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

This prior authorization applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Prior Authorization (PA) is to encourage appropriate selection of patients for treatment according to approved labeling and/or clinical studies and/or clinical guidelines and according to dosing recommended in product labeling. Approval will require a diagnosis of cystic fibrosis or another FDA approved indication and confirmed genetic status of the CFTR mutation. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

TARGET AGENTS

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

QUANTITY LIMIT TARGET AGENTS- RECOMMENDED LIMITS

Brand (generic)	GPI	Multisource Code	Quantity per Day Limit
Kalydeco (ivacaftor)			
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 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)			
100 mg/150 mg tablet and 150 mg ivacaftor tablet	4530990280B720	M, N, O, or Y	2 tablets

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

The requested 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 ALL of the following:
     - i. The patient is within the FDA labeled age for the requested agent
       - a. Kalydeco: 2 years of age or over
       - b. Orkambi: 6 years of age or over
       - c. Symdeko: 12 years of age and over

       AND

ii. The patient has *CFTR* gene mutations according to FDA label confirmed by genetic testing
    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)

AND

iii. The patient has had pre-therapeutic/baseline FEV_1 levels measured

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

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) is NOT greater than 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) is less than or equal to the 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 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 FDA labeled dose

        AND

        iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 6 months

Renewal Evaluation

The requested 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
   AND
2. If cystic fibrosis, the patient has shown improvement or stabilization in FEV_1 from pre-therapeutic/baseline levels
   AND
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 starting 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) is NOT greater than 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) is less than or equal to the 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 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 FDA labeled dose
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1-3]

Agent	Indication	Dosing and Administration
Kalydeco® (ivacaftor)	Treatment of cystic fibrosis (CF) in patients age 2 years 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	• Pediatric patients 2 to less than 6 years of age and less than 14 kg: 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 2 to less than 6 years of age and 14 kg or greater: 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 • Adults and pediatric patients age 6 years and older: one 150 mg tablet taken orally every 12 hours with fat-containing food
Orkambi® (lumacaftor/ivacaftor)	Treatment of cystic fibrosis (CF) in patients age 6 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.	• 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™ (tezcaftor/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	• 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

	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	

CLINICAL RATIONALE[2]

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.[4] 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.[5]

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.[6]

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 F580del 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.

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

REFERENCES

1. Kalydeco prescribing information. Vertex Pharmaceuticals Incorporated. July 2017.
2. Orkambi prescribing information. Vertex Pharmaceuticals Incorporated. January 2018.
3. Symdeko prescribing information. Vertex Pharmaceuticals Incorporated. February 2018.
4. Farrell, Philip M., MD, PhD., et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *Journal of Pediatrics.* S4-S15.e1. February 2017. Accessed at: http://www.jpeds.com/article/S0022-3476(16)31048-4/pdf. Accessed February 2018.
5. Katkin, Julie P., MD, et al. Cystic Fibrosis: Clinical Manifestations and Diagnosis. UpToDate. Last updated April 2017. Literature review current through January 2018.
6. Simon, Richard H., MD, et al. Cystic Fibrosis: Overview of the Treatment of Lung Disease. UpToDate. Last updated February 2018. Literature review current through January 2018.