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. Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek), improved upon the prior CFTR potentiators by including deutivacaftor, a once daily potentiator.

Length of Authorization

- Initial: Length of benefit

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
		5.8 mg packet oral granules	56 packets/28 days
		13.4 mg packet oral granules	56 packets/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
		94/75 mg oral granule packet	28 packets/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	Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg	56 tablets/28 days

	CFTR gene[a] that is responsive to ivacaftor/tezacaftor[b]	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
		Kit (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) 50/37.5/25mg; 75 mg	84 tablets/28 days
		Kit (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) 100/50/75mg; 75mg	56 packets/28 days
		Kit (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) 80/40/60mg; 59.5mg	56 packets/28 days
vanzacaftor/tezacaftor/ deutivacaftor (Alyftrek)	Cystic fibrosis, one F508del mutation or at least one mutation in the CFTR gene[a] that is responsive[b]	4mg/20mg/50mg tablet	90 tablets/30days
		10mg/50mg/125mg tablet	60tablets/30days

[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, Alyftrek) (*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 (CF)** when the following are met:

1. For ivacaftor (Kalydeco):

i. The member is one month 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); OR

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); **OR**
4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
   i. The member is two 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); **OR**
5. For vanzacaftor/tezacaftor/deutivacaftor (Alyftrek):
   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 has a mutation that is eligible for treatment with vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) defined in the FDA label; **AND**
   iii. Member Gene Mutation supported by Table in Package Insert: ALYFTREK™ (vanzacaftor/tezacaftor/deutivacaftor)

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

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. The safety of efficacy of Ivacaftor (Kalydeco) has been evaluated in several clinical trials.
   - Originally approved in 2012, 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.
   - In 2014, efficacy and safety of ivacaftor (Kalydeco) was evaluated in patients ages six and older with R117H mutation which showed a statistically significant change from baseline in FEV1 and CFQ-R score.
   - Between 2015 and 2018, the efficacy and safety of ivacaftor (Kalydeco) expanded into 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. Continued rare mutations were further added in 2020.
   - 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.

- In May 2023, the FDA approved an age expansion down to one month of age or older. This data was based on Trial 8 (ARRIVAL), a phase 3, 24-week, open-label, 2-part study that included patients one month of age or older. Oral granules were mixed with 5mL of age-appropriate soft food or liquid and administered with syringe or spoon (bottle use not recommended). The primary endpoint was safety, assessed by adverse events and clinical laboratory assessments, with secondary endpoints looking at absolute change from baseline in sweat chloride concentration at week 24. This data showed similar safety profile of those two years and older.
- 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.

IV. 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 percent predicted forced expiratory volume in one second (ppFEV1) 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.

V. 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 aged 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.

VI. Elexacaftor/tezacaftor/ivacaftor (Trikafta) safety and efficacy was evaluated in the following clinical trials:

- Trial 1: 24-week, randomized, double-blind, placebo-controlled trial in patients 12 and older (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 (primary endpoint) 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 (primary endpoint) compared to Symdeko was seen in this trial.
    i. Statistical and clinical improvement in sweat chloride, body mass index, and reduction in pulmonary exacerbations occurred in both trials 1 and 2.
- Trial 3: a 24-week phase 3 open label, multicenter study, 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.
- Trial 4: Phase 3, 24-week, open label study which enrolled patients 2-5 years (n=75). The primary endpoint was safety and secondary endpoints looked at change in sweat chloride concentration and change in lung clearance index. Both of these showed clinical improvement and there were no new safety signals that were not seen in the rest of the clinical program for Trikafta.

VII. 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.

VIII. Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) safety and efficacy was evaluated in the following clinical trials:

- Trial 1 and 2: two identical randomized, active-controlled, double-blind Phase 3 trials (SKYLINE 102 and 103) in individuals aged 12 years and older. Patients in the SKYLINE program were either homozygous for *F508del,* or heterozygous for *F508del* with a minimal function mutation, a gating mutation, a residual function mutation, or one other *CFTR* mutation identified as responsive to elexacaftor-tezacaftor-ivacaftor (Trikafta). All 971 patients had a four-week run-in period to the trial where they received elexacaftor-tezacaftor-ivacaftor (Trikafta) every 12 hours. Following this run-in period, patients were randomized 1:1 to remain on elexacaftor-tezacaftor-ivacaftor (Trikafta) every 12 hours or vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) once daily. The primary endpoint was the absolute change in ppFEV1 at week 24.
    i. Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) was noninferior to elexacaftor-tezacaftor-ivacaftor (Trikafta) in absolute change from baseline in ppFEV1 at week 24 in both trials (SKYLINE 102: least-squares [LS] mean difference, 0.2 [95% CI, -0.7, 1.1]; *P* <.0001) and SKYLINE 103: LS mean difference, 0.2 [95% CI, -0.5, 0.9]; *P* <.0001).
    ii. Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) also significantly reduced sweat chloride levels at week 24 compared with elexacaftor-tezacaftor-ivacaftor (Trikafta) in both trials (SKYLINE 102: LS mean difference, -8.4 [95% CI, -10.5, -6.3]; *P* <.0001 and SKYLINE 103: LS mean difference, -2.8 [95% CI, -4.7, -0.9]; *P* =.0034).
- Trial 3: a single-arm, Phase 3 trial (RIDGELINE cohort) in children aged six through eleven with at least one *CFTR* mutation, including *F508del* that was responsive to elexacaftor-tezacaftor-ivacaftor (Trikafta). All patients were stable on elexacaftor-tezacaftor-ivacaftor (Trikafta) for at least 28 days before the study period began or received a four-week run in. All 78 patients received vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) once daily based on weight. The primary endpoint was safety and toxicity at the end of 24 weeks. Key secondary endpoints included change from baseline to week 24 in the ppFEV1, sweat chloride concentration.
    i. Participants maintained normal baseline FEV1 % predicted (LS mean absolute change from baseline through week 24 was 0·0 percentage points [95% CI – 2·0 to 1·9] with transition to received vanzacaftor-tezacaftor-deutivacaftor (Alyftrek)
    ii. Participants improved upon baseline sweat chloride concentrations, average 40.4 mmol/L, by 8.6mmol/L (95%CI -11.0 to -6.3mmol/L) with vanzacaftor-tezacaftor-deutivacaftor (Alyftrek)

IX. Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) is still being studied in RIDGELINE in two other cohorts down to one year of age.
X. For ease of policy upkeep, each medication is linked to the manufacturer website for the latest package insert to be found.

Investigational or Not Medically Necessary Uses

I. The aforementioned indications listed as experimental and investigational in Section II 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
Addition of vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) to the policy. Removal of renewal criteria as the policy is for the length of benefit.	05/2025
Updated approval duration to be for length of approval	05/2024
Updated age expansion for Kalydeco and Trikafta with new approvals. Updated supporting evidence to mirror other age expansions.	06/2023
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