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

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO041

Description
Ivacaftor (Kalydeco) is an orally administered cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Ivacaftor/lumacaftor (Orkambi) combines the potentiating mechanism of ivacaftor with lumacaftor which improves the conformational stability of F508del-CFTR. Ivacaftor/tezacaftor (Symdeko) combines ivacaftor with tezacaftor, which is a CFTR modulator that acts as a CFTR corrector.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>ivacaftor (Kalydeco)</td>
<td>150 mg tablet</td>
<td>Cystic fibrosis, one mutation in the CFTR gene that is responsive to ivacaftor</td>
<td>60 tablets/30 days</td>
<td>171513, 171534</td>
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<tr>
<td></td>
<td>25 mg/packet oral granule</td>
<td></td>
<td>56 packets/28 days</td>
<td>206530, 206531</td>
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<tr>
<td></td>
<td>50 mg/packet oral granule</td>
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<td>56 packets/28 days</td>
<td>187743, 187761</td>
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<tr>
<td></td>
<td>75 mg/packet oral granule</td>
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<td>56 packets/28 days</td>
<td>187744, 187762</td>
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<tr>
<td>ivacaftor/lumacaftor (Orkambi)</td>
<td>125/200 mg tablet</td>
<td>Cystic fibrosis, homozygous for F508del mutation</td>
<td>120 tablets/30 days</td>
<td>189035, 189040</td>
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<tr>
<td></td>
<td>125/100 mg tablet</td>
<td></td>
<td>120 tablets/30 days</td>
<td>195012, 195013</td>
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<tr>
<td></td>
<td>125/100 mg oral granule packet</td>
<td></td>
<td>56 packets/28 days</td>
<td>203730, 203758</td>
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<tr>
<td></td>
<td>188/150 mg oral granule packet</td>
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<td>56 packets/28 days</td>
<td>203731, 203756</td>
</tr>
<tr>
<td>ivacaftor/tezacaftor (Symdeko)</td>
<td>Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg</td>
<td>Cystic fibrosis, 508del mutation or at least one</td>
<td>56 tablets/28 days</td>
<td>201686, 201699</td>
</tr>
</tbody>
</table>
**ivacaftor (Kalydeco®); lumacaftor/ivacaftor (Orkambi™); tezacaftor/ivacaftor (Symdeko™)**

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<table>
<thead>
<tr>
<th>Kit: (ivacaftor; lumacaftor/tezacaftor)</th>
<th>mutation in the CFTR gene(^a) that is responsive to ivacaftor/tezacaftor(^b)</th>
<th>56 tablets/28 days</th>
<th>TBD</th>
</tr>
</thead>
</table>

\(^a\) Specific mutations listed below in policy criteria

\(^b\) Based on clinical and/or in vitro assay data

**Initial Evaluation**

I. Agents listed in this policy may be considered medically necessary when the following criteria below are met:

A. The medication is prescribed by or in consultation with a specialist (e.g., pulmonologist); **AND**

B. The medication is not used in combination with other agents in this policy (i.e., use of only one of the following at a given time: Kalydeco, Orkambi, Symdeko) (please note if a previous approval has been granted for one of these agents, and criteria is met for another, the previous PA approval will be discontinued); **AND**

C. A diagnosis of **cystic fibrosis** when the following are met:

1. For ivacaftor (Kalydeco):
   i. The member is six months of age or older; **AND**

2. For ivacaftor/lumacaftor (Orkambi):
   i. The member is two years of age or older; **AND**
   ii. The member has homozygous (two copies) for the F508del mutation in the CFTR gene; **OR**

3. For ivacaftor/tezacaftor (Symdeko):
   i. The member is six years of age or older; **AND**
   ii. The member has one of the following:
      a. Homozygous (two copies) for the F508del CFTR gene (please note one copy of F508del in the absence of a responsive mutation listed below does not meet criteria); **OR**
ivacaftor (Kalydeco®); lumacaftor/ivacaftor (Orkambi™); tezacaftor/ivacaftor (Symdeko™)

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II. Medications listed in this policy are considered investigational when used for all other conditions, including but not limited to:
   A. Cystic fibrosis outside of the specific mutations listed above for each medication.
   B. Cystic fibrosis outside of ages listed above for each medication
   C. Chronic obstructive pulmonary disease and/or asthma
   D. Hyperglycemia or diabetes mellitus
   E. Premature termination codon mutations

Renewal Evaluation

I. Clinical documentation of response to therapy as indicated by disease stability or improvement (e.g., improvement in FEV1, decrease in pulmonary exacerbations, decrease in rate of hospitalizations, increased weight).

Supporting Evidence

I. Cystic fibrosis is an autosomal recessive disease that manifests primarily with pulmonary complications; however, may affect several other organ systems. Treatment and management of cystic fibrosis is complex and requires a myriad of treatment modalities. A specialist should direct, or at least be consulted, at every stage of the member’s care.

II. The use of the CFTR agents have not been studied in combination with other CFTR modulators, and due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.

III. Ivacaftor (Kalydeco) has been evaluated in several clinical trials. Two trials evaluated ivacaftor (Kalydeco) in patients with G551D mutation in the CFTR gene. The primary outcome in both studies was absolute change from baseline in percent predicted pre-dose FEV1 through 24 weeks of treatment. Trial one evaluated patients 12 years of age and older (10.6%; P<0.0001), and Trial 2 evaluated patients six to 11 years of age (12.5%; p<0.0001). Additional outcomes included change in body weight, change in sweat chloride, and relative risk of pulmonary exacerbation; all of which were statistically significant.

IV. Efficacy and safety of ivacaftor (Kalydeco) was also evaluated in patients with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, and S549R mutations. Outcomes included absolute change in pre-dose percent predicted FEV1, change in body weight, and CFQ-R Respiratory Domain Score; all of which had statistically significant outcomes; although, there was much variability among the responses per mutation type.

V. Efficacy and safety of ivacaftor (Kalydeco) was evaluated in patients with R117H mutation which showed a statistically significant change from baseline in FEV1 and CFQ-R score.

In April 2019, the FDA approved ivacaftor (Kalydeco) as the first CFTR modulator to treat eligible infants from six months of age. This was supported by data from the phase 3 ARRIVAL study. This was based on 11 patients with cystic fibrosis.

The efficacy and safety of ivacaftor/lumacaftor (Orkambi) was evaluated in patient homozygous for the F508del mutation in the CFTR gene. Two trials evaluated patients 12 years of age or older. Primary efficacy endpoint was change from baseline in FEV1 and the results were statistically significant in both trials. Secondary endpoints included body weight, CFQ-R Respiratory Domain score, and number of pulmonary exacerbations through week 24; however, with hierarchical testing, none of these were statistically significant.

Ivacaftor/tezacaftor (Symdeko) has been evaluated in several trials.

- Trial 1 evaluated ivacaftor/tezacaftor (Symdeko) against placebo in patients 12 years of age and older that were homozygous for F508del. The primary endpoint of change in FEV1 (4% vs 0% [3.1-4.8]; p<0.0001). Notable secondary outcomes included number of pulmonary exacerbations from baseline, absolute change in BMI from baseline, change in CFQ-R Respiratory Domain Score from baseline. Change in number of pulmonary exacerbations was significantly reduced (0.65 [0.48-0.88]; p<0.0054).

- Trial 2 evaluated patients heterozygous for F508del and a second mutation predicted to be responsive to tezacaftor/ivacaftor (Symdeko). Outcomes evaluated were similar to Trial 1. The change in FEV1 was 6.8 percentage point (CI 5.7-7.8; p<0.0001), change in CF-R Reparatory Domain Score was 11.1 points (CI 8.7-13.6); p<0.0001).

- Trial 3 evaluated patients who were heterozygous for F508del mutation and a second mutation not predicted to be responsive to tezacaftor/ivacaftor (Symdeko). The primary efficacy endpoint, change in FEV1 compared to baseline, was 1.2 percentage points (CI -0.3-2.6), and was not significant. The study was terminated early.

- The efficacy of ivacaftor/tezacaftor (Symdeko) for patients age six to 12 years was supported by data from a 24-week, open-label treatment period of 70 patients. Observations of safety were noted to be similar to that of the data available for age 12 years and above.

Investigational or Not Medically Necessary Uses

I. The aforementioned indications listed as experimental and investigational are currently being evaluated in clinical trials and/or have not yet shown efficacy and safety in moderate or high quality clinical trials.
References

10. A study to evaluate the safety, pharmacokinetics, and pharmacodynamics of Ivacaftor in subjects with cystic fibrosis who are less than 24 months of age and have a CFTR gating mutation. 2017. ClinicalTrials.gov (Identifier NCT02725567).

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>February 2012</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>June 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>June 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>04/2014, 05/2018, 09/2018, 06/2019</td>
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</tbody>
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Action and Summary of Changes

| Criteria combined, transitioned to policy format for all medications. Added new indication for Kalydeco for ages 6 months and older. Symdeko now approved down to six years of age. | 06/2019 |
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<table>
<thead>
<tr>
<th>Criteria update</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>New indication for Orkambi, approved in CF patients two years of age and older. New approval in CF for patients between the ages of 12 and 24 months for Kalydeco, previously approved only for 24 months and older. Criteria added to not allow concomitant use.</td>
<td>09/2018</td>
</tr>
<tr>
<td>Updated criterias to new format, removed question assessing liver enzymes levels, added references, added question regarding combination therapy with other CFTR modulating medications. Symdeko criteria created.</td>
<td>05/2018</td>
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<tr>
<td>Criteria update: Excluded samples and updated renewal language to general improvement.</td>
<td>01/2016</td>
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