Clinical Policy: Lumacaftor-Ivacaftor (Orkambi)

Reference Number: PA.CP.PHAR.213
Effective Date: 01/2018
Last Review Date: 07/2024

Description
Lumacaftor/ivacaftor (Orkambi®) is a combination drug for cystic fibrosis (CF). Lumacaftor improves the conformational stability of F508del-cystic fibrosis transmembrane conductance regulator (CFTR), while ivacaftor is a CFTR potentiator.

FDA Approved Indication(s)
Orkambi is indicated for the treatment of 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.

Limitation(s) of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the F508del mutation.

Policy/Criteria
It is the policy of PA Health & Wellness that Orkambi is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cystic Fibrosis (must meet all)**:**

1. Diagnosis of cystic fibrosis (CF);
2. Confirmation the member is homozygous for the *F508del* mutation in the *CFTR* gene;
3. Age ≥ 1 year;
4. Prescribed by or in consultation with a pulmonologist or cystic fibrosis specialist;
5. Documentation indicates member has baseline forced expiratory volume in 1 second (FEV1), unless member is unable to perform spirometry testing;
6. Orkambi is not prescribed concurrently with other ivacaftor-containing CFTR modulator combination products (e.g., Kalydeco, Symdeko, Trikafta);
7. Dose does not exceed one of the following (a, b, c, or d):
   a. Age 1 to 2 years, and one of the following (i, ii, or iii):
      i. Weight 7 kg to < 9 kg (both 1 and 2):
         1. Lumacaftor 150 mg/ivacaftor 188 mg per day;
         2. 2 packets per day;
      ii. Weight 9 kg to < 14 kg (both 1 and 2):
         1) Lumacaftor 200 mg/ivacaftor 250 mg per day;
         2) 2 packets per day;
      iii. Weight ≥ 14 kg (both 1 and 2):
         1) Lumacaftor 300 mg/ivacaftor 376 mg per day;
         2) 2 packets per day;
   b. Age 2 to 5 years, and one of the following (i or ii):

i. Weight < 14 kg (both 1 and 2):
1. Lumacaftor 200 mg/ivacaftor 250 mg per day;
2. 2 packets per day;

ii. Weight ≥ 14 kg (both 1 and 2):
1) Lumacaftor 300 mg/ivacaftor 376 mg per day;
2) 2 packets per day;

c. Age 6 to 11 years (both i and ii):
i. Lumacaftor 400 mg/ivacaftor 500 mg per day;
ii. 4 tablets per day;

d. Age ≥ 12 years (both i and ii):
i. Lumacaftor 800 mg/ivacaftor 500 mg per day;
ii. 4 tablets per day.

Approval duration: 6 months

B. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. Cystic Fibrosis (must meet all)**:**

1. Currently, receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy OR the member continues to benefit from therapy based on the prescriber's assessment;
3. Orkambi is not prescribed concurrently with other ivacaftor-containing CFTR modulator combination products (e.g., Kalydeco, Symdeko, Trikafta);
4. If request is for a dose increase, new dose does not exceed one of the following (a, b, c, or d):
   a. Age 1 to 2 years, and one of the following (i, ii, or iii):
      i. Weight 7 kg to < 9 kg (both 1 and 2):
         1. Lumacaftor 150 mg/ivacaftor 188 mg per day;
         2. 2 packets per day;
      ii. Weight 9 kg to < 14 kg (both 1 and 2):
         1. Lumacaftor 200 mg/ivacaftor 250 mg per day;
         2. 2 packets per day;
      iii. Weight ≥ 14 kg (both 1 and 2):
         1. Lumacaftor 300 mg/ivacaftor 376 mg per day;
         2. 2 packets per day;
   b. Age 2 to 5 years, and one of the following (i or ii):
      i. Weight < 14 kg (both 1 and 2):
         1. Lumacaftor 200 mg/ivacaftor 250 mg per day;
         2. 2 packets per day;
      ii. Weight ≥ 14 kg (both 1 and 2):
         1. Lumacaftor 300 mg/ivacaftor 376 mg
         2. 2 packets per day;
   c. Age 6 to 11 years (both i and ii):
      i. Lumacaftor 400 mg/ivacaftor 500 mg per day;

ii. 4 tablets per day;

d. Age ≥ 12 years (both i and ii):
   i. Lumacaftor 800 mg/ivacaftor 500 mg;
   ii. 4 tablets per day.

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2)**:**

1. Currently, receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACFLD: advanced cystic fibrosis lung disease
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
FDA: Food and Drug Administration
LCI: lung clearance index
MBW: multiple-breath washout
ppFEV1: percent predicted forced expiratory volume in 1 second

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- The Cystic Fibrosis Foundation (CFF) Mutation Analysis Program (MAP) available here: https://www.cff.org/medical-professionals/mutation-analysis-program. The MAP is a free and confidential genetic testing program for people with a strongly suspected or confirmed diagnosis of CF.
- Regarding the diagnostic criteria for CF of "genetic testing confirming the presence of two disease-causing mutations in CFTR gene," this is to ensure that whether heterozygous or homozygous, there are two disease-causing mutations in the CFTR gene, one from each parental allele.
- Most children can do spirometry by age 6, though some preschoolers are able to perform the test at a younger age. Some young children aren't able to take a deep enough breath and blow out hard and long enough for spirometry. Forced oscillometry is another way to test lung function in young children. This test measures how easily air flows in the lungs (resistance and compliance) with the use of a machine.
- The two most commonly reported parameters from multiple-breath washout (MBW) tests are the lung clearance index (LCI) and moment ratios (MRs). Measurements of LCI and MR are taken during the washout period. During the washout phase, subjects inhale gases that do not contain the test gas of interest. The principles of the washout are the same

regardless of the test gas measured. The washout is stopped once the test gas reaches 1/40 of the initial gas concentration
- The LCI is feasible to perform and is a more sensitive outcome measure than ppFEV1.
- NHS Clinical Guidelines: Care of Children with Cystic Fibrosis: Normal ranges for LCI are device specific and still being established, but in general a value > 8.0 is above the normal range and > 10.0 is significantly abnormal.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CF	Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) PO Q12H Pediatric patients age 6 through 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) PO Q12H Pediatric patients age 2 through 5 years and weighing < 14 kg: one packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) PO Q12H Pediatric patients age 2 through 5 years and weighing ≥ 14 kg: one packet of granules (each containing lumacaftor 150 mg/ivacaftor 188 mg) PO Q12H Pediatric patients age 1 through 2 years and weighing 7 kg to < 9 kg: one packet of granules (each containing lumacaftor 75 mg/ivacaftor 94 mg) PO Q12H Pediatric patients age 1 through 2 years and weighing 9 kg to < 14 kg: one packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) PO Q12H Pediatric patients age 1 through 2 years and weighing ≥ 14 kg: one packet of granules (each containing 150 mg/ivacaftor 188 mg) PO Q12H	Adults and pediatric patients age 12 years and older: lumacaftor 800 mg/ivacaftor 500 mg per day Pediatric patients age 6 through 11 years: lumacaftor 400 mg/ivacaftor 500 mg per day Pediatric patients age 2 through 5: <14 kg - lumacaftor 200 mg/ivacaftor 250 mg per day ≥ 14 kg - lumacaftor 300 mg/ivacaftor 376 mg per day Pediatric patients age 1 through 2: 7 kg to < 9 kg: lumacaftor 150 mg/ivacaftor 188 mg per day 9 kg to < 14 kg: lumacaftor 200 mg/ivacaftor 250 mg per day ≥ 14 kg: lumacaftor 300 mg/ivacaftor 376 mg per day

V. Product Availability

- Tablets: lumacaftor 100 mg and ivacaftor 125 mg, lumacaftor 200 mg and ivacaftor 125 mg

- Oral granule packets (56 packets per carton): lumacaftor 75 mg and ivacaftor 94 mg; lumacaftor 100 mg and ivacaftor 125 mg, lumacaftor 150 mg and ivacaftor 188 mg

VI. References

1. Orkambi Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; August 2023. Available at https://www.orkambihcp.com/. Accessed May 4, 2024.
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3. Farrell PM, White TB, Ren CL et al. Diagnosis of cystic fibrosis: Consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017; 181S: S4-15.
4. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation pulmonary guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018; 15(3): 271-280.
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6. Alexander S, Alshafi K, Al-Yaghchi C, et al. Clinical Guidelines: Care of Children with Cystic Fibrosis. Royal Brompton and Harefield NHS. 2020;(8):22-23.
7. Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros. 2020 May;19(3):344-354.
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9. Cystic Fibrosis Foundation: Clinical Care Guidelines. Available at: https://www.cff.org/medical-professionals/clinical-care-guidelines. Accessed May 17, 2024.
10. Perrem L, Rayment JH, Ratjen F. The lung clearance index as a monitoring tool in cystic fibrosis: ready for the clinic? Curr Opin Pulm Med. 2018 Nov;24(6):579-585. doi: 10.1097/MCP.0000000000000515. PMID: 30095491.

Reviews, Revisions, and Approvals	Date
References reviewed and updated.	02/2018
1Q 2019 annual review: updated age limit with corresponding dosing for pediatric patients down to 2 years of age per updated prescribing information; references reviewed and updated.	01/2019
1Q 2020 annual review: added the following criteria to initial approval: prescriber requirement of pulmonologist or cystic fibrosis specialist, requirement for baseline FEV1 unless unable to perform spirometry, requirement that Orkambi not be prescribed concurrently with other ivacaftor-containing CFTR modulator combination products; added the following to continued therapy criteria: not prescribed concurrently with other CFTR modulators; references reviewed and updated.	01/2020
1Q 2021 annual review: references reviewed and updated.	01/2021
1Q 2022 annual review: references reviewed and updated.	01/2022

Reviews, Revisions, and Approvals	Date
1Q 2023 annual review: updated FDA approved indication, criteria, and dosing per FDA approved pediatric extension for ages 1 through < 2 years; added new lumacaftor 75 mg and ivacaftor 94 mg oral granule packet strength; updated Appendix D; updated template wording for continued therapy and other diagnoses/indication sections; references reviewed and updated.	01/2023
3Q 2023 annual review: no significant changes; references reviewed and updated.	07/2023
3Q 2024 annual review: no significant changes; updated Appendix D; references reviewed and updated.	07/2024