Clinical Policy Title:	lumacaftor/ivacaftor
Policy Number:	RxA.435
Drug(s) Applied:	Orkambi®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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. Orkambi® is indicated for the treatment of 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.
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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
lumacaftor/Ivacaftor (Orkambi®)	CF	Adults and pediatric patients age ≥ 12 years: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally every 12 hours Pediatric patients age 6 - 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) orally every 12 hours Pediatric patients age 2 - 5 years and weighing < 14 kg: one packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) orally every 12 hours Pediatric patients age 2 -5 years and weighing ≥ 14 kg: one packet	Adults and pediatric patients age ≥ 12 years: lumacaftor 800 mg/ivacaftor 500 mg per day Pediatric patients age 6 - 11 years: lumacaftor 400mg/ivacaftor 500 mg per day Pediatric patients age 2 -5: <14 kg - lumacaftor 200 mg/ivacaftor 250 mg per day ≥ 14 kg - lumacaftor 300 mg/ivacaftor 376 mg per day

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		of granules (each containing lumacaftor 150 mg/ivacaftor 188 mg) orally every 12 hours Hepatic Impairment: Reduce dose in patients with moderate or severe hepatic impairment. Initiating Orkambi® in patients taking strong CYP3A inhibitors, reduce Orkambi® dose for the first week of treatment.	

Dosage Forms

- Tablets: lumacaftor 100 mg and ivacaftor 125 mg, lumacaftor 200 mg and ivacaftor 125 mg.
- Oral granules: Unit-dose packets of lumacaftor 100 mg and ivacaftor 125 mg, lumacaftor 150 mg and ivacaftor 188 mg.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

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

1. Diagnosis of CF;
2. Age ≥ 2 years;
3. Member is homozygous for the F508del mutation in the CFTR gene;
4. Dose does not exceed one of the following (a, b, c, or d):
   a. Age 2 to 5 years weighing < 14 kg: lumacaftor 200 mg/ivacaftor 250 mg per day;
   b. Age 2 to 5 years weighing ≥ 14 kg: lumacaftor 300 mg/ivacaftor 376 mg per day;
   c. Age 6 to 11 years: lumacaftor 400 mg/ivacaftor 500 mg per day;
   d. Age ≥ 12 years: lumacaftor 800 mg/ivacaftor 500 mg per day.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed one of the following (a, b, c, or d):
   a. Age 2 to 5 years weighing < 14 kg: lumacaftor 200 mg/ivacaftor 250 mg per day (2 packets per

day);
b. Age 2 to 5 years weighing ≥ 14 kg: lumacaftor 300 mg/ivacaftor 376 mg per day (2 packets per day);
c. Age 6 to 11 years: lumacaftor 400 mg/ivacaftor 500 mg per day (4 tablets per day);
d. Age ≥ 12 years: lumacaftor 800 mg/ivacaftor 500 mg per day (4 tablets per day).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. APPENDICES

APPENDIX A: Abbreviation/Acronym Key
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
aztreonam (Azactam®)	Nebulized dosage: 75 mg nebulized 3 times daily for 28 days than 28 days off aztreonam. Intravenous dosage: 2 g intravenously every 6 to 8 hours	225 mg/day nebulized: 8 g/day IV/IM
tobramycin (Bethkis®)	Administer the entire contents of one ampule twice daily by oral inhalation in repeated cycles of 28 days on drug, followed by 28 days off drug.	224 mg/day oral powder for inhalation
Symdeko®	Adults and pediatric patients age ≥ 12 years or pediatric patients age 6 to <12 years weighing 30 kg or more: one tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart.	1 tablet (tezacaftor 100 mg; ivacaftor 150 mg) and 1 tablet (ivacaftor 150 mg) per day (total daily dose: tezacaftor 100 mg/ivacaftor 300 mg)
Pulmozyme®	2.5 mg single-use ampule inhaled once daily using a recommended nebulizer	2.5 mg via inhalation twice daily.

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- 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.

References

1. Orkambi® Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc. July 2019. Available at: https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf Accessed July 1, 2021.
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.Available at: https://pubmed.ncbi.nlm.nih.gov/23540878/ Accessed July 1, 2021.
3. 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. Available at: https://pubmed.ncbi.nlm.nih.gov/29342367/ Accessed July 1, 2021.
4. 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. Available at: https://pubmed.ncbi.nlm.nih.gov/28129811/ Accessed July 1, 2021.
5. Orkambi®.Therapeutic Alternative. Lexicomp. Wolters Kluwer. Hudson, Oh. Available at https://online.lexi.com . Accessed July 1, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1) Policy title was updated. 2) Continued Therapy Approval criteria II.A.1 was rephrased. 3) Appendices updated. 4) References were updated.	03/06/2020	09/14/2020
Policy was reviewed: 1. Dosing Information was updated to include hepatic impairment dosing regimen, "Hepatic Impairment: Reduce dose in patients with moderate…" and "Initiating Orkambi® in patients taking strong CYP3A inhibitors…". 2. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 3. Initial Approval Criteria and Continued Therapy Approval criteria were updated to remove HIM approval duration.	7/1/2021	9/14/2021

4. Continued Therapy Approval Criteria II.A.1 was rephrased to " Member is currently receiving medication that has been authorized by RxAdvance...". 5. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 6. .Appendix B: Therapeutic Alternatives was updated to include alternative drugs "aztreonam (Azactam®)", "tobramycin (Bethkis®)", "Symdeko®", and "Pulmozyme®". 7. Statement about drug listing format in Appendix B is updated to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 8. References were reviewed and updated.		