Washington State Health Care Authority

Cystic Fibrosis Agents (Oral)

Medical policy no. 45.30.00 Effective: **TBD**

Note:
New-to-market drugs included in this class based on the Apple Health Preferred Drug List are non-preferred and subject to this prior authorization (PA) criteria. Non-preferred agents in this class require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed. If a drug within this policy receives a new indication approved by the Food and Drug Administration (FDA), medical necessity for the new indication will be determined on a case-by-case basis following FDA labeling.

To see the list of the current Apple Health Preferred Drug List (AHPDL), please visit: https://www.hca.wa.gov/assets/billers-and-providers/apple-health-preferred-drug-list.xlsx

Background:

Cystic fibrosis (CF) occurs from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene resulting in dysfunctional transport of electrolytes across epithelial linings. Chloride transport is most affected resulting in thick mucus build-up in the lungs, digestive tract, and other organ systems. Although many CFTR gene mutations can lead to CF, *F508del* is most common. Homozygous *F508del* CFTR mutations account for up to 50% of CF cases. CFTR modulators target specific changes on the CFTR gene, and have demonstrated improved clinical outcomes associated with CF including increased FEV1, weight gain, symptom reduction, and decreased pulmonary exacerbations.

Medical necessity:

Drug	Medical Necessity
ivacaftor **(KALYDECO)**	KALYDECO may be considered medically necessary when used for the treatment of: • Cystic fibrosis with at least one CFTR gene mutation responsive to ivacaftor (See Table 1).
lumacaftor/ivacaftor **(ORKAMBI)**	ORKAMBI may be considered medically necessary when used for the treatment of: • Cystic fibrosis with homozygous (two copies) *F508del* mutation in the CFTR gene.
Tezacaftor/ivacaftor and ivacaftor **(SYMDEKO)**	SYMDEKO may be considered medically necessary when used for the treatment of: • Cystic fibrosis with homozygous (2 copies) *F508del* mutation or at least one CFTR gene mutation that is responsive to tezacaftor/ivacaftor (See Table 1).
Elexacaftor/tezacaftor/ivacfator and ivacaftor **(TRIKAFTA)**	TRIKAFTA may be considered medically necessary when used for the treatment of: • Cystic fibrosis with at least one *F508del* mutation in the CFTR gene.

Clinical policy:

Drug	Clinical Criteria (Initial Approval)
ivacaftor **(KALYDECO)** lumacaftor/ivacaftor **(ORKAMBI)** Tezacaftor/ivacaftor and ivacaftor **(SYMDEKO)** Elexacaftor/tezacaftor/ivacaftor and ivacaftor **(TRIKAFTA)**	KALYDECO, ORKAMBI, SYMDEKO, and TRIKAFTA may be authorized when **ALL** of the following criteria are met: 1. Diagnosis of cystic fibrosis; **AND** 2. Documentation of one of the following CFTR gene mutations: a. At least one responsive mutation (See Table 1) for Kalydeco or Symdeko; **OR** b. Homozygous *F508del* CFTR mutation (2 copies) for Orkambi or Symdeko; **OR** c. At least one *F508del* CFTR mutation for Trikafta; **AND** 3. Patient is at least: a. 4 months of age for Kalydeco; **OR** b. 2 years of age for Orkambi: **OR** c. 6 years of age for Symdeko: **OR** d. 12 years of age for Trikafta; **AND** 4. Patient has baseline body mass index, percent predicted FEV1 and liver function tests; **AND** 5. Patient does not have severe hepatic impairment (Child-Pugh Class C); **AND** 6. Baseline ophthalmic examination was performed to monitor lens opacities/cataracts in pediatric patients (not required in adults 18 or older); **AND** 7. Patient has not had a lung transplant; **AND** 8. Not taken simultaneously with a strong CYP3A4 inducer (See Table 2); **AND** 9. Prescribed by or in consultation with a provider who specializes in the treatment of cystic fibrosis If all of the above criteria are met, the request will be **approved for 6 months** If all criteria are not met, but there are circumstances supported by clinical judgement and documentation, requests may be approved by a clinical reviewer on a case-by-case basis up to initial authorization duration.
Drug	**Transitioning to TRIKAFTA (Initial Approval)**
Elexacaftor/tezacaftor/ivacaftor and ivacaftor **(TRIKAFTA)**	If patient is currently stable on Kalydeco, Symdeko or Orkambi, a request to transition to Trikafta may be approved if all of the following conditions are met: 1. The patient meets initial approval criteria above; **AND** 2. The request for Trikafta will not be effective until at least 85% of patient's current supply of Kayldeco, Symdeko or Orkambi has been depleted (based on pharmacy claims data)

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	If all of the above criteria are met, the request will be **approved for 6 months**
Drug	**Criteria (Reauthorization)**
ivacaftor **(KALYDECO)** lumacaftor/ivacaftor **(ORKAMBI)** Tezacaftor/ivacaftor and ivacaftor **(SYMDEKO)** Elexacaftor/tezacaftor/ivacaftor and ivacaftor **(TRIKAFTA)**	CFTR modulators may be reauthorized when all of the following are met: 1. Documentation of liver function tests within the last 6 months 2. Patient demonstrates disease response as indicated by at least one of the following: a. Improvement of FEV1over baseline; **OR** b. Decreased pulmonary exacerbations or infections; **OR** c. Decreased hospitalizations; **OR** d. Increase in weight or growth; **OR** e. Decrease in the decline of lung function If **ALL** of the above criteria are met, the request may be **reauthorized for 12 months** If all criteria are not met, but there are circumstances supported by clinical judgement and documentation, requests may be approved by a clinical reviewer on a case-by-case basis up to the reauthorization duration.

Dosage and quantity limits:

Drug Name	How Supplied	Dose and Quantity Limits
ivacaftor (KALYDECO)	• 150 mg tablet • 25 mg packet • 50 mg packet • 75 mg packet	• Tablets: One tablet twice daily*; 60 tablets (1 bottle) per 30-days • Granule packets: One packet twice daily*; 56 packets (1 carton) per 28 days
lumacaftor/ivacaftor (ORKAMBI)	• 100 mg/125 mg tablet • 200 mg/125 mg tablet • 100 mg/125 mg packet • 150 mg/188 mg packet	• Tablets: Two tablets twice daily*; 112 tablets (1 box) per 28 days • Granules: One packet twice daily; 56 packets (1 carton) per 28days
Tezacaftor/ivacaftor and ivacaftor (SYMDEKO)	• Kit: 50 mg/75 mg tablet plus 75 mg ivacaftor tablet • Kit: 100 mg/150 mg tablet plus 150 mg ivacaftor tablet	• Tablets: One tablet twice daily*; 56 tablets (1 carton) per 28days
Elexacaftor/tezacaftor/ivacaftor and ivacaftor (TRIKAFTA)	• Kit: 100 mg/50 mg/75 mg fixed-dose tablet plus 150 mg ivacaftor tablet	• Tablet: Two fixed-dose tablets daily and one ivacaftor tablet nightly*; 84 tablets (1 carton) per 28 days.

*Dose should be reduced with concurrent use of moderate to strong CYP3A4 inhibitors or hepatic insufficiency (refer to specific package inserts)

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Appendix:

Table 1: Responsive CFTR mutations by drug

KALYDECO (ivacaftor)			SYMDEKO (tezacaftor/ivacaftor and ivacaftor)		
2789+5G→A	*E831X*	*R1070W*	2789+5G→A	E831X	S977F
3272-26A→G	*F1052V*	*R117C*	3272-26A→G	F1052V	
3849+10kbC→T	*F1074L*	*R117H*	3849+10kbC→T	F1074L	
711+3A→G	*G1069R*	*R347H*	711+3A→G	F508del*	
A1067T	*G1244E*	*R352Q*	A1067T	K1060T	
A455E	*G1349D*	*R74W*	A455E	L206W	
D110E	*G178R*	*S1251N*	D110E	P67L	
D110H	*G551D*	*S1255P*	D110H	R1070W	
D1152H	*G551S*	*S549N*	D1152H	R117C	
D1270N	*K1060T*	*S549R*	D1270N	R347H	
D579G	*L206W*	*S945L*	D579G	R352Q	
E193K	*P67L*	*S977F*	*E193K*	R74W	
E56K	*R1070Q*		*E56K*	S945L	

*Must have 2 copies of F508del mutation **OR** at least one other responsive mutation

Table 2: Strong CYP3A4 Inducers

Carbamazepine	Phenobarbital	Phenytoin	Rifabutin	Rifampin	St. John's Wort

References:

1. KALYDECO [prescribing information]. Boston, MA: Vertex Pharmaceuticals incorporated; September 2020
2. ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals incorporated; July 2019,
3. SYMDECO [prescribing information]. Boston, MA: Vertex Pharmaceuticals incorporated; December 2019
4. TRIKAFTA [prescribing information]. Boston, MA: Vertex Pharmaceuticals incorporated; November 2020.
5. Vertex Pharmaceuticals. Gene Mutations and Their Role in Cystic Fibrosis. Available at: https://www.cfsourcehcp.com/files/the_role_of_cftr_mutations_in_causing_cystic_fibrosis.pdf. Accessed April 21, 2020.
6. Taylor-cousar JL, Munck A, Mckone EF, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. N Engl J Med. 2017;377(21):2013-2023.
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8. Safety and pharmacokinetic study of lumacaftor/ivacaftor in subjects aged 2 through 5 years with cystic fibrosis, homozygous for F508del. 2017. ClinicalTrials.gov (Identifier NCT02797132).
9. Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med. 2017;5(7):557-567.
10. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med. 2015;373(3):220-31.

11. A study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with cystic fibrosis who are less than 24 months of age and have a CFTR gating mutation. 2017. ClinicalTrials.gov (Identifier NCT02725567).
12. Quittner A, Suthoff E, Rendas-baum R, et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. Health Qual Life Outcomes. 2015;13:93.
13. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med. 2015;3(7):524-33.
14. De boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros. 2014;13(6):674-80.
15. Van goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros. 2014;13(1):29-36.
16. Heijerman HGM, Mckone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet. 2019.
17. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med. 2019;381(19):1809-1819.
18. Jakharia K, Doligalski L, Lobo L, Coakley R. Impact of Trikafta on lung function in a cystic fibrosis transplant patient. American College of Chest Physicians. Oct, 2020. Available at: IMPACT OF TRIKAFTA ON LUNG FUNCTION IN A CYSTIC FIBROSIS TRANSPLANT PATIENT (chestnet.org)

History

Date	Action and Summary of Changes
12/2/2020	Kalydeco age extended to 4 months or older Orkambi age extended to 2 years or older Symdeko age extended to 6 years or older Added criteria for Trikafta Formatting
4/21/2020	New Policy (1st internal draft)
03/21/2018	New Policy (unpublished)

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Please provide the information below, please print your answer, attach supporting documentation, sign, date, and return to our office as soon as possible to expedite this request. **Without this information, we may deny the request in seven (7) working days.**

Date of request:	Reference #:	MAS:	
Patient	Date of birth	ProviderOne ID	
Pharmacy name	Pharmacy NPI	Telephone number	Fax number
Prescriber	Prescriber NPI	Telephone number	Fax number
Medication and strength	Directions for use	Qty/Days supply	

1. Is this request for a continuation of existing therapy? ☐ Yes ☐ No
   If yes, is there documentation showing any of the following? (check all that apply)
   - ☐ Improvement in FEV1
   - ☐ Decrease in the decline of lung function
   - ☐ Decreased pulmonary exacerbations or infections
   - ☐ Decreased hospitalizations
   - ☐ Increased weight or growth

2. Indicate patient's diagnosis:
   - ☐ Cystic Fibrosis
   - ☐ Other. Specify:

3. Will the patient be taking the requested medication simultaneously with a CYP3A4 inducer? ☐ Yes ☐ No
   If yes, what CYP3A4 inducer patient will be taking?

4. Does patient have any of the following (check all that apply):
   - ☐ At least one mutation in the CFTR gene that is responsive to ivacaftor (Kalydeco)
   - ☐ At least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor (Symdeko)
   - ☐ At least one F508del CFTR mutation for elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)
   - ☐ Homozygous F508del CFTR mutation (2 copies) for lumacaftor/ivacaftor (Orkambi) or tezacaftor/ivacaftor (Symdeko)

5. Does patient have severe hepatic insufficiency (Child-Pugh class C)? ☐ Yes ☐ No

6. Has the patient had a lung transplant? ☐ Yes ☐ No

7. Patient does not meet criteria for treatment with any other CFTR modulator? ☐ Yes ☐ No

8. **For pediatric patients under 18 years of age:** Was there a baseline ophthalmic examination performed to monitor lens opacities/cataracts? ☐ Yes ☐ No

9. Is this prescribed by or in consultation with a provider who specializes in the treatment of cystic fibrosis? ☐ Yes ☐ No

CHART NOTES, CFTR GENE MUTATION TESTING AND LABS ARE REQUIRED WITH THIS REQUEST

Prescriber signature	Prescriber specialty	Date