Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

Table of Contents

Overview .............................................................. 1
Coverage Policy ................................................... 1
FDA Approved Indications and Recommended Dosing .................. 4
General Background ............................................ 6
Coding/Billing Information .................................... 8
References ........................................................ 9

Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions
Pharmacogenetic Testing
Quantity Limitations

Overview

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators addressed within this policy include the following products:

- Kalydeco® (ivacaftor tablets)
- Orkambi® (lumacaftor/ivacaftor tablets)
- Symdeko® (tezacaftor/ivacaftor tablets)
- Trikafta™ (elexacaftor/tezacaftor/ivacaftor tablets and ivacaftor tablets)

Coverage Policy

Kalydeco

Ivacaftor (Kalydeco®) is considered medically necessary when ALL of the following criteria are met:

- Individual is 4 months of age or older
- Documented diagnosis of cystic fibrosis (CF)
• Documentation the individual has at least ONE mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor (Kalydeco) as specified in the FDA product label*
• Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

* Click here for a list of CFTR gene mutations that produce CFTR protein and are responsive to ivacaftor (Kalydeco)

Ivacaftor (Kalydeco®) is considered experimental, investigational, or unproven for ANY other use including the following (this list may not be all-inclusive):
• Diagnosis of CF with homozygous F508del mutations in the CFTR gene (i.e. 2 copies of the F508del mutation)
• Cystic fibrosis with an unknown CFTR gene mutation
• CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
• CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
• Combination therapy with Orkambi (lumacaftor/ivacaftor tablets), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor).

Orkambi
Lumacaftor/ivacaftor (Orkambi®) is considered medically necessary when ALL of the following criteria are met:
• Individual is 2 years of age or older
• Documented diagnosis of cystic fibrosis (CF)
• Documentation the individual is homozygous for the F508del mutation in the CFTR gene (i.e. 2 copies of the F508del mutation)
• Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

Lumacaftor/ivacaftor (Orkambi®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):
• Diagnosis of CF with heterozygous F508del mutations in the CFTR gene. (i.e. 1 copy of the F508del mutation)
• Cystic fibrosis patients with an unknown CFTR gene mutation
• CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
• CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
• Combination therapy with Kalydeco (ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor).

Symdeko
Tezacaftor/Ivacaftor (Symdeko®) is considered medically necessary when ALL of the following criteria are met:
• Individual is 6 years of age or older
• Documented diagnosis of cystic fibrosis (CF)
• EITHER of the following:
  • Documentation the individual is homozygous for the F508del mutation in the CFTR gene (i.e. 2 copies of the F508del mutation)
  • Documentation the individual has at least ONE mutation that is responsive to tezacaftor/ivacaftor (Symdeko®) as specified in the FDA product label*
• Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis
*Click here for a list of CFTR gene mutations that produce CFTR protein and are responsive to tezacaftor/ivacaftor (Symdeko)*

Tezacaftor/ivacaftor (Symdeko®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):

- Cystic fibrosis patients with an unknown CFTR gene mutation
- CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
- CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
- Combination therapy with Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor)

**Trikafta**

Elexacaftor/tezacaftor/ivacaftor (Trikafta™) is considered medically necessary when the following criteria are met:

- Individual is 12 years of age or older
- Documented diagnosis of cystic fibrosis (CF)
- Documentation of at least ONE copy of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

Elexacaftor/tezacaftor/ivacaftor (Trikafta™) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):

- Cystic Fibrosis with an unknown CFTR gene mutation
- CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
- CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
- Combination therapy with Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), or Symdeko (tezacaftor/ivacaftor)

Coverage for CFTR modulators varies across plans. Refer to the customer’s benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following will apply in addition to criteria listed above:

<table>
<thead>
<tr>
<th>Product</th>
<th>Initial and reauthorization for CFTR modulator therapy (Kalydeco®, Orkambi®, Symdeko® or Trikafta™) is up to 12 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco® (ivacaftor tablets)</td>
<td>ONE of the following:</td>
</tr>
<tr>
<td></td>
<td>- Documented failure, inadequate response, contraindication per FDA label, intolerance or not a candidate for elexacaftor/tezacaftor/ivacaftor (Trikafta™)</td>
</tr>
<tr>
<td></td>
<td>- Individual has previously been started on, or is currently receiving Kalydeco®</td>
</tr>
<tr>
<td>Orkambi® (lumacaftor/ivacaftor tablets)</td>
<td>ONE of the following:</td>
</tr>
<tr>
<td></td>
<td>- Documented failure, inadequate response, contraindication per FDA label, intolerance or not a candidate for elexacaftor/tezacaftor/ivacaftor (Trikafta™)</td>
</tr>
<tr>
<td></td>
<td>- Individual has previously been started on, or is currently receiving Orkambi®</td>
</tr>
<tr>
<td>Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets)</td>
<td>ONE of the following:</td>
</tr>
<tr>
<td></td>
<td>- Documented failure, inadequate response, contraindication per FDA label, intolerance or not a candidate for elexacaftor/tezacaftor/ivacaftor (Trikafta™)</td>
</tr>
<tr>
<td></td>
<td>- Individual has previously been started on, or is currently receiving Symdeko®</td>
</tr>
</tbody>
</table>
CFTR modulator therapy (Kalydeco®, Orkambi®, Symdeko® or Trikafta™) is considered medically necessary for continued use when initial criteria are met and ONE of the following:

- For individuals who already have measureable lung disease or end organ involvement, documentation of beneficial clinical response (for example, improvement in, stabilization of, or a decrease in the rate of decline of FEV1, reduced number of pulmonary exacerbations, improvement in body mass index [BMI], or improvement on the patient reported Cystic Fibrosis Questionnaire-Revised respiratory domain score).
- For individuals who are previously asymptomatic, or have mild clinical manifestations, there is no evidence of clinical decline.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

### FDA Approved Indications and Recommended Dosing

#### FDA Approved Indication

<table>
<thead>
<tr>
<th></th>
<th>Indications</th>
<th>Dosing</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kalydeco®</strong>&lt;br&gt;(ivacaftor tablets and oral granules)</td>
<td>Indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.&lt;br&gt;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.</td>
<td>Oral granules: 4 months to less than 6 months (weight based see package insert (5kg or greater)): One 25 mg packet Q12 H.&lt;br&gt;≥ 6 years of age: One 150 mg tablet Q12H.&lt;br&gt;≥ 6 months to &lt; 6 years of age and ≥ 5 kg to &lt; 7 kg: One 25 mg packet mixed with 1 tsp of soft food or liquid Q12H.&lt;br&gt;≥ 6 months to &lt; 6 years of age and ≥ 7 kg to &lt; 14 kg: One 50 mg packet mixed with 1 tsp of soft food or liquid Q12H.&lt;br&gt;≥ 6 months to &lt; 6 years of age and ≥ 14 kg: One 75 mg packet mixed with 1 tsp of soft food or liquid Q12H.&lt;br&gt;A fat-containing meal or snack should be consumed just before or just after dosing for all formulations.&lt;br&gt;Reduce dose in patients with moderate and severe hepatic impairment. Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.</td>
<td>Oral granules containing 25 mg, 50 mg, or 75 mg per packet.&lt;br&gt;Tablets containing 150 mg ivacaftor.</td>
</tr>
<tr>
<td><strong>Orkambi®</strong>&lt;br&gt;(lumacaftor/ivacaftor)</td>
<td>Treatment of CF in patients ≥ 2 years of age who are</td>
<td>≥ 12 years of age: Two 200/125 mg tablets Q12H.</td>
<td>Oral granules containing 100 mg lumacaftor and 125 mg ivacaftor.</td>
</tr>
<tr>
<td>Indications</td>
<td>Dosing</td>
<td>Availability</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-------------</td>
<td></td>
</tr>
</tbody>
</table>
| tablets)    | homzygous for F508del mutation in the CFTR gene. Limitation of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homzygous for the F508del mutation. | ≥ 6 to ≤ 11 years of age: Two 100/125 mg tablets Q12H.  
≥ 2 to ≤ 5 years of age weighing < 14 kg: One 100/125 mg packet of granules Q12H.  
≥ 2 to ≤ 5 years of age weighing ≥ 14 kg: One 150/188 mg packet of granules Q12H.  
A fat-containing meal or snack should be consumed just before or just after dosing for all formulations.  
Reduce the dose in patients with moderate or severe hepatic impairment.  
When initiating Orkambi in patients taking strong CYP3A inhibitors, reduce Orkambi dose for the first week of treatment. | Oral granules containing 150 mg lumacaftor and 188 mg ivacaftor per packet.  
Tablets containing 100 mg lumacaftor and 125 mg ivacaftor.  
Tablets containing 200 mg lumacaftor and 125 mg ivacaftor. |
| Symdeko® (tezacaftor/ivacaftor tablets) | Treatment of CF in patients ≥ 6 years age: · Homozygous for the F508del mutation; OR · Have at least one mutation in the CFTR that is responsive to Symdeko based on in vitro data and/or clinical evidence. | ≥ 12 years of age: One tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart.  
≥ 6 to ≤ 12 years of age weighing < 30 kg: One tablet (tezacaftor 50 mg/ivacaftor 75 mg) taken in the morning and one tablet (ivacaftor 75 mg) taken in the evening, approximately 12 hours apart.  
≥ 6 to ≤ 12 years of age weighing ≥ 30 kg: One tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart.  
There are dose modifications for moderate or severe hepatic impairment and for use with moderate or strong CYP3A inhibitors. | Symdeko is co-packaged as a fixed-dose combination tablet and an ivacaftor tablet.  
Tablets containing 100 mg tezacaftor and 150 mg ivacaftor and tablets containing 150 mg of ivacaftor.  
Tablets containing 50 mg tezacaftor and 75 mg ivacaftor and tablets containing 75 mg of ivacaftor. |
| Trikafta™ (elexacaftor/tezacaftor/ivacaftor tablets) | Treatment of CF in patients ≥ 12 years of age who have at least one F508del mutation in the CFTR gene. | Two co-formulated tablets in the morning and one ivacaftor tablet in the evening, approximately 12 hours apart. | Trikafta is co-packaged as a fixed-dose combination tablet (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) |
### General Background

#### Disease Overview

Cystic fibrosis (CF) is an autosomal recessive disease of epithelial chloride transport. In the US, there are approximately 29,887 individuals with CF; 53.5% of individuals are ≥ 18 years of age and the remainder are < 18 years of age (46.5%). CF is caused by mutations in the gene encoding the CFTR protein. To date, > 1,800 mutations have been found in the CFTR gene. Some mutations result in almost no CFTR function and the others are associated with some residual function. In general, CFTR mutations cause reduced quantity or quality of CFTR protein at the cell surface, but the specific mechanisms leading to CFTR deficiency are distinct among different classes of mutations. The malfunctioning CFTR leads to an accumulation of unusually thick and sticky mucus in the lungs, pancreas, and other organs. The most common CFTR mutation is F508del. In the CF Registry (2017) 85.8% of patients had at least one copy of F508del; 45.3% of patients had two copies of F508del (homozygous), 40.9% of patients had one copy of F508del (heterozygous), and the remaining 13.9% of patients had no copies of F508del or their mutation status was unknown. (Farrel, 2017; CFF Patient Registry, 2017)
Pulmonary function is one of the two key measures of health in patients with CF (the other is nutritional outcome). For children, the goal is a percent predicted forced expiratory volume in 1 second (ppFEV1) ≥ 100% and body mass index (BMI) percentile ≥ 50th percentile. For adults, the goal is ppFEV1 ≥ 75% and BMI ≥ 22 kg/m² or 23 kg/m² for women and men, respectively. The majority of patients who are 18 years of age (a typical age of transition to adult care) have a ppFEV1 ≥ 70%. The proportion of individuals with CF who are ≥ 18 years of age with normal/mild CF (ppFEV1 ≥ 70%) has increased over time to 74%. The proportion of patients in the severe category (ppFEV1 < 40%) has decreased over time to 4%. Although pulmonary function in individuals with CF has improved over time, the pattern of decreasing pulmonary function beginning in adolescence persists. Research shows that people with CF of all ages, including infants, have some lung damage, even when ppFEV1 is within the normal range. This damage to the lungs is primarily the result of mucus buildup and lung infections. (Farrel, 2017; CFF Patient Registry, 2017)

Pulmonary exacerbations are associated with morbidity, mortality, and decreased quality of life in patients with CF. Despite notable improvements in pulmonary function and nutritional status over the years, there has been a minimal reduction in the proportion of individuals with CF who are treated with intravenous antibiotics for pulmonary exacerbations. (CFF Patient Registry, 2017)

There are four targeted therapies for patients with CF. All of the targeted therapies have different age indications; however, some general indications overlap. Approximately 80% of patients with CF are eligible for treatment with at least one of the four approved CFTRs. It is estimated that Kalydeco is indicated in 16% of patients (n = 4,600), Orkambi in 44% of patients (n = 12,600), Symdeko in 46% of patients (n = 13,300), and Trikafta in 60% of patients (n = 17,300).

Symdeko and Kalydeco are indicated in patients with similar non-F508del CFTR mutations (E56K, P67L, R74W, D110ED110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3AaG, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5GàA, 3849+10kbCàT); Symdeko is indicated in patients ≥ 6 years of age and Kalydeco is indicated for those ≥ 6 month of age. Kalydeco is uniquely indicated in patients with the following mutations: R117H, G178R, S549N, S549R, G551D, G551S, G1069R, R1069R, R1070Q, Q1244E, S1251N, and S1255P. According to the CF patient registry data, only two of these mutations are among the top 25 mutations identified in individuals with CF (R117H in 2.9% of patients and G551D in 4.5% of patients); the other mutations unique to Kalydeco occur in < 0.5% of the total CF population. Trikafta is the only targeted product with data to support use in patients with one F508del mutation a minimal function mutation. A minimal function mutation is defined as a mutation in which there is complete absence of protein production or lack of in vitro responsiveness to ivacaftor and tezacaftor/ivacaftor. (CFF Patient Registry, 2017; Middleton, 2019)

Professional Societies/Organizations
Guidelines

Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis
Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Symdeko and Trikafta are not addressed in published guidelines at this time.

For adults and children (aged 6 years and older) that have Cystic Fibrosis that is due to gating mutations other than G551D or R117H, the guidelines conditionally recommended treatment with Ivacaftor. For those CF patients with a R117H mutation, the guidelines conditionally recommend treatment with Ivacaftor for the following:
1) Adults aged 18 years or older
2) Children aged 6–17 years and a forced expiratory volume in 1 second (FEV₁) that is less than 90% predicted

For those with the R117H mutation, the guidelines conditionally recommend against treatment with Ivacaftor for the following:
1) Children aged 12–17 years with an FEV₁ that is greater than 90% predicted
2) Children less than 6 years of age

Among those patients with two copies of the F508del, the guidelines made a strong recommendation for treatment with Ivacaftor/Lumacaftor for adults and children aged 12 years and older with an FEV1 less than 90% predicted. Additionally, the guidelines conditionally recommend treatment with Ivacaftor/Lumacaftor for the following:
1) Adults and children aged 12 years or older with an FEV1 greater than 90% predicted
2) Children aged 6–11 years. (Ren et al, 2018)

American College of Medical Genetics (ACMG)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for CFTR modulator therapy (Kalydeco, ® Orkambi, ® Symdeko® or Trikafta™).

Other Uses with Supportive Evidence
AHFS Drug Information 2020 Edition does not support any off-label uses of Kalydeco, ® Orkambi, ® Symdeko® or Trikafta™.

Other Uses without Supportive Evidence
- Kalydeco Use in Cystic Fibrosis Individuals with Homozygous F508del CFTR Mutation - Efficacy results from a double-blind, placebo controlled trial in patients with CF who were homozygous for the phe508del mutation in the CFTR gene showed no statistically significant difference in FEV1 over 16 weeks of Kalydeco treatment compared with placebo. In a Phase II trial in patients homozygous for the F508del (n = 112) Kalydeco did not result in an improvement in FEV1 relative to placebo. (Flume, 2012)
- Cystic Fibrosis (CF) Patients with Unknown Cystic Fibrosis TransmembraneRegulator (CFTR) Gene Mutation. According to the prescribing information for all of the CFTR modulators a Food and Drug Administration (FDA)-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of any CFTR modulator therapy.
- Combination Therapy with other CFTR modulators - Orkambi, Symdeko, and Trikafta contain ivacaftor, the active agent in Kalydeco and therefore are not indicated in combination with Kalydeco or with each other. Symdeko also contains tezacaftor, part of Trikafta.
- Orkambi use in Cystic Fibrosis Individuals Heterozygous for the F508del Mutation in the CFTR Gene. Orkambi is not indicated for patients with only one copy of the F508del mutation in the CFTR gene. (Vertex [Orkambi PI], 2018) Patients who are heterozygous for the F508del mutation and have one of the following mutations are potential candidates for Kalydeco therapy: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or R117H. (Vertex [Kalydeco PI], 2019)

Coding/Billing Information

Note: Kalydeco, Orkambi, Symdeko, and Trikafta are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.
References