Medical Policy

BlueCross BlueShield of Kansas
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Blue Cross Blue Shield Association

Title: Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

- **Prime Therapeutics will review Prior Authorization requests.**
  Prior Authorization Forms:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6609KS-CFTR.pdf

  Link to Drug List (Formulary):
  https://www.bcbsks.com/drugs/

Professional
Original Effective Date: September 1, 2012
Revision Date(s): September 1, 2012; March 1, 2013; August 12, 2014; April 17, 2015; January 1, 2016; April 15, 2016; April 29, 2016; November 1, 2016; April 1, 2017; June 1, 2017; April 1, 2018; June 15, 2018; September 10, 2018; November 1, 2018
Current Effective Date: November 1, 2018

Institutional
Original Effective Date: September 1, 2012
Revision Date(s): September 1, 2012; March 1, 2013; August 12, 2014; April 17, 2015; January 1, 2016; April 15, 2016; April 29, 2016; November 1, 2016; April 1, 2017; June 1, 2017; April 1, 2018; June 15, 2018; September 10, 2018; November 1, 2018
Current Effective Date: November 1, 2018

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

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)

FDA Approved Indications and Dosage[1-3]

Agent	Indication	Dosing and Administration
Kalydeco® (ivacaftor)	Treatment of cystic fibrosis (CF) in patients age 12 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	• Pediatric patients 12 months to less than 6 years of age and weighing 7 kg to 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 12 months 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	• 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 weighting 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

Agent	Indication	Dosing and Administration
	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™ (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 sequencing when recommended by the mutation test instructions for use	• 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

POLICY

Prior Authorization and Quantity Limits 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: 12 months through up to 6 years of age
            b. Kalydeco tablets: 6 years of age and over
            c. Orkambi granules: 2 years through to 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
   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

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 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 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 intended diagnosis

Length of Approval: 6 months

CFTR Gene Mutations

Kalydeco (ivacaftor)	A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, *E831X,* F1052V, F1074L, G1069R, *G1244E, G1349D, G178R, G551D, G551S,* K1060T, L206W, P67L, R1070Q, R1070W, R117C, *R117H,* R347H, R352Q, R74W, *S1251N, S1255P, S549N, S549R,* S945L, S977F, *711+3A-G, 2789+5G-A, 3272-26A-G, 3849+10kbC-T, or another FDA approved genotype*
Orkambi (lumacaftor/ivacaftor)	Both alleles of F508del
Symdeko (tezcaftor/ivacaftor and ivacaftor)	A1067T, A455E, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R117C, R347H, R352Q, R1070W, S945L, S977F, 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G, both alleles of F508del, or another FDA approved gene mutation

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. The prescriber has submitted documentation that the patient has shown clinical improvement or stabilization with the requested agent (e.g. improvement in FEV_1 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 breaking), and/or reduced number of pulmonary exacerbations)
   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 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 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 intended diagnosis

Length of Approval: 12 months

Program Quantity Limits	
Brand (generic)	**Quantity Per Day Limit**
Kalydeco (ivacaftor)	
50 mg oral granules	2 packets
75 mg oral granules	2 packets
150 mg tablet	2 tablets
Orkambi (lumacaftor/ivacaftor)	
100 mg/125 mg oral granules	2 packets
100 mg/188 mg oral granules	2 packets
100 mg/125 mg tablet	4 tablets
200 mg/125 mg tablet	4 tablets
Symdeko (tezacaftor/ivacaftor and ivacaftor co-packaged)	
100 mg/150 mg tablet and 150 mg ivacaftor tablet	2 tablets

FDA Labeled Contraindications	
Agent	**Contraindication**
Kalydeco (ivacaftor)	None
Orkambi (lumacaftor/ivacaftor)	None
Symdeko (tezacaftor/ivacaftor and ivacaftor)	None

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.[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.

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 lumcaftor-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 ppFEV1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. In both trials, treatment with lumcaftor-ivacaftor resulted in a statistically significant improvement in ppFEV1. The treatment difference between lumcaftor-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]

REVISIONS	
09-01-2012	Policy added to the bcbsks.com web site.
03-01-2013	Title revised from, "Kalydeco™ (ivacaftor) Prior Authorization (with Quantity Limit) Program Summary" to, "Kalydeco™ (ivacaftor)".
	Updated Description section
	In policy section: ▪ In A 2 added the criteria of, "b. The patient is not homozygous for the F508del mutation" ▪ Added Renewal Evaluation criteria of, "B. Renewal Evaluation Kalydeco will be approved when BOTH of the following are met: 1. The patient has been approved previously for ivacaftor through the Prime Therapeutics PA process AND 2. The patient has shown improvement in FEV_1 AND 3. ONE of the following: a. The quantity requested is less than or equal to the program quantity limit (2 tablets) OR b. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist. Length of Approval: 12 months"
	Updated Rationale section
08-12-2014	In Title section: ▪ Added "Prime Therapeutics will review Prior Authorization requests."
	Description section updated
	In Policy section: ▪ In Item A 2 a added "ONE of the following CFTR gene mutations:" and "G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R" and removed "mutation of CFTR gene" to read, "The patient has ONE of the following CFTR gene mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R as confirmed by genetic testing AND" ▪ In Item B 1 removed "BOTH" and added "ALL" to read, "…will be approved when ALL of the following are met:" ▪ In Item B 2 added "from pre-ivacaftor therapy levels" to read, "The patient has shown improvement in FEV_1 from pre-ivacaftor therapy levels AND"
	Rationale section updated
	▪ Coding Section added to include "There are no specific HCPCS codes for Kalydeco™ (ivacaftor)."
	References updated
04-17-2015	Published on 03-17-2015.
	Description section updated
	In Policy section: ▪ In header added "and Quantity Limits" to read "Prior Authorization and Quantity Limits Criteria for Approval" ▪ In Initial Evaluation, changed to current criteria from:

REVISIONS	
	"Kalydeco will be approved when the following are met: 1. The patient has a diagnosis of cystic fibrosis AND 2. ALL of the following: a. The patient has ONE of the following CFTR gene mutations: G551D G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R as confirmed by genetic testing AND b. The patient is not homozygous for the F508del mutation AND c. ONE of the following: 1) The quantity requested is less than or equal to the program quantity limit (2 tablets per day) OR 2) The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis." ▪ In Renewal Evaluation changed to current criteria from: "Kalydeco will be approved when ALL of the following are met: 1. The patient has been approved previously for ivacaftor AND 2. The patient has shown improvement in FEV_1 from pre-ivacaftor therapy levels AND 3. ONE of the following: a. The quantity requested is less than or equal to the program quantity limit (2 tablets per day) OR b. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis" ▪ Added Program Quantity Limits chart ▪ Note: Quantity Limits is not new to the policy, but reflected in a chart rather than within the policy language section.
	Rational section updated
	Coding section removed
	References updated
01-01-2016	Policy published 12-30-2015. Policy effective 01-01-2016.
	Added Orkambi™ (lumacaftor/ivacaftor) to the policy.
	In Title added Orkambi™ (lumacaftor/ivacaftor) revising Title from Kalydeco™ (ivacaftor) to Kalydeco™ (ivacaftor), Orkambi™ (lumacaftor/ivacaftor)
	Description section updated to include adding Orkambi™ (lumacaftor/ivacaftor) to Target Drugs and updating FDA Indications and Dosage
	In Policy section ▪ In Initial Evaluation Item A added "and Orkambi "lumacaftor/ivacaftor)" to read "Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor) will be approved when the following are met:" ▪ In Item 1 A ii added "ONE of the following:" ▪ In Item 1 A ii a added Kalydeco is requested and" to read Kalydeco is requested and ALL of the following:" ▪ In Item 1 A ii b added "Orkambi is requested and the patient has the presence of the F508del mutation on both alleles of the CFTR gene confirmed by genetic testing" ▪ In Item 1 A iii added "The patient has had pre-therapeutic/baseline FEV_1 levels measured" ▪ In Initial Evaluation Length of Approval revised "12 months" to "6 months" ▪ In Item B Renewal Evaluation removed "Kalydeco" to read "Renewal Evaluation will be approved when ALL of the following are met:" ▪ In Item B 1 removed "for ivacaftor"

REVISIONS	
	▪ In Item B 2 removed "ivacaftor therapy" and added "or stabilization" and "therapeutic/baseline" to read "If cystic fibrosis, the patient has shown improvement or stabilization in FEV_1 from pre-therapeutic/baseline levels" Updated Program Quantity Limits chart
	Rationale section updated
04-15-2016	Policy language reviewed with no changes.
	Description section updated
04-29-2016	Corrected Current Effective Date from 04-15-2016 to 01-01-2016 since no policy language changes were made.
11-01-2016	In Description section: ▪ Updated FDA Indications for Orkambi from "12 years and older" to "6 years and older" ▪ Updated Dosing for Orkambi adding dosing direction for a younger age
	In Policy section ▪ Updated Quantity Limits for Orkambi adding "100 mg / 125 mg tablet" at "4 tablets" per day limit.
	References updated
04-01-2017	In Policy Section: ▪ Added Item A 1 A ii "The patient is at least the minimal age noted in the FDA labeled indication (e.g., Kalydeco: 2 years of age or older; Orkambi: 6 years of age or older)"
	Rationale Section updated
	References updated
06-01-2017	Policy published 08-01-2017. Policy retro-effective to 06-01-2017.
	In Policy section: ▪ Added a CFTR gene mutations chart for reference. No changes to the intent of the policy were made by this addition.
04-01-2018	Description section updated
	In Policy section: ▪ Updated CFTR gene mutations list
	References updated
06-15-2018	Title changed to "Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)" from "Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor)"
	Description section updated ▪ Added Symdeko as target with quantity limit ▪ Revised FDA Approved Indications and Dosage from narrative to chart format.
	In Policy section: <u>Initial Evaluation</u> ▪ In header removed "Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor)" and added "The requested agent" and "ALL" to read "The requested agent will be approved when ALL of the following are met:" ▪ In Item 1 A i removed "at least the minimal age noted in" to "within" and "age for the requested agent" to read "The patient is within the FDA labeled age for the requested agent." ▪ In 1 A i added "c. Symdeko: 12 years of age and over" ▪ In 1 A ii removed "ONE of the following: a. Kalydeco is requested and ALL of the following: i. The patient has ONE of the CFTR gene mutations as indicated in the FDA label as confirmed by genetic testing AND ii. The patient is not homozygous for the F508del mutation OR b. Orkambi is requested and the patient has the presence of the F508del mutation on both alleles of the CFTR gene confirmed by genetic testing"

REVISIONS	
	and added "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 added "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" ▪ Updated CFTR Gene Mutations chart <u>Renewal Evaluation</u> ▪ In Item 3 added "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" ▪ Added "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" ▪ Updated Program Quantity Limits chart to add Symdeko ▪ Added Contraindications chart
	Rationale section updated
	References updated
09-10-2018	<u>Policy published 10-10-2018. Policy retro-effective to 09-10-2018.</u>
	In Description section: FDA Approved Indications and Dosage chart updated
	In Policy section: Summary of revisions: • Addition of Orkambi granules • <u>Updated ages according to FDA label update for Kalydeco and Orkambi</u> In Item 1 A i revised "a. Kalydeco: 2 years of age or over b. Orkambi: 6 years of age or over c. Symdeko: 12 years of age and over" to read "a. Kalydeco granules: 12 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"

REVISIONS	
	Updated Quantity Limits chart.
	References updated
11-01-2018	In Policy section: Summary of revisions: • Addition of documentation of CFTR gene mutations in program summary • Removal of FEV1 measurement – with new FDA age requirements (Kalydeco > 12 months, Orkambi > 2 years) would be hard to obtain FEV1 for those under 6 years old. No clinical evidence that its appropriate to assess FEV1 in patients under 6 years of age. • Renewal – modification for clinical improvement/stabilization to include other parameters besides FEV1; examples are secondary end points in clinical trials. This is to accommodate for pediatric patients Initial Evaluation ▪ In Item 1 A removed "ALL" and added "BOTH" ▪ In Item 1 A ii removed "according to FDA label" and added "prescriber has submitted documentation that the" to read "The prescriber has submitted documentation that the patient has CFTR gene mutations according to FDA label confirmed by genetic testing" ▪ In Item 1 A removed "iii. The patient has had pre-therapeutic/baseline FEV1 levels measured" ▪ In Item 5 B ii added "maximum" to read "The requested quantity (dose) is less than or equal to the maximum FDA labeled dose" ▪ In Item 5 C ii add "maximum" to read "The requested quantity (dose) is greater than the maximum FDA labeled dose" Renewal Evaluation ▪ In Item 2 removed "pre-therapeutic levels" and added "The prescriber has submitted documentation that", "with the requested agent (e.g. improvement" and "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 breaking), and/or reduced number of pulmonary exacerbations)" to read "The prescriber has submitted documentation that the patient has shown clinical improvement or stabilization with the requested agent (e.g. improvement in FEV_1 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 breaking), and/or reduced number of pulmonary exacerbations)" ▪ In Item 6 B ii added "maximum" to read "The requested quantity (dose) is less than or equal to the maximum FDA labeled dose" ▪ In Item 6 C ii add "maximum" to read "The requested quantity (dose) is greater than the maximum FDA labeled dose"
	Rationale section updated

REFERENCES

1. Kalydeco prescribing information. Vertex Pharmaceuticals Incorporated. August 2018.
2. Orkambi prescribing information. Vertex Pharmaceuticals Incorporated. August 2018.
3. Symdeko prescribing information. Vertex Pharmaceuticals Incorporated. February 2018.
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