Orkambi® (lumacaftor/ivacaftor)

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 2 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."[1]

Dosage Form/Strength:

Tablet: lumacaftor 200 mg and ivacaftor 125 mg
Tablet: lumacaftor 100 mg and ivacaftor 125 mg
Granule: lumacaftor 100 mg and ivacaftor 125 mg per packet
Granule: lumacaftor 150 mg and ivacaftor 188 mg per packet

Criteria for Approval: [1]

- Diagnosis of Cystic Fibrosis, accompanied with results from a positive sweat test; **AND**,
- The patient is homozygous for the F508del mutation in the CFTR gene from a FDA-cleared CF mutation test; **OR**,
    - If lab results from the patient's CF mutation test are not available, provide documentation relating to how the prescriber knows that the patient has the F580del mutation; **AND**,
- The patient is greater than or equal to 2 years of age; **AND**,
- Orkambi is not being used concomitantly with a strong CYP3A inducer
    OR
    - If being used concomitantly with a strong CYP3A inducer, there has been dosage adjustment of the inducer to minimize the effect of the interaction; **AND**,
- Orkambi is not being used concomitantly with a sensitive CYP3A substrate, or a CYP3A substrate with a narrow therapeutic index
    OR
    - If being used with a sensitive CYP3A substrate, or a CYP3A substrate with a narrow therapeutic index, there has been a dosage adjustment or discontinuation the interacting medication to minimize the clinical effect of the interaction.

Criteria for Denial:

- Patient does not have a confirmed diagnosis of Cystic Fibrosis; **OR**,
- The patient is less than 2 years of age; **OR**,
- The patient has an unknown F580del mutation status, or is not homozygous for the F508del mutation; **OR**,

- Orkambi is being co-administered with a strong CYP3A inducer, or a sensitive CYP3A substrate, or a CYP3A substrate with a narrow therapeutic index, without adjusting therapy to compensate for the drug/drug interaction.

Criteria for Reauthorization Approval- After 3 Months of Treatment:

- The patient meets all of the criteria for the initial authorization; **AND**,
- There is no evidence of Orkambi causing detriment or harm to the patient.

Criteria for Reauthorization Approval- After 9 Months of Treatment:

- The patient meets all of the criteria for the initial authorization; **AND**,
- There is no evidence of Orkambi causing detriment or harm to the patient; **AND**,
- The patient has experienced one of the following: a slowed rate of clinical decline or disease progression, clinical stabilization, or clinical improvement
    - Documentation must be submitted.

Length of Authorization:

- Initial coverage may be approved for 3 months.
- For re-authorization at treatment month 3:
    - Prescriber must follow-up with the patient (via phone call, email, or office visit) to determine if the medication has been detrimental or harmful to the patient.
    - Treatment month 3 authorizations may then be approved for 6 more months.
- For re-authorization at treatment month 9 (after the initial 3 month approval and the subsequent 6 month approval):
    - Documentation must be submitted showing clinical improvement or lack of disease progression (i.e. disease symptoms have improved, stabilized, or the rate of decline/disease progression have slowed).
    - Documentation must also be submitted showing that the medication is not detrimental to, or harming the patient.
    - Treatment month 9 authorizations may be then approved for 1 year.

Quantity Limit:

- Maximum 4 tablets per day : 100mg/125mg and 200mg/125mg
- Maximum 2 packets per day : 100mg/125mg and 150mg/188mg

Mechanism of Action:

"The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The F508del mutation results in protein misfolding, causing a defect in cellular processing and trafficking that targets the protein for degradation and therefore reduces the quantity of CFTR at the cell surface. The small amount of F508del-CFTR that reaches the cell surface is less stable and has low channel-open probability (defective gating activity) compared to wild-type CFTR protein.

Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased

chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. In vitro studies have demonstrated that both lumacaftor and ivacaftor act directly on the CFTR protein in primary human bronchial epithelial cultures and other cell lines harboring the F508del-CFTR mutation to increase the quantity, stability, and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. In vitro responses do not necessarily correspond to in vivo pharmacodynamic response or clinical benefit." [1]

References / Footnotes:

[1] Orkambi® package insert. Vertex Pharmaceuticals, Inc. Boston, MA. 2018. http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf Accessed 3/5/2019.