This drug requires a written request for prior authorization. All requests for Orkambi (lumacaftor/ivacaftor) require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

1. Does the patient have a diagnosis of cystic fibrosis (CF) and meets all the following criteria?
   - Patient is homozygous for the F508del-CFTR mutation (as documented by copy of lab report)
   - Age 12 years and older
   - Prescribed by or in consultation with a pulmonologist or CF expert
   - Stable disease as defined by previous or current treatment with another agent used in the treatment of CF (examples include oral inhaled corticosteroid, bronchodilator, inhaled antibiotics, dornase alfa, or acetylcysteine)
   - Baseline FEV1 of at least 40% (as documented by lab report or chart notes)
   - Patient is not on concurrent therapy with Kalydeco
   - Patient is not currently pregnant

   If yes, **approve for 24 weeks with a quantity limit of #4 tablets per day.**
   If no, do not approve.

INITIAL DENIAL TEXT: Our guideline for LUMACAFTOR/IVACAFTOR requires a diagnosis of cystic fibrosis. In addition, the following criteria must also be met:

   - Patient is homozygous for the F508del-CFTR mutation (as documented by copy of lab report)
   - Age 12 years and older
   - Prescribed by or in consultation with a pulmonologist or CF expert
   - Stable disease as defined by previous or current treatment with another agent used in the treatment of CF (examples include oral inhaled corticosteroid, bronchodilator, inhaled antibiotics, dornase alfa, or acetylcysteine)
   - Baseline FEV1 of at least 40% (as documented by lab report or chart notes)
   - Patient is not on concurrent therapy with Kalydeco
   - Patient is not currently pregnant

CONTINUED ON NEXT PAGE
LUMACAFTOR/IVACAFTOR

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

1. Does the patient have a diagnosis of cystic fibrosis (CF) and meets all the following criteria?
   - Improvement in CF as indicated by ONE of the following: maintained or improvement in FEV1 or BMI, OR reductions in pulmonary exacerbations (documentation must be provided)
   - Patient is not currently pregnant

   If yes, approve for 12 months with a quantity limit of #4 tablets per day.
   If no, do not approve.

RENEWAL DENIAL TEXT: Our guideline for LUMACAFTOR/IVACAFTOR renewal requires a diagnosis of cystic fibrosis. In addition, the following criteria must also be met:
   - Improvement in CF as indicated by ONE of the following: maintained or improvement in FEV1 or BMI, OR reductions in pulmonary exacerbations (documentation must be provided)
   - Patient is not currently pregnant

RATIONALE
Promote appropriate utilization of Orkambi based on FDA approved indication.

CF is an inherited chronic disease that affects about 30,000 patients in the US. A defective cystic fibrosis transmembrane conductance regulator (CFTR) protein leads to production of unusually thick, sticky mucus that clogs the lungs and prevents the body from breaking down and absorbing food. About 47% of CF patients are homozygous for the F508 del-CFTR gene. There is no cure for this disease however current treatments that offer symptomatic relief include Cayston, Pulmozyme, Bethkis, Tobi, Tobi Podhaler, and Kitabis Pak.

Orkambi treats patients who are homozygous for the F508 del mutation. This is the most common CF-causing mutation and 46.5% of the US population is homozygous for it. This mutation, classified as a “processing” mutation is a deletion of three nucleotides that comprise the codon for phenylalanine at position 508. A person with F508 del CFTR mutation will produce a truncated F508 del-CFTR that does not fold correctly, and the majority of it is degraded in the endoplasmic reticulum. A small amount of F508del-CFTR reaches the cell surface with a reduced function, leading to a more severe disease phenotype.

CONTINUED ON NEXT PAGE
LUMACAFTOR/IVACAFTOR

RATIONALE (CONTINUED)
Lumacaftor and ivacaftor have complementary mechanisms of action. IVA is a CFTR potentiator that increases the channel-open probability of CFTR protein at the cell surface. IVA increases the gating or proportion of time the channel is open. LUM is a CFTR corrector that improves the processing and trafficking of the F508del-CFTR protein. This results in an increase in the quantity of F508del-CFTR protein at the cell surface. IVA enhances cell transport by increasing the channel open probability of the F508del-CFTR protein delivered to the cell surface by LUM. In the absence of LUM, there is very little F508del-CFTR protein at the cell surface for IVA to potentiate. The combination of LUM and IVA results in an increased in quantity and improvement in function of F508del-CFTR at the cell surface.

Ivacaftor as a single agent is not indicated for the treatment of patients who are homozygous for the F580del-CFTR mutation.

FDA APPROVED INDICATIONS
ORKAMBI is a combination of lumacaftor and ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, indicated for the treatment of cystic fibrosis (CF) in patients age 12 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.

Limitations of Use:
The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation.

DOSEAGE
- Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours with fat containing food.
- Reduce dose in patients with moderate or severe hepatic impairment.
- When initiating ORKAMBI in patients taking strong CYP3A inhibitors, reduce ORKAMBI dose for the first week of treatment.

REFERENCES

<table>
<thead>
<tr>
<th>Library</th>
<th>Commercial</th>
<th>NSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Created: 07/15
Effective: 01/01/16
Client Approval: 11/15