Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

Requests for an oral liquid form of a drug must be approved if BOTH of the following apply:

1) the indication is FDA approved AND

2) the patient is using an enteral tube for feeding or medication administration

POLICY REVIEW CYCLE

Effective Date	Date of Origin
02-01-2024	07-01-2012

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Kalydeco® (ivacaftor) Oral granules Tablets	Treatment of cystic fibrosis (CF) in patients age 1 month and older who have at least one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.		1
Orkambi® (lumacaftor/ivacaftor) Oral granules Tablet	Treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the *F508del* 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 *F508del* mutation on both alleles of the *CFTR* gene. Limitations of Use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation.		2
Symdeko® (tezacaftor/ivacaftor and ivacaftor co-packaged) Tablet	Treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ ivacaftor based on *in vitro* data and/or clinical evidence. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.		3
Trikafta® (elexacaftor/tezacaftor/ivac	Treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data.		8

Agent(s)	FDA Indication(s)	Notes	Ref#
aftor and ivacaftor co-packaged) Oral granules Tablet	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 or a mutation that is responsive based on in vitro data.		

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Cystic Fibrosis	Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease among Caucasian populations. CF is a multisystem disorder caused by mutations in the gene for the CF transmembrane conductance regulator (CFTR), which encodes an ion channel protein. Defects in the ion channel protein cause deranged transport of chloride and other CFTR-affected ions (e.g., sodium and bicarbonate), which leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions.(5) Pulmonary disease remains the leading cause of morbidity and mortality in patients with CF.(6)
	
	Diagnosis of CF is based upon compatible clinical findings with biochemical or genetic confirmation. Both of the following criteria must be met to diagnose CF:(4,5)
	
	• Clinical symptoms consistent with CF in at least one organ system, OR positive newborn screen, OR history of CF in a sibling
	AND
	• Evidence of CFTR dysfunction (i.e., elevated sweat chloride greater than or equal to 60 mmol/L, two mutations on separate alleles known to cause CF, abnormal nasal potential difference)
	
	Treatment of CF requires a multidisciplinary approach to care that is best provided at one of more than 120 CF Care Centers (accredited by the CF Foundation), most of which have dedicated programs for both children and adults. Patients treated at these centers are seen by physicians, nurses, dietitians, respiratory therapists, physical therapists, and social workers with special competence in CF care.(4) Sinus infection, nutritional status, glucose control, and psychosocial issues should be assessed at regular intervals. Antibiotics, bronchodilators, anti-inflammatory agents, agents that promote airway secretion clearance, nutritional support, and CFTR modulators are possible therapies for CF patients.(6)
	
	CFTR modulators are a new class of drugs that act by improving production, intracellular processing, and/or function of the defective CFTR protein. These drugs represent an important advance in management of CF because they target the defective CFTR protein rather than its downstream consequences. Indications and efficacy of CFTR drugs depend upon the CFTR mutations in the individual patient. Therefore, all CF patients should undergo CFTR genotyping to determine if they carry a mutation that makes them eligible for CFTR modulator therapy.(7,9,10)
	
	The following approach is recommended for CFTR modulators, guided by both genotype and age:(7)
	
	• F508del homozygotes:
	  ○ Age 1 to less than 2 years – lumacaftor/ivacaftor (LUM/IVA)
	  ○ Age greater than or equal to 2 years – elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)
	• F508del heterozygotes

	○ Age greater than or equal to 1 month to less than 2 years - IVA (only if the second mutation is responsive to this therapy) ○ Age greater than or equal to 2 years - ELZ/TEZ/IVA • If a patient has a genotype that is eligible for more than one therapy, start on the maximal therapy available for their age group (i.e., triple therapy before dual therapy before monotherapy) • For patients with no gating mutations, residual function mutations, or F508del mutations, CFTR therapy should be used in the setting of a clinical trial.
Efficacy	Ivacaftor was the first approved CFTR modulator therapy. It was originally approved for patients 12 years or older with a G551D mutation in at least one of their CFTR genes. A phase 3 multicenter randomized trial studied the effect of 48 weeks of ivacaftor, 150 mg twice daily, compared with placebo in 161 subjects aged 12 years or older with at least one G551D mutation. The FEV1 increased 10.4% from baseline in the treated patients compared with −0.2% for those receiving placebo at 24 weeks (*p* less than 0.001). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than those receiving placebo (p less than 0.001). There were significant improvements in QOL, as measured by Cystic Fibrosis Questionnaire Revised (CFQ-R), as well as nutritional status. The authors observed a 48.1 mmol/L decrease in sweat chloride concentration in treated patients compared with placebo (p less than 0.001), reflecting the impact of the drug on the basic defect in CF.(1,7,9) Other trials have evaluated the efficacy of ivacaftor in patients with CF and mutations in additional CFTR genes (e.g., G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, S549R, R117H) and have showed beneficial results similar to those reported for patients with the G551D mutation.(1,7,10) Further clinical trials and in vitro studies with ivacaftor have expanded the approved label to 6 years of age and additional CFTR mutations. However, even with the expanded indication only about 10% of patients with CF in the United States carry mutations responsive to ivacaftor.(7,10) The most common CFTR mutation that causes CF is F508del; 50% of CF patients with CF are homozygous, and another 40% are heterozygous.(5,10) Ivacaftor alone is ineffective in treating F508del mutation since these mutations result in decreased CFTR expression (due to incorrect CFTR protein folding) at the respiratory epithelial cell surface, whereas ivacaftor's mechanism of action is augmentation of ion conductance via gating channel.(1,9,10) Combination lumacaftor and ivacaftor has shown improvements in pulmonary function and reduced the risk of pulmonary exacerbations in CF patients who are homozygous for the F580del mutation.(2,7,10) Lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality. Neither drug is effective as monotherapy for F508del homozygotes.(7,10) The efficacy of lumacaftor-ivacaftor in patients with CF who are homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials. The primary efficacy endpoint in both trials was change in lung function as determined by absolute change from baseline in percent predicted FEV1 (ppFEV1) at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. In both trials, treatment with lumacaftor-ivacaftor resulted in a statistically significant improvement in ppFEV1.(2,7,10) Key secondary efficacy variables included relative change from baseline in ppFEV1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24; absolute change from baseline in BMI at Week 24; absolute change from baseline in CFQ-R score at Week 24, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing; proportion of patients achieving greater than or equal to 5% relative change from baseline in ppFEV1 using the average of Week 16 and Week 24; and number of pulmonary exacerbations through Week 24. For the purposes of these trials, 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 sino-pulmonary signs/symptoms.(2,10) In patients who are heterozygous for the F508del mutation, lumacaftor-ivacaftor does not appear to have clinically meaning benefit.(2,7)

	Tezacaftor-ivacaftor combination has shown modest improvements in pulmonary function and reduced the risk of pulmonary exacerbations for individuals who are homozygous for the F508del mutation or a heterozygous F508del mutation in combination with a residual function mutation. Tezacaftor partially corrects the CFTR misfolding, while ivacaftor is a potentiator that improves the gating abnormality.(7) A trial involving F508del homozygotes resulted in modest improvement in FEV1 (absolute change, 4 percentage points versus placebo) and modest improvement in CFQ-R score (5.1 points versus placebo). The rate of pulmonary exacerbations was 35 percent lower in the treatment group compared with placebo (hazard ratio [HR] 0.64, 95% CI 0.46-0.88).(2,7) The October 2019 Priority Review FDA approval of Trikafta (elexacaftor-tezacaftor-ivacaftor combination) brought another CFTR agent to the market with additional benefit for the 50% of CF patients with homozygous F508del mutation, but particularly the 40% of CF patients with heterozygous F508del mutation who were previously unable to be treated unless their other CFTR mutation was an approved mutation for Kalydeco or Symdeko. The efficacy of Trikafta was demonstrated in two trials. The first trial was a 24-week, randomized, double-blind, placebo-controlled trial in 403 patients who had an F508del mutation and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor or tezacaftor/ivacaftor alone. The second trial was a four-week, randomized, double-blind, active-controlled trial in 107 patients who had two identical F508del mutations. Trikafta increased the ppFEV1 in both trials (Trial 1 increased mean ppFEV1 13.8% from baseline compared to placebo; Trial 2 increased mean ppFEV1 10% from baseline compared to tezacaftor/ivacaftor). In the first trial, treatment with Trikafta also resulted in improvements in sweat chloride, number of pulmonary exacerbations (worsening respiratory symptoms and lung function), and body mass index (weight-to-height ratio) compared to placebo.(8) The safety of elexacaftor-tezacaftor-ivacaftor in younger children was evaluated in a 24-week open-label study in 66 children 6 to 11 years old who were homozygous for F508del or heterozygous for F508del with a second minimal function mutation. The safety profile and pharmacokinetics were similar to those in older individuals, and patients experience improvement in percent predicted FEV1 (10.2 percentage points; 95% CI 7.9-12.6), respiratory symptoms, sweat chloride, and body weight.(7,11) On the basis of this study, the drug combination was approved for this age group in June 2021.(8)
Safety	Kalydeco, Orkambi, Symdeko, and Trikafta do not have any boxed warnings nor contraindications.(1,2,3,8)

REFERENCES

Number	Reference
1	Kalydeco prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
2	Orkambi prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
3	Symdeko prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
4	Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017 Feb;181S:S4-S15.e1.
5	Katkin JP, et al. Cystic Fibrosis: Clinical Manifestations and Diagnosis. UpToDate. Last updated March 2023. Literature review current through August 2023.
6	Simon RH, et al. Cystic Fibrosis: Overview of the Treatment of Lung Disease. UpToDate. Last updated June 2023. Literature review current through August 2023.
7	Simon RH, et al. Cystic Fibrosis: Treatment with CFTR Modulators. UpToDate. Last updated May 2023. Literature review current through August 2023.
8	Trikafta prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
9	Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al, of the Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. Am J Respir Crit Care Med. 2013 Apr;187(7):680-689.

Number	Reference
10	Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with Cystic Fibrosis. Ann Am Thorac Soc. 2018 Mar;15(3):271-280.
11	Zemanick ET, Taylor-Cousar JL, Davies J, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med. 2021;203(12):1522.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Trikafta	elexacaf-tezacaf-ivacaf	100-50-75 & 75 MG ; 80-40-60 & 59.5 MG	M ; N ; O ; Y	N		
Trikafta	elexacaf-tezacaf-ivacaf	100-50-75 & 150 MG ; 50-25-37.5 & 75 MG	M ; N ; O ; Y	N		
Kalydeco	ivacaftor packet	13.4 MG ; 25 MG ; 5.8 MG ; 50 MG ; 75 MG	M ; N ; O ; Y	N		
Kalydeco	ivacaftor tab	150 MG	M ; N ; O ; Y	N		
Orkambi	lumacaftor-ivacaftor granules packet	100-125 MG ; 150-188 MG ; 75-94 MG	M ; N ; O ; Y	N		
Orkambi	lumacaftor-ivacaftor tab	100-125 MG ; 200-125 MG	M ; N ; O ; Y	N		
Symdeko	tezacaftor-ivacaftor	100-150 & 150 MG ; 50-75 & 75 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Kalydeco	ivacaftor packet	5.8 MG	60	Packets	30	DAYS			
Kalydeco	ivacaftor packet	13.4 MG	60	Packets	30	DAYS			
Kalydeco	Ivacaftor Packet 25 MG	25 MG	60	Packets	30	DAYS			
Kalydeco	Ivacaftor Packet 50 MG	50 MG	60	Packets	30	DAYS			
Kalydeco	Ivacaftor Packet 75 MG	75 MG	60	Packets	30	DAYS			
Kalydeco	Ivacaftor Tab 150 MG	150 MG	60	Tablets	30	DAYS			
Orkambi	Lumacaftor-Ivacaftor Granules Packet	75-94 MG	60	Packets	30	DAYS			
Orkambi	lumacaftor-ivacaftor granules packet	100-125 MG	60	Packets	30	DAYS			
Orkambi	lumacaftor-ivacaftor granules packet	150-188 MG	60	Packets	30	DAYS			

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Orkambi	lumacaftor-ivacaftor tab	100-125 MG	120	Tablets	30	DAYS			
Orkambi	Lumacaftor-Ivacaftor Tab 200-125 MG	200-125 MG	120	Tablets	30	DAYS			
Symdeko	Tezacaftor-Ivacaftor 100-150 MG & Ivacaftor 150 MG Tab TBPK	100-150 & 150 MG	60	Tablets	30	DAYS			
Symdeko	Tezacaftor-Ivacaftor 50-75 MG & Ivacaftor 75 MG Tab TBPK	50-75 & 75 MG	60	Tablets	30	DAYS			
Trikafta	elexacaf-tezacaf-ivacaf	80-40-60 & 59.5 MG	56	Packets	28	DAYS			
Trikafta	elexacaf-tezacaf-ivacaf	100-50-75 & 75 MG	56	Packets	28	DAYS			
Trikafta	Elexacaf-Tezacaf-Ivacaf	50-25-37.5 & 75 MG	90	Tablets	30	DAYS			
Trikafta	Elexacaf-Tezacaf-Ivacaf 100-50-75 MG &Ivacaftor 150 MG TBPK	100-50-75 & 150 MG	90	Tablets	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Kalydeco	ivacaftor packet	13.4 MG ; 25 MG ; 5.8 MG ; 50 MG ; 75 MG	Medicaid
Kalydeco	ivacaftor tab	150 MG	Medicaid
Orkambi	lumacaftor-ivacaftor granules packet	100-125 MG ; 150-188 MG ; 75-94 MG	Medicaid
Orkambi	lumacaftor-ivacaftor tab	100-125 MG ; 200-125 MG	Medicaid
Symdeko	tezacaftor-ivacaftor	100-150 & 150 MG ; 50-75 & 75 MG	Medicaid
Trikafta	elexacaf-tezacaf-ivacaf	100-50-75 & 75 MG ; 80-40-60 & 59.5 MG	Medicaid
Trikafta	elexacaf-tezacaf-ivacaf	100-50-75 & 150 MG ; 50-25-37.5 & 75 MG	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Kalydeco	ivacaftor packet	13.4 MG	Medicaid
Kalydeco	ivacaftor packet	5.8 MG	Medicaid
Kalydeco	Ivacaftor Packet 25 MG	25 MG	Medicaid
Kalydeco	Ivacaftor Packet 50 MG	50 MG	Medicaid
Kalydeco	Ivacaftor Packet 75 MG	75 MG	Medicaid
Kalydeco	Ivacaftor Tab 150 MG	150 MG	Medicaid
Orkambi	Lumacaftor-Ivacaftor Granules Packet	75-94 MG	Medicaid
Orkambi	lumacaftor-ivacaftor granules packet	150-188 MG	Medicaid
Orkambi	lumacaftor-ivacaftor granules packet	100-125 MG	Medicaid
Orkambi	lumacaftor-ivacaftor tab	100-125 MG	Medicaid
Orkambi	Lumacaftor-Ivacaftor Tab 200-125 MG	200-125 MG	Medicaid
Symdeko	Tezacaftor-Ivacaftor 100-150 MG & Ivacaftor 150 MG Tab TBPK	100-150 & 150 MG	Medicaid

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Symdeko	Tezacaftor-Ivacaftor 50-75 MG & Ivacaftor 75 MG Tab TBPK	50-75 & 75 MG	Medicaid
Trikafta	elexacaf-tezacaf-ivacaf	80-40-60 & 59.5 MG	Medicaid
Trikafta	elexacaf-tezacaf-ivacaf	100-50-75 & 75 MG	Medicaid
Trikafta	Elexacaf-Tezacaf-Ivacaf	50-25-37.5 & 75 MG	Medicaid
Trikafta	Elexacaf-Tezacaf-Ivacaf 100-50-75 MG &Ivacaftor 150 MG TBPK	100-50-75 & 150 MG	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Target Agent(s) will be approved when ONE of the following are met:

1. ALL of the following:
   - A. ONE of the following:
     1. ALL of the following:
        - A. The patient has a diagnosis of cystic fibrosis **AND**
        - B. Information has been provided that indicates the patient has a CFTR gene mutation(s), confirmed by genetic testing, according to the FDA label for the requested agent (medical records required) **AND**
        - C. If the requested agent is Kalydeco, the patient does NOT have F508del mutation on BOTH alleles of CFTR gene (NOT homozygous) **OR**
     2. The patient has another FDA approved indication for the requested agent **AND**
   - B. If the patient has an FDA approved indication, then ONE of the following:
     1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
     2. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND**
   - C. The patient will NOT be using the requested agent in combination with another CFTR modulator agent for the requested indication **AND**
   - D. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cystic fibrosis, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
   - E. The patient does NOT have any FDA labeled contraindications to the requested agent **OR**
2. If the request is for an oral liquid form of a medication, then BOTH of the following:
   - A. The patient has an FDA approved indication **AND**
   - B. The patient uses an enteral tube for feeding or medication administration

Length of Approval: 6 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ONE of the following are met:

Module	Clinical Criteria for Approval
	1. ALL of the following: A. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** B. ONE of the following: 1. If the patient has a diagnosis of cystic fibrosis, the prescriber has provided information that the patient has had clinical improvement or stabilization with the requested agent from baseline (prior to treatment with the requested agent) [e.g., improvement in FEV1, increase in weight/BMI, improvement in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score, improvements in respiratory symptoms related to patients with CF (cough, sputum production, and difficulty breathing), and/or reduced number of pulmonary exacerbations] **OR** 2. If the patient has another FDA approved indication for the requested agent, the patient has had clinical benefit with the requested agent **AND** C. The patient will NOT be using the requested agent in combination with another CFTR modulator agent for the requested indication **AND** D. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cystic fibrosis, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** E. The patient does NOT have any FDA labeled contraindications to the requested agent **OR** 2. If the request is for an oral liquid form of a medication, then BOTH of the following: A. The patient has an FDA approved indication **AND** B. The patient uses an enteral tube for feeding or medication administration **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval**: Initial: 6 months; Renewal: 12 months