ORKAMBI
(lumacaftor / ivacaftor)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background
Orkambi (lumacaftor/ivacaftor) is used for the treatment of cystic fibrosis (CF) in patients who have two copies of the F508del mutation in their CFTR gene. Having two copies of this mutation (one inherited from each parent) is the leading cause of CF. Orkambi is a transmembrane conductance regulator (CFTR) potentiator which causes the production of an abnormal protein that disrupts how water and chloride are transported in the body (1-2).

CF is a serious genetic disorder that results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body leading to severe respiratory and digestive problems, as well as other complications such as infections and diabetes (1).

Regulatory Status
FDA-approved indication: 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 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 (1).

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. Orkambi should not be used in patients other than those who have two copies of the F508del mutation in their CFTR gene (1).

Orkambi may cause worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease and should be used with caution and only if the benefits are expected to outweigh the risks. If Orkambi is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced. A dose reduction to 2 tablets in the morning and 1 tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) is recommended for patients with moderate hepatic impairment (Child-Pugh Class B). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg/ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after
weighing the risks and benefits of treatment (1).

Transaminases (ALT or AST) should be assessed prior to initiating Orkambi, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (1).

Based on the clinical studies that were done for Orkambi patients who meet any of the following exclusion criteria were not eligible to for the study. Any of the following abnormal laboratory values at screening: (1)

1. Hemoglobin <10 g/dL
2. Abnormal liver function defined as any 3 or more of the following: ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST), ≥3 × ULN alanine aminotransferase (ALT), ≥3 × ULN gamma-glutamyl transpeptidase (GGT), ≥3 × ULN alkaline phosphatase
3. Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m².
4. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*).
   a. The subject should have had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures
   b. These 2 respiratory tract cultures should have been separated by at least 3 months.
   c. One of these 2 respiratory tract cultures should have been obtained within the past 6 months

The safety and efficacy of Orkambi in patients with CF younger than 6 years of age have not been studied (1).

**Summary**

Orkambi is a potentiator of the CFTR protein and is effective only in cystic fibrosis patients who are homozygous for the *F508del* mutation in the *CFTR* gene. Cystic fibrosis is caused by mutations in a gene that encodes for a protein called cystic fibrosis transmembrane regulator (CFTR) which regulates chloride and water transport in the body. The defect results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body. Orkambi is not effective in patients who are not homozygous for the *F508del* mutation in the CFTR gene. Orkambi is indicated for patients 6 years of age and older (1-2).
Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Orkambi while maintaining optimal therapeutic outcomes.

References