This program applies to Medicaid formularies.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing and Administration</th>
</tr>
</thead>
</table>
| **Kalydeco®** (ivacaftor) tablets oral granules | Treatment of cystic fibrosis (CF) in patients age 6 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. | • Kalydeco should be taken with fat-containing food.  
  • Adults and pediatric patients age 6 years and older:  
    - One 150 mg tablet taken orally every 12 hours  
  • Pediatric patients 6 months to less than 6 years of age and weighing 5 kg to less than 7 kg:  
    - One 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours  
  • Pediatric patients 6 months to less than 6 years of age and 7 kg to 14 kg:  
    - One 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours  
  • Pediatric patients less than 6 months of age: not recommended |
| **Orkambi®** (lumacaftor/ivacaftor) tablets oral granules | Treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the F508del mutation in the CFTR gene. | • Orkambi should be taken with fat-containing food.  
  • Pediatric patients age 2 through 5 years and weighing less than 14 kg: one packet of granules (each containing 50 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours  
  • Pediatric patients age 6 through 11 years and weighing less than 14 kg: two packets of granules (each containing 50 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours  
  • Pediatric patients age 6 through 11 years and weighing 14 kg or greater: three packets of granules (each containing 50 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours  
  • Pediatric patients less than 6 months of age: not recommended |
<table>
<thead>
<tr>
<th><strong>Symdeko®</strong> <em>(tezacaftor/ivacaftor and ivacaftor copackaged)</em> tablets</th>
<th>If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the <em>F508del</em> mutation on both alleles of the <em>CFTR</em> gene. Limitations of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the <em>F508del</em> mutation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trikafta™</strong> <em>(elexacaftor/tezacaftor/ivacaftor and ivacaftor copackaged)</em> tablets</td>
<td>Treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one <em>F508del</em> mutation in the <em>CFTR</em> gene.</td>
</tr>
<tr>
<td>lumacaftor 100 mg/ivacaftor 125 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours</td>
<td></td>
</tr>
<tr>
<td>• Pediatric patients age 2 through 5 years and weighing 11 kg or greater: one packet of granules (each containing lumacaftor 150 mg/ivacaftor 188 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours</td>
<td></td>
</tr>
<tr>
<td>• Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours</td>
<td></td>
</tr>
<tr>
<td>• Trikafta should be taken with a meal.</td>
<td></td>
</tr>
</tbody>
</table>
| • Adults and pediatric patients age 12 years and older: two tablets (containing elexacaftor 100 mg/
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.

tezacaftor 50 mg/ivacaftor 75 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart.

**CLINICAL RATIONALE**

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 diagnosis CF:

- Clinical symptoms consistent with CF in at least one organ system (e.g., chronic pulmonary disease, chronic sinusitis, gastrointestinal and nutritional abnormalities, salt loss syndromes, obstruct azoospermia), OR positive newborn screen, OR history of CF in a sibling AND
- Evidence of CFTR dysfunction (i.e., elevated sweat chloride concentration on two or more occasions, two mutations on separate alleles known to cause CF, abnormal nasal potential difference)\(^4,5\)

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:\(^7\)

- Patients with gating mutations: for patients who carry at least one copy of G551D or other gating mutation (as listed in FDA label) and is age 6 months and older, ivacaftor is recommended
- Patients with residual function mutations: for patients with at last one residual function CFTR mutation, therapy is recommended based on age:
  - Age 6 months to 5 years – ivacaftor monotherapy
  - Age ≥6 years – tezacaftor/ivacaftor
- F508del homozygotes: for patients who are homozygous for F508del, therapy is recommended based on age:
  - Age 2 to 5 years – lumacaftor/ivacaftor
Age ≥6 years – tezacaftor/ivacaftor

Patients ≥6 years who are currently on lumacaftor/ivacaftor should be switched to tezacaftor/ivacaftor due to its slightly greater improvement in pulmonary function, fewer adverse effects, and fewer drug interactions

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 \((P < 0.001)\). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than those receiving placebo \((P < 0.001)\). 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 \((P < 0.001)\), 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 showed 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 percent predicted BMI (ppBMI), 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 ≥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. 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 (tezacaftor-ivacaftor-ivacaftor combination) brings 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

For additional clinical information see the Prime Therapeutics Formulary Chapter 6.5: Cystic Fibrosis.

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

TARGET AGENTS
Kalydeco® (ivacaftor)
Orkambi® (lumacaftor/ivacaftor)
Symdeko® (tezacaftor/ivacaftor and ivacaftor)
Trikafta™ (elexacaftor/tezacaftor/ivacaftor and ivacaftor)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity per Day Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kalydeco (ivacaftor)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>25 mg oral granules</td>
<td>45302030003010</td>
<td>M, N, O, or Y</td>
<td>2 packets</td>
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<td>50 mg oral granules</td>
<td>45302030003020</td>
<td>M, N, O, or Y</td>
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<td>75 mg oral granules</td>
<td>45302030003030</td>
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<tr>
<td>150 mg tablet</td>
<td>45302030000320</td>
<td>M, N, O, or Y</td>
<td>2 packets</td>
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<tr>
<td><strong>Orkambi (lumacaftor/ivacaftor)</strong></td>
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</tr>
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<td>100 mg/125 mg oral granules</td>
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<td>150 mg/188 mg oral granules</td>
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<td>2 packets</td>
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<td>100 mg/125 mg tablet</td>
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<td>M, N, O, or Y</td>
<td>4 tablets</td>
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<td>200 mg/125 mg tablet</td>
<td>45309902300320</td>
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<td>4 tablets</td>
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<td><strong>Symdeko (tezacaftor/ivacaftor and ivacaftor co-packaged)</strong></td>
<td>4530990280B70</td>
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<tr>
<td>50 mg/75 mg tablet and 75 mg ivacaftor tablet</td>
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<td></td>
<td></td>
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<tr>
<td>100 mg/150 mg tablet and 150 mg ivacaftor tablet</td>
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<tr>
<td><strong>Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor co-packaged)</strong></td>
<td>4530990340B740</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
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<td>100 mg/50 mg/75mg tablet and 150 mg ivacaftor tablet</td>
<td></td>
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</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Target Agent will be approved when ALL of the following are met:

1. ONE of the following:
   a. The patient has a diagnosis of cystic fibrosis AND BOTH of the following:
      i. The patient’s age is within FDA labeling for the requested agent
      AND
      ii. 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
      a. Kalydeco:
         i. CFTR gene mutation: ONE mutation based on FDA label
         AND
         ii. Does NOT have F508del mutations on BOTH alleles of CFTR gene (NOT homozygous)
      b. Orkambi:
         i. F508del mutation on BOTH alleles of CFTR gene (homozygous)
      c. Symdeko:
i. CFTR gene mutation: ONE mutation based on FDA label  
   **OR**
ii. F508del mutation on BOTH alleles of CFTR gene (homozygous)

d. Trikafta:
   i. F508del mutation on at least ONE allele (heterozygous) or both alleles (homozygous) of the CFTR gene

   e. Another FDA approved CFTR modulator agent:
      i. CFTR gene mutation(s) based on FDA label  
      **OR**
      
   B. The patient has another FDA approved indication for the requested agent  
   **AND**

2. ONE of following:
   A. The patient is NOT currently being treated with another CFTR modulator agent (e.g., Kalydeco, Orkambi, Symdeko, Trikafta)  
   **OR**

   B. The patient is currently being treated with another CFTR modulator agent AND will discontinue prior to starting the requested agent  
   **AND**

3. The prescriber is a specialist in cystic fibrosis or the prescriber has consulted with a specialist in cystic fibrosis  
   **AND**

4. The patient does NOT have any FDA labeled contraindications to the requested agent  
   **AND**

5. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit  
   **OR**

   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit  
      **AND**

      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose  
      **AND**

      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit  
      **OR**

   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit  
      **AND**

      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose  
      **AND**

      iii. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

Length of Approval: 6 months

Renewal Evaluation  
**Target Agent** will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the plan’s Prior Authorization process

   AND

2. ONE of the following:
   A. If the patient has a diagnosis of cystic fibrosis, the prescriber has submitted information that the patient has had clinical improvement or stabilization with the requested agent [e.g., improvement in FEV1 from baseline, increase in weight/BMI, improvement from baseline 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
   B. If the patient has another FDA approved indication for the requested agent, the patient has had improvement or stabilization with the requested agent

   AND

3. ONE of the following:
   A. The patient is NOT currently being treated with another CFTR modulator agent (e.g., Kalydeco, Orkambi, Symdeko, Trikafta)
   OR
   B. The patient is currently being treated with another CFTR modulator agent AND will discontinue prior to continuing the requested agent

   AND

4. The prescriber is a specialist in cystic fibrosis or the prescriber has consulted with a specialist in cystic fibrosis

   AND

5. The patient does NOT have any FDA labeled contraindications to the requested agent

   AND

6. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
   OR
   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose
      AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
   OR
   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose
      AND
      iii. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months