Title: Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor)

- Prime Therapeutics will review Prior Authorization requests.

Prior Authorization Forms:

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

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 Kalydeco and Orkambi prior authorization (PA) is to encourage appropriate selection of cystic fibrosis patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. Criteria will limit the approved dose to at or below the maximum FDA labeled dose, it will require confirmed genetic status and a diagnosis of cystic fibrosis. The criteria will also allow for a patient who has any FDA approved diagnosis that is not already addressed in the criteria set. 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 Drugs
- Kalydeco® (ivacaftor)
- Orkambi™ (lumacaftor/ivacaftor)

FDA Approved Indications and Dosage

FDA Indication¹,⁴:
- Kalydeco: For the treatment of cystic fibrosis (CF) in patients age 2 years of age and older who have ONE of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H. If the patient’s genotype is unknown, an FDA-cleared 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.

  Limitation of use: Ivacaftor is ineffective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.

- Orkambi: For the 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.
**Dosing**\(^{1,4}\):

- **Kalydeco:**
  - The recommended dose for adults and pediatric patients age 6 and older is 150 mg orally every 12 hours with a fat-containing food.
  - The recommended dose for pediatric patients 2 to less than 6 years of age that weighs less than 14 kg is one 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid administered orally every 12 hours with fat-containing food.
  - The recommended dose for pediatric patients 2 to less than 6 years of age that weighs 14 kg or greater is 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.

- **Orkambi:**
  - Age 6 through 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours. Total daily dose of lumacaftor 400 mg/ivacaftor 500 mg.
  - Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours. Total daily dose of lumacaftor 800 mg / ivacaftor 500 mg.

Dose reductions are recommended for moderate and severe hepatic impairment and when co-administered with moderate to strong CYP3A4 inhibitors. Co-administration with CYP3A4 inducers (e.g. rifampin, St. John’s Wort) is not recommended.

Additionally, specific to Orkambi, co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.
POLICY

Prior Authorization and Quantity Limits Criteria for Approval

A. Initial Evaluation

**Kalydeco** (ivacaftor) and **Orkambi** (lumacaftor/ivacaftor) will be approved when 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. 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) **AND**
      iii. **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 **AND**
          iv. The patient has had pre-therapeutic/baseline FEV₁ levels measured **OR**
   B. The patient has another FDA approved indication for the requested agent **AND**

2. **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

**Length of Approval:** 6 months

<table>
<thead>
<tr>
<th><strong>CFTR gene mutations</strong></th>
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</thead>
</table>

B. **Renewal Evaluation** will be approved when **ALL of the following** are met:
   1. The patient has been approved previously **AND**
   2. If cystic fibrosis, the patient has shown improvement or stabilization in FEV₁ from pre-therapeutic/baseline levels **AND**
   3. **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

**Length of Approval:** 12 months

<table>
<thead>
<tr>
<th>Program Quantity Limits</th>
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<tbody>
<tr>
<td><strong>Brand (generic)</strong></td>
</tr>
<tr>
<td><strong>Kalydeco (ivacaftor)</strong></td>
</tr>
<tr>
<td>50 mg oral granules</td>
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<tr>
<td>75 mg oral granules</td>
</tr>
<tr>
<td>150 mg tablet</td>
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<tr>
<td><strong>Orkambi (lumacaftor/ivacaftor)</strong></td>
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<tr>
<td>100 mg/125 mg tablet</td>
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<tr>
<td>200 mg/125 mg tablet</td>
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**RATIONALE**

**Clinical Rationale**
CF is a life threatening, inherited condition that affects the cells that produce mucus, sweat and digestive enzymes. CF is caused by defects in the CFTR (cystic fibrosis transmembrane regulator) gene which encodes for a protein that functions as a chloride channel and regulates the flow of other ions across the surface of epithelial cells. Mutations in the CFTR gene result in abnormalities of chloride transport across epithelial cells on mucosal surfaces. The failure results in chloride and water transport abnormalities which causes viscid secretions in the respiratory tract, pancreas, gastrointestinal tract, sweat glands, and other exocrine issues. The increased viscosity makes these secretions hard to clear. Thus far, 1,893 CFTR mutations have been identified with half of all individuals of northern European descent have the ΔF508 mutation. Another 25%-30% have one copy of ΔF508 plus another mutation. About 4% of those with CF (roughly 1,200) people are believed to have the G551D mutation. There is no cure for CF but antibiotics, mucus-thinning drugs and bronchodilators can ease symptoms and reduce complications.

**Efficacy**
The efficacy of ivacaftor was evaluated in 4 different trials. The first two were randomized, double-blind, placebo-controlled trials in 213 CF patients with the G551D mutation. In both trials patients were randomized to either 150 mg of ivacaftor twice daily or placebo. The primary efficacy endpoint in both trials was improvement in lung function as determined by the mean absolute change from baseline in percent predicted per-dose FEV₁ through 24 weeks of
treatment. Trial 1 was evaluated in 161 patients 12 years of age and older with baseline FEV₁ between 40-90% predicted [mean FEV₁ 64% predicted (range: 32%-98%)]. Trial 2 evaluated 52 patient’s age 6 to 11 years old with a baseline FEV₁ between 40-105% predicted [mean FEV₁ 84% predicted (range: 44% to 134%)]. The treatment difference in mean absolute change in percent of FEV₁ between ivacaftor and placebo at week 24 in Trial 1 was 10.6% (P<0.0001) and 12.5% (P<0.0001) in Trial 2. These changes persisted through week 48. In both studies treatment with ivacaftor resulted in significant improvement in FEV₁.

Trial 3 was a 16-week randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF aged 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV₁ ≥40% predicted. Patients were randomized 4:1 to be treated with Kalydeco 150mg (n=112) every 12 hours or placebo (n=28). Patients were able to continue their currently prescribed CF therapies. The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through week 16 in percent predicted FEV₁. Results showed there was no improvement in the primary endpoint in the Kalydeco treated group relative to the placebo group and also no meaningful difference in the secondary endpoints of change in CF symptoms, change in weight, or change in sweat chloride concentration.1

Trial 4 assessed the efficacy and safety of Kalydeco in patients with CF who have a G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene. The randomized, double-blind, placebo-controlled, crossover design clinical trial consisted of 2 parts and included 39 patients with CF. Patients 6 years of age and older and those with a FEV₁ ≥40% at screening were included. Patients were randomized 1:1 to get treated with either Kalydeco 150mg twice daily or placebo for 8 weeks and then were switched to the other treatment for another 8 weeks after a 4-8 week washout period. The primary efficacy endpoint was improvement in lung function as determined by the mean absolute baseline in percent predicted FEV₁ through 8 weeks of treatment. Secondary endpoints included absolute change from baseline in sweat chloride, absolute change from baseline in body mass index, and improvement in CF symptoms, all though week 8. For the overall population of the 9 mutations studied, treatment with Kalydeco compared to placebo resulted in significant improvement in percent predicted FEV₁ [10.7 through Week 8 (P < 0.0001)], BMI [0.66 kg/m² at Week 8 (P < 0.0001)], and cystic fibrosis respiratory symptom score [9.6 through Week 8 (P = 0.0004)]; however, there was a high degree of variability of efficacy responses among the 9 mutations.1

The efficacy of lumacaftor/ivacaftor in patients with cystic fibrosis (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 (TRANSPORT AND TRAFFIC). These studies included 1108 clinically stable patients with CF; of whom 369 patients received lumacaftor/ivacaftor twice daily. TRAFFIC evaluated 549 patients with CF who were aged 12 years and older (mean age 25.1 years) with ppFEV₁ at screening between 40-90 [mean ppFEV₁ 60.7 at baseline (range: 31.1 to 94.0)] while TRANSPORT evaluated 559 patients aged 12 years and older (mean age 25.0 years) with ppFEV₁ at screening between 40-90 [mean ppFEV₁ 60.5 at baseline (range: 31.3 to 99.8)].

Patients in both trials were randomized 1:1:1 to receive either lumacaftor/ivacaftor (lumacaftor 400 mg q12h/ivacaftor 250 mg q12h; or lumacaftor 600 mg once daily/ivacaftor 250 mg q12h) or placebo. Patients took the study drug with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline). 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 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 (assessed as the average of the treatment effects at Week 16 and at Week 24) was 2.6%
[95% CI (1.2, 4.0)] in TRAFFIC (P=0.0003) and 3.0% [95% CI (1.6, 4.4)] in TRANSPORT
(P<0.0001). These changes persisted throughout the 24-week treatment period (Figure 1).
Improvements in ppFEV1 were observed regardless of age, disease severity, sex, and geographic
region.

Absolute change in BMI at week 24 was not significant in TRAFFIC; it was statistically significant
in TRANSPORT [0.36 (95% CI 0.17 to 0.54; p<0.001)]. Absolute change in CFQ-R Respiratory
Score at Week 24 was not statistically significant in TRAFFIC or TRANSPORT.
As a secondary endpoint, the number of pulmonary exacerbations significantly decreased with
LUM/IVA in both TRAFFIC [Rate ratio (RR): 0.66 (95% CI 0.47 to 0.93); p=0.02] and
TRANSPORT [RR: 0.57 (0.42, 0.76); p<0.001].

Safety\textsuperscript{1,4}
There are no contraindications to therapy with ivacaftor or the combination of lumacaftor with
ivacaftor.

<table>
<thead>
<tr>
<th>REVISIONS</th>
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<tbody>
<tr>
<td><strong>09-01-2012</strong></td>
<td>Policy added to the bcbsks.com web site.</td>
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<tr>
<td><strong>03-01-2013</strong></td>
<td>Title revised from, “Kalydeco™ (ivacaftor) Prior Authorization (with Quantity Limit) Program Summary” to, “Kalydeco™ (ivacaftor)”.</td>
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<td><strong>03-01-2013</strong></td>
<td>Updated Description section</td>
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<tr>
<td><strong>03-01-2013</strong></td>
<td>In policy section:</td>
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<tr>
<td><strong>03-01-2013</strong></td>
<td>- In A 2 added the criteria of, “b. The patient is not homozygous for the F508del mutation”</td>
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<td><strong>03-01-2013</strong></td>
<td>- Added Renewal Evaluation criteria of,</td>
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<tr>
<td><strong>03-01-2013</strong></td>
<td>“B. Renewal Evaluation”</td>
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<td>Kalydeco will be approved when BOTH of the following are met:</td>
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<td>1. The patient has been approved previously for ivacaftor through the Prime Therapeutics PA process AND</td>
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<tr>
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<td>2. The patient has shown improvement in FEV\textsubscript{1} AND</td>
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<tr>
<td><strong>03-01-2013</strong></td>
<td>3. ONE of the following:</td>
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<td>a. The quantity requested is less than or equal to the program quantity limit (2 tablets) OR</td>
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<tr>
<td><strong>03-01-2013</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>03-01-2013</strong></td>
<td>Length of Approval: 12 months”</td>
</tr>
<tr>
<td><strong>03-01-2013</strong></td>
<td>Updated Rationale section</td>
</tr>
<tr>
<td><strong>08-12-2014</strong></td>
<td>In Title section:</td>
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<tr>
<td><strong>08-12-2014</strong></td>
<td>- Added &quot;Prime Therapeutics will review Prior Authorization requests.&quot;</td>
</tr>
<tr>
<td><strong>08-12-2014</strong></td>
<td>Description section updated</td>
</tr>
<tr>
<td><strong>08-12-2014</strong></td>
<td>In Policy section:</td>
</tr>
</tbody>
</table>
REVISIONS

- 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 FEV1 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:
  "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 FEV1 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


Added Orkambi™ (lumacaftor/ivacaftor) to the policy.

In Title added Orkambi™ (lumacaftor/ivacaftor) revising Title from Kalydeco™ (ivacaftor)
## REVISIONS

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 FEV1 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”
- 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 FEV1 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


**In Policy section**

- Added a CFTR gene mutations chart for reference. No changes to the intent of the policy were made by this addition.

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### REFERENCES

3. Deleted.