, acts on multiple CFTR forms in vitro [abstract]. Pediatr Pulmonol. 2010;45(suppl 33):318-319

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
Trikafta™	Elexacaftor/tezacaftor/ivacaftor and ivacaftor
Symdeko®	Tezacaftor/ivacaftor

Cross References:

Off-Label Use Rx.01.33

Policy Version Number:	20.00
P&T Approval Date:	March 18, 2021
Policy Effective Date:	July 01, 2021
Next Required Review Date:	March 18, 2022