Clinical Policy: Lumacaftor/Ivacaftor (Orkambi)

Reference Number: CP.PHAR.213
Effective Date: 05.01.16
Last Review Date: 02.24
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Orkambi is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of CF confirmed by all of the following (a, b, and c):
   a. Clinical symptoms consistent with CF in at least one organ system, or positive newborn screen or genetic testing for siblings of patients with CF;
   b. Evidence of CFTR dysfunction confirmed by one of the following (i or ii) (*see Appendix D*):
      i. Elevated sweat chloride ≥ 60 mmol/L;
      ii. Genetic testing confirming the presence of two disease-causing mutations in CFTR gene, one from each parental allele;
   c. Confirmation that member is homozygous for the *F508del* mutation in the CFTR gene;
2. Age ≥ 1 year;
3. Prescribed by or in consultation with a pulmonologist;

4. Documentation of one of the following pulmonary function tests performed within the last 90 days (a or b, see *Appendix D*):
   a. Member's baseline percent predicted forced expiratory volume in 1 second (ppFEV1) that is between 40-90%;
   b. For age < 6 years: Lung clearance index (LCI) that is ≥ 7.4;
5. Orkambi is not prescribed concurrently with other CFTR modulators (e.g., Kalydeco®, Symdeko®, Trikafta™);
6. 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 (must meet 1 or 2):
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
2. Member is responding positively to therapy as evidenced by one of the following (a or b, see *Appendix D*):
   a. Stabilization or improvement in ppFEV1;
   b. For age < 6 years: Stabilization or decrease in LCI from baseline;
3. Orkambi is not prescribed concurrently with other CFTR modulators (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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. 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
- 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.
- The expanded approval to treat patients 12 months to < 24 months of age is based on a phase 3, open-label, multicenter study that evaluated the pharmacokinetics, safety, and tolerability of Orkambi in 46 children between 1 and 2 years of age with two copies of the F508del mutation genotype. Orkambi was shown to be well tolerated and the safety profile and pharmacokinetics were similar to those observed in other patients.

V. 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	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

Indication	Dosing Regimen	Maximum Dose
	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	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

VI. 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

VII. References

1. Orkambi Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; February 2023. Available at: https://www.orkambihcp.com/. Accessed May 4, 2023.
2. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013; 187(7): 680-689.
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.
5. Davies J, Sheridan P, Lee P, et al. Effect of ivacaftor on lung function in subjects with CF who have the G551D-CFTR mutation and mild lung disease: a comparison of lung clearance index (LCI) vs. spirometry. Journal of Cystic Fibrosis. 2012;11(1):S15.
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.
8. ClinicalTrials.gov. Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects 1 to Less than 2 years of Age with Cycstic Fibrosis, Homozygous for F508del. Available at: https://clinicaltrials.gov/ct2/show/NCT03601637. Accessed May 4, 2023.
9. Cystic Fibrosis Foundation: Clinical Care Guidelines. Available at: https://www.cff.org/medical-professionals/clinical-care-guidelines. Accessed May 4, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2020 annual review: added the following criteria to initial approval: comprehensive diagnostic criteria (e.g., clinical symptoms in at least one organ, positive newborn screen, siblings genetic testing, and evidence of CFTR dysfunction) to confirm diagnosis of CF, prescriber requirement of pulmonologist, chart notes indicate that pulmonary function tests (ppFEV1 between 40-90%), not prescribed concurrently with other CFTR modulators; added the following to continued therapy criteria: positive response as evidenced by stabilization in ppFEV1 in lieu of an increase is acceptable if baseline was ≥ 70%, not prescribed concurrently with other CFTR modulators; added Appendix D; changed approval durations of commercial from length of benefit to 6 months initial and 12 months continued; references reviewed and updated.	12.17.19	02.20
Revised initial approval criteria requiring chart notes for pulmonary function test: added "for age > 2 years" for ppFEV1; added alternative option for ppFEV1 for age < 6 years to allow for LCI ≥ 7.4; revised continuation criteria to include stabilization in LCI if baseline was ≥ 7.4; added information regarding LCI in Appendix D.	05.19.20	08.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.09.20	02.21
1Q 2022 annual review: added legacy Wellcare initial approval duration (WCG.CP.PHAR.213 to be retired); references reviewed and updated.	10.22.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
1Q 2023 annual review: RT4: 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; consolidated Legacy Wellcare initial approval duration from 12 months to 6 months consistent with standard Medicaid initial approval duration; updated Appendix D; references reviewed and updated.	10.07.22	02.23
3Q 2023 annual review: no significant changes; references reviewed and updated.	05.04.23	08.23
Revised initial approval criteria: removed "for age 2 > years" and "ppFEV1 that is between 40 – 90%" in criteria stating documentation of member's ppFEV1; revised "chart notes that indicate pulmonary function tests" to "documentation of one of the following pulmonary function tests"; for continued therapy criteria: revised criteria from "stabilization in ppFEV1 if baseline was ≥ 70%, or increase in ppFEV1 if baseline was <70%" to "stabilization or improvement in ppFEV1" and revised "stabilization in LCI if baseline was ≥ 7.4" to	01.11.24	02.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
"stabilization or decrease in LCI from baseline"; revised Appendix D to remove information on advanced Cystic Fibrosis disease.		

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.