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 F*508del* mutation in their cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is a progressive disease 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. 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 (1-2).

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 aged 1 year 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).

<u>Limitations of Use</u>:

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 (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).

Respiratory events may be observed in patients during initiation of Orkambi. These events can be serious, particularly in patients with advanced lung disease. Clinical experience in patients with $ppFEV_1$<40 is limited, and additional monitoring of these patients is recommended during initiation of therapy (1).

Based on the clinical studies that were done for Orkambi, patients who had 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 (AP) or total bilirubin ≥2 × ULN) were not eligible for the study (1).

For newly diagnosed older adults, other cystic fibrosis options for *F508del* mutation should be considered due to the increased drug interactions, increases in blood pressure, and the risk of hepatic encephalopathy with Orkambi (1).

Orkambi has not studied in patients with mild, moderate, or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using Orkambi in patients with severe renal impairment (creatinine clearance ≤30 mL/min) or end-stage renal disease (1).

The safety and efficacy of Orkambi in patients less than 1 year of age have not been established (1).

Summary

Cystic fibrosis (CF) 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 (lumacaftor/ivacaftor) is a potentiator of the CFTR protein and is

effective only in CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene. Orkambi is not effective in patients who are not homozygous for the *F508del* mutation in the CFTR gene. Orkambi is indicated for patients 1 year 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

1. Orkambi [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2023.
2. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015; 373:220-23. DOI: 10.1056/NEJMoa1409547.