Cystic Fibrosis, CFTR Modulators

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO041

Description

Ivacaftor (Kalydeco) is an orally administered cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Ivacaftor/lumacaftor (Orkambi) combines the potentiating mechanism of ivacaftor with lumacaftor which improves the conformational stability of F508del-CFTR. Ivacaftor/tezacaftor (Symdeko) includes tezacaftor, which is a CFTR modulator that acts as a CFTR corrector. Elexacaftor/tezacaftor/ivacaftor (Trikafta), adds an addition CFTR corrector with elexacaftor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ivacaftor (Kalydeco)	Cystic fibrosis, one mutation in the CFTR gene[a] that is responsive to ivacaftor[b]	150 mg tablet	56 tablets/28 days
		25 mg/packet oral granules	56 packets/28 days
		50 mg/packet oral granules	56 packets/28 days
		75 mg/packet oral granules	56 packets/28 days
ivacaftor/ lumacaftor (Orkambi)	Cystic fibrosis, homozygous for F508del mutation	125/200 mg tablet	112 tablets/28 days
		125/100 mg tablet	112 tablets/28 days
		125/100 mg oral granule packet	56 packets/28 days
		188/150 mg oral granule packet	56 packets/28 days
ivacaftor/ tezacaftor (Symdeko)	Cystic fibrosis, homozygous F508del mutation or at least one mutation in the CFTR gene[a] that is responsive to ivacaftor/tezacaftor[b]	Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg	56 tablets/28 days
		Kit: (ivacaftor; ivacaftor/tezacaftor) 75mg; 75/50 mg	56 tablets/28 days
elexacaftor/ tezacaftor/ ivacaftor (Trikafta)	Cystic fibrosis, one F508del mutation or at least mutation if the CFTR gene[a] that is responsive[b]	Kit (elexacaftor/ tezacaftor/ ivacaftor; ivacaftor) 100/50/75mg; 150 mg	84 tablets/28 days

[a] Specific mutations listed below in policy criteria

[b] Based on clinical and/or *in vitro* assay data

Initial Evaluation

I. Agents listed in this policy may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   B. The medication is not used in combination with other agents in this policy (i.e., use of only one of the following at a given time: Kalydeco, Orkambi, Symdeko, Trikafta) (*please note: if a previous approval has been granted for one of these agents, and criteria is met for another, the previous PA approval will be discontinued)*; **AND**
   C. A diagnosis of **cystic fibrosis** when the following are met:
      1. For ivacaftor (Kalydeco):
         i. The member is four months of age or older; **AND**
         ii. Documentation that the member has a mutation that is eligible for treatment with ivacaftor (Kalydeco) as defined in the FDA label; **AND**
         iii. Member Gene Mutation supported by Table in Package Insert: KALYDECO® (ivacaftor)
      2. For ivacaftor/lumacaftor (Orkambi):
         i. The member is one year of age or older; **AND**
         ii. The member is homozygous (two copies) for the F508del mutation in the CFTR gene; **OR**
      3. For ivacaftor/tezacaftor (Symdeko):
         i. The member is six years of age or older; **AND**
         ii. The member has **ONE** of the following:
            a. The member is homozygous (two copies) for the F508del mutation (*please note: one copy of F508del in the absence of a responsive mutation listed below does not meet criteria)*; **OR**
            b. Documentation that the member as a mutation that is eligible for treatment with ivacaftor/tezacaftor (Symdeko) defined in the FDA label; **AND**
         iii. Member Gene Mutation supported by Table in Package Insert: SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)
      4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
         i. The member is six years of age or older: **AND**
         ii. The member has **ONE** of the following:
            a. The patient has at least one copy of the F508del mutation; **OR**
            b. Documentation that the member as a mutation that is eligible for treatment with elexacaftor/tezacaftor/ivacaftor (Trikafta) defined in the FDA label; **AND**

iii. Member Gene Mutation supported by Table in Package Insert: TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor)

II. Medications listed in this policy are considered investigational when used for all other conditions, including but not limited to:
   A. Cystic fibrosis outside of the specific mutations listed above for each medication.
   B. Cystic fibrosis outside of ages listed above for each medication
   C. Chronic obstructive pulmonary disease and/or asthma
   D. Hyperglycemia or diabetes mellitus
   E. Premature termination codon mutations

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Clinical documentation of response to therapy as indicated by disease stability or improvement as defined by **one** of the following:
   A. Improvement in FEV1
   B. Decrease in pulmonary exacerbations
   C. Decrease in rate of hospitalizations
   D. Decrease in pulmonary infections
   E. Increased weight
   F. Improvement in sweat chloride

Supporting Evidence

I. Cystic fibrosis is an autosomal recessive disease that manifests primarily with pulmonary complications and may often affect several other organ systems. Treatment and management of cystic fibrosis is complex and requires a myriad of treatment modalities. A specialist should direct, or at least be consulted, at every stage of the member's care.
II. The use of the CFTR agents has not been studied in combination with other CFTR modulators, and due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.
III. Ivacaftor (Kalydeco) has been evaluated in several clinical trials. Two trials evaluated ivacaftor (Kalydeco) in patients with G551D mutation in the CFTR gene. The primary outcome in both

studies was absolute change from baseline in percent predicted pre-dose FEV1 through 24 weeks of treatment. Trial one evaluated patients 12 years of age and older (10.6%; p<0.0001), and Trial 2 evaluated patients six to 11 years of age (12.5%; p<0.0001). Additional outcomes included change in body weight, change in sweat chloride, and relative risk of pulmonary exacerbation, all of which were statistically significant.

IV. Efficacy and safety of ivacaftor (Kalydeco) was also evaluated in patients with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, and S549R mutations. Outcomes included absolute change in percent predicted FEV1, change in body weight, and CFQ-R Respiratory Domain Score, all of which had statistically significant outcomes; although, there was much variability among the responses per mutation type.

V. Efficacy and safety of ivacaftor (Kalydeco) was evaluated in patients with R117H mutation which showed a statistically significant change from baseline in FEV1 and CFQ-R score.

VI. Ivacaftor (Kalydeco) has not been shown to have efficacy in those with the F508del mutation or any of the following: A46D, G85E, E92K, P205S, R334W, R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K.

VII. In April 2019, the FDA approved ivacaftor (Kalydeco) as the first CFTR modulator to treat eligible infants from six months of age. This was supported by data from the Phase 3 ARRIVAL study. This was based on 11 patients with cystic fibrosis. Furthermore, in September 2020, the FDA approved ivacaftor (Kalydeco) to treat patients four months of age and older. This was supported by a 24-week open-label cohort of the ARRIVAL trial, showing a similar safety profile to other FDA-approved age groups.

VIII. The efficacy and safety of ivacaftor/lumacaftor (Orkambi) has been evaluated in patients homozygous for the F508del mutation in the CFTR gene across several clinical trials.

- Trials 1 and 2 were 24-week, Phase 3, randomized, double-blind, placebo-controlled studies of patients aged 12 years and older with CF who were homozygous for the *F508del-CFTR* mutation. The primary endpoint in both trials was an absolute change in $ppFEV_1$ from baseline at Week 24 assessed as the average of the treatment effects at Week 16 and at Week 24. The treatment difference between ORKAMBI and placebo for the mean absolute change in ppFEV1 from baseline at Week 24 was 2.6 percentage points [95% CI (1.2, 4.0)] in Trial 1 (P=0.0003) and 3.0 percentage points [95% CI (1.6, 4.4)] in Trial 2 (P<0.0001). Additional key second endpoints were also met for relative change in percent predicted FEV1 at week 24, absolute change in BMI at week 24 in trial 2.
- Trials 3 and 4 was an expansion in ages 6 to 12; both open-label studies assessing safety and tolerability of ivacaftor/lumacaftor (Orkambi) in younger patients with stable CF and the homozygous *F508del-CFTR* mutation. There were no new safety markers and an additional lung function measurement of precent predicted FEV1 at week 24 supported a 2.5% within group improvement.
- Trial 6 was an open-label study evaluating safety, tolerability and pharmacokinetics of patients aged 2-5 with stable CF and the homozygous*F508del-CFTR* mutation.

This study reported same similar safety and tolerability in the 24 weeks as the prior studies

- Trial 7 was a similar open-label study assessing safety in those aged 1-2 with stable CF and homozygous *F508del-CFTR* mutations. No new safety signals were found in the studies' 24 weeks.

IX. Ivacaftor/tezacaftor (Symdeko) has been evaluated in several trials.

- Trial 1 evaluated ivacaftor/tezacaftor (Symdeko) against placebo in patients 12 years of age and older that were homozygous for F508del, with the primary endpoint of change in FEV1 (4% vs 0% [3.1-4.8]; p<0.0001). Notable secondary outcomes included number of pulmonary exacerbations from baseline, absolute change in BMI from baseline, and change in CFQ-R Respiratory Domain Score from baseline. The change in number of pulmonary exacerbations was significantly reduced (0.65 [CI 0.48-0.88; p<0.0054).
- Trial 2 evaluated patients heterozygous for F508del and a second mutation predicted to be responsive to Ivacaftor/tezacaftor (Skydeko). Outcomes evaluated were similar to Trial 1. The change in FEV1 was 6.8 percentage point (CI 5.7-7.8; p<0.0001), while the change in CF-R Reparatory Domain Score was 11.1 points 9CI 8.7-13.6); p<0.0001).
- Trial 3 evaluated patients who were heterozygous for F508del mutation and a second mutation not predicted to be responsive to tezacaftor/Ivacaftor (Symdeko). The primary efficacy endpoint, a change in FEV1 compared to baseline, was 1.2 percentage points (CI -0.3-2.6), and was not significant. The study was terminated early.
- The efficacy of ivacaftor/tezacaftor (Symdeko) for patients age six to 12 years was supported by data from a 24-week, open-label treatment period of 70 patients. Observations of safety were noted to be similar to that of the data available for ages 12 years and above.

X. Elexacaftor/tezacaftor/ivacaftor (Trikafta) was evaluated in two trials in subjects 12 years of age and older with a primary outcome of percent predicted forced expiratory volume in one second (ppFEV1):

- Trial 1: 24-week, randomized, double-blind, placebo-controlled trial (n=403). Subjects had an F508del mutation and a second mutation that resulted in no CFTR protein or a CFTR protein that was nonresponsive to ivacaftor (Kalydeco) or ivacaftor/tezacaftor (Symdeko). A change of 13.8% ppFEV1 compared to placebo was seen in this trial.
- Trial 2: 4-week, randomized, double-blind, active-controlled trial in 107 patients, homozygous for F508del. A change of 10% ppFEV1 compared to Symdeko was seen in this trial.

XI. Elexacaftor/tezacaftor/ivacaftor (Trikafta) was also evaluated in a 24-week phase 3 open label, multicenter study, which enrolled 66 children ages six to 11 years old with CF who had either two copies of the *F508del* mutation or one copy of the *F508del* mutation and one minimal

function mutation to evaluate safety, pharmacokinetics, and efficacy. The treatment was generally well tolerated, and safety data was similar to those 12 and older.

XII. Statistical and clinical improvement in sweat chloride, body mass index, and reduction in pulmonary exacerbations occurred in the first trial. As of November 2019, the medication was being evaluated for safety and efficacy in patients down to six years of age. Additionally, the manufacturer has stated a plan to evaluate in patients younger than six years of age; however, clinical trials have not yet been started.

XIII. In a published update from 12/2020, Vertex released that the FDA approved updated CFTR gene mutations that were shown to be responsive from *in vitro* data for ivacaftor (Kalydeco), elexacaftor/tezacaftor/ivacaftor (Trikafta), and ivacaftor/tezacaftor (Symdeko). The package inserts have all been included in each drug policy section.

Investigational or Not Medically Necessary Uses

I. The aforementioned indications listed as experimental and investigational are currently being evaluated in clinical trials and/or have not yet shown efficacy and safety in moderate or high-quality clinical trials.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated age expansion for Orkambi with new approval. Updated supporting evidence to mimic other age expansion trial data.	10/2022
Updated age for Trikafta with new FDA approval. Updated links to the PI to reflect a link to each manufacturer page	08/2021
Updated *CFTR* gene mutation indications with new *in vitro data,* adding additional attestation and PI for verification to that mutation.	02/2021
Kalydeco age requirement updated to four months of age (previous six) based on updated FDA-approval.	10/2020
New FDA-approved therapy, Trikafta, added to the policy. Grammatical changes and formatting edits.	02/2020
Criteria combined, transitioned to policy format for all medications. Added new indication for Kalydeco for ages 6 months and older. Symdeko now approved down to six years of age.	06/2019

Criteria update: New indication for Orkambi, approved in CF patients two years of age and older. New approval in CF for patients between the ages of 12 and 24 months for Kalydeco, previously approved only for 24 months and older. Criteria added to not allow concomitant use.	09/2018
Updated criteria to new format, removed question assessing liver enzymes levels, added references, added question regarding combination therapy with other CFTR modulating medications. Symdeko criteria created.	05/2018
Criteria update: Excluded samples and updated renewal language to general improvement.	01/2016
Policy created	02/2012