### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing and Administration</th>
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</table>
| Kalydeco®      | 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. | - Adults and pediatric patients age 6 years and older:  
  o One 150 mg tablet taken orally every 12 hours with fat-containing food  
- Pediatric patients 6 months to less than 6 years of age and weighing 5 kg to less than 7 kg:  
  o One 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food  
- Pediatric patients 6 months to less than 6 years of age and weighing 7 kg to 14 kg:  
  o One 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food  
- Pediatric patients 6 months to less than 6 years of age and 14 kg or greater:  
  o One 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food  
- Pediatric patients less than 6 months of age: not recommended  
- Reduce dose in patients with moderate to severe hepatic impairment |
| **Orkambi® (lumacaftor/ivacaftor)** | Treatment of cystic fibrosis (CF) in patients age 2 years 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.  
Limitation of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation. | Reduce dose when co-administered with drug that are moderate or strong CYP3A inhibitors  
• Pediatric patients age 2 through 5 years and weighing less than 14 kg: one packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food  
• Pediatric patients age 2 through 5 years and weighing 14 kg or greater: one packet of granules (each containing lumacaftor 150mg/ivacaftor 188 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food  
• Pediatric patients age 6 through 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours  
• Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours |  
| **Symdeko™ (tezacaftor/ivacaftor and ivacaftor)** | Treatment of patients with cystic fibrosis (CF) aged 12 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 |  
• Adults and pediatric patients ages 12 years and older: one tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart. Symdeko should be taken with fat-containing food |
sequencing when recommended by the mutation test instructions for use

CLINICAL RATIONALE
Cystic Fibrosis (CF) is the most common life-threatening autosomal recessive disease in the US. CF is a multisystem disorder caused by mutations in the gene for the CF transmembrane conductance regulator (CFTR), which encodes an ion channel protein. There are more than 2000 mutations identified to date for the CFTR gene. CF is diagnosed when a patient has both clinical presentation of CF and evidence of CFTR dysfunction. Sweat chloride test should be considered first, then CFTR genetic analysis, and then CFTR physiologic tests. Diagnosis of CF can be challenging because the age of onset and severity of symptoms can differ greatly due to highly variable levels of CFTR dysfunction. Presenting manifestations can include pancreatitis, respiratory symptoms, chronic sinusitis, and male infertility. Respiratory manifestations of CF include persistent, productive cough, hyperinflation of the lung fields on chest radiograph, and pulmonary function tests that are consistent with obstructive airway disease. Infections of the airway with pathogenic bacteria occurs.

There are approximately 115 CF Care Centers that comprise of physicians, nurses, dietitians, respiratory therapists, physical therapists, and social workers with special competence in CF care. Patients that receive the medical care at specialized CF centers have better clinical outcomes compared with patients followed in general community. Multi-organs systems should be considered when assessing therapies for CF. 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.

CFTR modulators are a new class of drugs that act by improving production, intracellular processing and/or function of the defective CFTR protein. Indications and efficacy of CFTR drugs depend upon CFTR mutations in the patient. Ivacaftor was the first approved CF therapy that restores the functioning of a mutant CF protein rather than trying to target downstream consequences. It was approved for patients who have a G551d mutation in at least one of their CFTR genes. Further clinical trials and in vitro studies have expanded the approved label for ivacaftor to 33 mutations. 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 F508del mutation. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality. Unfortunately, neither drug is effective when used alone for F508del homozygotes. In patients who are heterozygous for the F508del mutation, lumacaftor-ivacaftor does not appear to have clinically meaning benefit. 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 is a CFTR corrector that improves the intracellular processing and trafficking of CFTR, while ivacaftor is a potentiator that improves the gating abnormality after CFTR is expressed in the cell surface.

All patients with CF should undergo CFTR genotyping to determine if they carry one of the mutations approved for CFTR modulator therapy. The following approach is recommended for CFTR modulators:

- 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 12 months and older, ivacaftor is recommended
• Patients with residual function mutations: for patients with at least one residual function CFTR mutation, therapy is recommended based on age:
  o Age 1 to 11 years – ivacaftor monotherapy
  o Age ≥12 years – tezacaftor/ivacaftor
  o Tezacaftor/ivacaftor is probably more effective than ivacaftor monotherapy, but tezacaftor/ivacaftor combination has not been approved for children <12 years of age
• F508del homozygotes: for patients who are homozygous for F508 del, therapy is recommended based on age:
  o Age 2 to 11 years – lumacaftor/ivacaftor
  o Age ≥12 years – tezacaftor/ivacaftor
  o Patients 12 years and older 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

The efficacy of ivacaftor in patients with CF and mutations (e.g. G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, S549R, or R117H) in the CFTR gene was evaluated in several randomized, double-blind, placebo-controlled clinical trials. The primary efficacy endpoint in the studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV1 through 24 weeks of treatment. Other efficacy variables included absolute change from baseline in sweat chloride, time to first pulmonary exacerbation (Trial 1 only), absolute change from baseline in weight, and improvement from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing. The study defined a pulmonary exacerbation 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. Patients treated with ivacaftor demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight.¹

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 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. The treatment difference between lumacaftor-ivacaftor and placebo for the mean absolute change in pPFEV1 from baseline at Week 24. 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 Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain 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

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

REFERENCES


CFTR Prior Authorization with Quantity Limit

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

QUANTITY LIMIT TARGET AGENTS- RECOMMENDED LIMITS

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<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity per Day Limit</th>
</tr>
</thead>
<tbody>
<tr>
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<td>M, N, O, or Y</td>
<td>2 packets</td>
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<td>25 mg oral granules</td>
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<td>75 mg oral granules</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>150 mg tablet</td>
<td>4530203000320</td>
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<td>Orkambi (lumacaftor/ivacaftor)</td>
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<td></td>
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<td>200 mg/125 mg tablet</td>
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<td>Symdeko (tezacaftor/ivacaftor and ivacaftor co-packaged)</td>
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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 is within the FDA labeled age for the requested agent
         a. Kalydeco granules: 6 months through up to 6 years of age
         b. Kalydeco tablets: 6 years of age and over
         c. Orkambi granules: 2 years through up to 6 years of age
         d. Orkambi tablets: 6 years of age and over
         e. Symdeko: 12 years of age and over
   AND
   ii. The prescriber has submitted documentation that the patient has CFTR gene mutations, confirmed by genetic testing, according to FDA label for the requested agent
      a. Kalydeco:
         1. CFTR gene mutation: ONE mutation based on FDA label
            AND
         2. Does NOT have F508del mutations on BOTH alleles of CFTR gene (NOT homozygous)
      b. Orkambi:
         1. F508del mutation on BOTH alleles of CFTR gene (homozygous)
      c. Symdeko:
         1. CFTR gene mutation: ONE mutation based on FDA label OR
            2. F508del mutation on BOTH alleles of CFTR gene (homozygous)
   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 agent (e.g., Kalydeco, Orkambi, Symdeko)
   - OR
   - B. The patient is currently being treated with another CFTR agent AND will discontinue the other CFTR agent prior to starting the requested agent

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

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

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 documentation 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 Prime Therapeutics PA process

2. The prescriber has submitted documentation that the patient has shown 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 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)

3. **ONE of the following:**
   - A. The patient is NOT currently being treated with another CFTR agent (e.g., Kalydeco, Orkambi, Symdeko)
   - OR
B. The patient is currently being treated with another CFTR agent (e.g., Kalydeco, Orkambi, Symdeko) AND will discontinue the other CFTR agent 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 documentation in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months