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

FDA APPROVED INDICATIONS AND DOSAGE[1-3,8]

Agent(s)	Indication(s)	Dosage
Kalydeco® (ivacaftor) Tablets Oral granules	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. 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.	Adults and pediatric patients age 6 years and older: One 150 mg tablet taken orally every 12 hours Pediatric patients 4 months to less than 6 years of age and: - weighing 5 kg to < 7 kg: One 25 mg packet every 12 hours - weighing 7 kg to < 14 kg: One 50 mg packet every 12 hours - weighing 14 kg or greater: One 75 mg packet every 12 hours
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. 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. <u>Limitations of use:</u> The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation.	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) every 12 hours - weighing 14 kg or greater: One packet of granules (each containing lumacaftor 150 mg/ivacaftor 188 mg) every 12 hours Pediatric patients age 6 through 11 years: Two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours Adults and pediatric patients age 12 years and older: Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours

Symdeko® (tezacaftor/ivacaftor and ivacaftor co-packaged) Tablets	Treatment of patients with cystic fibrosis (CF) age 6 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 sequencing when recommended by the mutation test instructions for use.	Pediatric patients age 6 to less than 12 years weighing < 30 kg: One tablet (containing tezacaftor 50 mg/ ivacaftor 75 mg) in the morning and one tablet (containing ivacaftor 75 mg) in the evening, approximately 12 hours apart Adults and pediatric patients age 12 years and older, or pediatric patients age 6 to less than 12 years weighing ≥ 30 kg: 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
Trikafta® (elexacaftor/tezacaftor/ ivacaftor and ivacaftor co-packaged) Tablets	Treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data. 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 or a mutation that is responsive based on *in vitro* data.	Adults and pediatric patients age 6 years and older weighing 30 kg or more: Two tablets (each containing elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart Pediatric patients age 6 to 12 years of age weighing less than 30 kg: Two tablets (each containing elexacaftor 50 mg/ tezacaftor 25 mg/ ivacaftor 37.5 mg) in the morning and one tablet (containing ivacaftor 75 mg) in the evening, approximately 12 hours apart

CLINICAL RATIONALE

Cystic Fibrosis

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 diagnose CF:[4,5]

- Clinical symptoms consistent with CF in at least one organ system, OR positive newborn screen, OR history of CF in a sibling
  AND
- Evidence of CFTR dysfunction (i.e., elevated sweat chloride greater than or equal to 60 mmol/L, two mutations on separate alleles known to cause CF, abnormal nasal potential difference)

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, guided by both genotype and age:[7]

- F508del homozygotes:
  - Age 2 to 5 years – lumacaftor/ivacaftor (LUM/IVA)
  - Age greater than or equal to 6 years – elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) rather than tezacaftor/ivacaftor (TEZ/IVA) or LUM/IVA
- F508del heterozygotes
  - Age greater than or equal to 6 years – ELZ/TEZ/IVA
  - Age 4 months through 5 years – IVA (if the second mutation is responsive to this therapy)
  -
- If a patient has a genotype that is eligible for more than one therapy, start on the maximal therapy available for their age group (i.e., triple therapy before dual therapy before monotherapy).
- For patients with no gating mutations, residual function mutations, or F508del mutations, CFTR therapy should be used in the setting of a clinical trial. This represents approximately 10% of the CF population in the United States.

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 FEV_1 increased 10.4% from baseline in the treated patients compared with −0.2% for those receiving placebo at 24 weeks (*P* less than 0.001). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than those receiving placebo (*P* less than 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* less than 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 shown 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 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 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 greater than or equal to 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.[7] A trial involving F508del homozygotes resulted in modest improvement in FEV_1 (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 (elexacaftor-tezacaftor-ivacaftor combination) brought 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]

The safety of elexacaftor-tezacaftor-ivacaftor in younger children was evaluated in a 24-week open-label study in 66 children 6 to 11 years old who were homozygous for F508del or heterozygous for F508del with a second minimal function mutation. The safety profile and pharmacokinetics were similar to those in older individuals, and patients experience improvement in percent predicted FEV1 (10.2 percentage points; 95% CI 7.9-12.6), respiratory symptoms, sweat chloride, and body weight.[7,11] On the basis of this study, the drug combination was approved for this age group in June 2021.[8]

References

1. Kalydeco prescribing information. Vertex Pharmaceuticals Incorporated. December 2020.
2. Orkambi prescribing information. Vertex Pharmaceuticals Incorporated. July 2019.
3. Symdeko prescribing information. Vertex Pharmaceuticals Incorporated. December 2020.
4. Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr.* 2017 Feb;181S:S4-S15.e1.
5. Katkin JP, et al. Cystic Fibrosis: Clinical Manifestations and Diagnosis. UpToDate. Last updated August 2020. Literature review current through September 2021. Accessed October 2021.
6. Simon RH, et al. Cystic Fibrosis: Overview of the Treatment of Lung Disease. UpToDate. Last updated August 2021. Literature review current through September 2021. Accessed October 2021.
7. Simon RH, et al. Cystic Fibrosis: Treatment with CFTR Modulators. UpToDate. Last updated September 2021. Literature review current through September 2021. Accessed October 2021.
8. Trikafta prescribing information. Vertex Pharmaceuticals Incorporated. October 2021.
9. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al, of the Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med.* 2013 Apr;187(7):680-689.
10. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with Cystic Fibrosis. *Ann Am Thorac Soc*. 2018 Mar;15(3):271-280.
11. Zemanick ET, Taylor-Cousar JL, Davies J, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. *Am J Respir Crit Care Med*. 2021;203(12):1522.

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

TARGET AGENT(S)
Kalydeco® (ivacaftor)
Orkambi® (lumacaftor/ivacaftor)
Symdeko® (tezacaftor/ivacaftor and ivacaftor)
Trikafta® (elexacaftor/tezacaftor/ivacaftor and ivacaftor)

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as listed)
Kalydeco (ivacaftor)			
25 mg oral granules	45302030003010	M, N, O, or Y	2 packets
50 mg oral granules	45302030003020	M, N, O, or Y	2 packets
75 mg oral granules	45302030003030	M, N, O, or Y	2 packets
150 mg tablet	45302030000320	M, N, O, or Y	2 tablets
Orkambi (lumacaftor/ivacaftor)			
100 mg/125 mg oral granules	45309902303010	M, N, O, or Y	2 packets
150 mg/188 mg oral granules	45309902303020	M, N, O, or Y	2 packets
100 mg/125 mg tablet	45309902300310	M, N, O, or Y	4 tablets
200 mg/125 mg tablet	45309902300320	M, N, O, or Y	4 tablets
Symdeko (tezacaftor/ivacaftor and ivacaftor co-packaged)			
50 mg/75 mg tablet and 75 mg ivacaftor tablet	4530990280B710	M, N, O, or Y	2 tablets
100 mg/150 mg tablet and 150 mg ivacaftor tablet	4530990280B720	M, N, O, or Y	2 tablets
Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor co-packaged)			
50 mg/25 mg/37.5 mg tablet and 75 mg ivacaftor tablet	4530990340B720	M, N, O, or Y	3 tablets
100 mg/50 mg/75 mg tablet and 150 mg ivacaftor tablet	4530990340B740	M, N, O, or Y	3 tablets

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. ONE of the following:
   A. ALL of the following:
      i. The patient has a diagnosis of cystic fibrosis
      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 (medical records required)
      AND
      iii. If the requested agent is Kalydeco, the patient does NOT have F508del mutation on BOTH alleles of CFTR gene (NOT homozygous)
   OR
   B. The patient has another FDA approved indication for the requested agent
   AND
2. ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent

OR

B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication

AND

3. The patient will NOT be using the requested agent in combination with another CFTR modulator agent for the requested indication

AND

4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cystic fibrosis, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

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 for the requested indication

      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 for the requested indication

      AND

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

Length of Approval: 6 months

Renewal Evaluation

Target Agent(s) 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 provided information that the patient has had clinical improvement or stabilization with the requested agent from baseline (prior to treatment with the requested agent) [e.g., improvement in FEV1, increase in weight/BMI, improvement in 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 clinical benefit with the requested agent

AND

3. The patient will NOT be using the requested agent in combination with another CFTR modulator agent for the requested indication

AND

4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cystic fibrosis, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

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 for the requested indication

      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 for the requested indication

      AND

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

Length of Approval: 12 months

