



Prior Authorization Criteria Update: Cystic Fibrosis

Purpose of Update:

The purpose of this prior authorization (PA) update is to review current criteria for the use of lumacaftor/ivacaftor (LUM/IVA) (Orkambi®) in pediatric patients. The combination of LUM/IVA was approved after phase 3 trials demonstrated its efficacy for the management of cystic fibrosis (CF) in patients 12 years of age and older who were homozygous for the F508del mutation in the CFTR gene.¹ It is currently FDA-approved for those age 2 years and older who are homozygous for the F508del mutation in the CFTR gene.² This patient group includes approximately 34% of the United States CF population.³ Studies of LUM/IVA did not demonstrate clinically significant results on meaningful outcomes. It was associated with only an absolute 2.8% improvement in FEV₁ (estimated by averaging the absolute change at weeks 16 and 24) and a nominal decrease in pulmonary exacerbations compared to placebo (RR 0.61; 95% CI 0.49 to 0.76).¹

Initial PA criteria included a manual review and assessment of clinical severity of disease from the medical director for all patients younger than 12 years of age prescribed LUM/IVA. This decision was based on insufficient evidence that LUM/IVA improves lung function in children ages 6 to 11 years old with CF homozygous for the F508del mutation. Approval was based on an open-label study resulting in no significant changes in percent predicted forced expiratory volume (ppFEV₁).⁴ Additionally, a total of 11 patients (19.3%) had elevations in liver transaminases more than 3-times the upper-limit-of-normal (ULN) and 5 patients (8.8%) had elevations more than 5-times ULN.⁴ Another phase 3 study evaluating nonclinical outcomes demonstrated a decrease in lung clearance index, which indicates an improvement in lung ventilation, with LUM/IVA compared to placebo.⁵

Approval for patients 2 to 5 years of age was based on a 24-week, phase 3, non-randomized open-label trial in 60 patients.⁶ This study was designed as a safety and pharmacokinetic study and funded by Vertex Pharmaceuticals. FDA approved the expanded indication based on the study results that demonstrated treatment with the drug for 24 weeks was generally safe and well tolerated, with a safety profile similar to patients aged 6 years of age and older. The most common adverse event was cough (63%). Three patients discontinued treatment due to elevated liver enzymes. During the 24 weeks, 9 (15%) of the patients had elevated liver transaminases more than 3-times ULN.⁶ An ongoing extension study is underway to assess longer-term safety and durability of the beneficial effects of lumacaftor and ivacaftor in this age group.

Recommendation:

- Remove manual review by medical director for consistent with FDA labeling and standard of care from PA criteria for use of LUM/IVA in patients less than 12 years of age (**Appendix 1**).
- Add a link to FDA labeling in the PA criteria to ensure all approved CFTR mutations are current.

References:

1. Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine*. Oct 29 2015;373(18):1783-4. doi:10.1056/NEJMc1510466
2. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. September 2016. http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf.
3. Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. *Thorax*. May 2016;71(5):454-61. doi:10.1136/thoraxjnl-2015-208123
4. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. *American journal of respiratory and critical care medicine*. Apr 1 2017;195(7):912-920. doi:10.1164/rccm.201608-1754OC
5. Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *The Lancet Respiratory medicine*. Jul 2017;5(7):557-567. doi:10.1016/s2213-2600(17)30215-1
6. McNamara JJ, McColley SA, Marigowda G, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *The Lancet Respiratory medicine*. Apr 2019;7(4):325-335. doi:10.1016/s2213-2600(18)30460-0

Oral Cystic Fibrosis Modulators

Goals:

- To ensure appropriate drug use and limit to patient populations in which they have demonstrated to be effective and safe.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization: 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)
- Elexacaftor/Tezacaftor/Ivacaftor (Trikafta™)

Preferred Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Approved and Funded Indications for Oral Cystic Fibrosis Modulators

Drug Name	FDA approved CFTR mutation	Age
Ivacaftor (Kalydeco)	E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N, R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbC –T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X, R117H or a mutation in the CFTR gene that is responsive based on in vitro	4 months to < 6 months AND ≥ 5 kg ≥ 6 months

	data. See drug labeling for a comprehensive list of approved mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203188	
Lumacaftor/ivacaftor (Orkambi)	Homozygous Phe508del	≥ 2 years
Tezacaftor/ivacaftor (Symdeko)	Homozygous Phe508del, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of approved mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=210491	≥ 6 years
Elexacaftor/tezacaftor/ivacaftor (Trikafta)	At least one Phe508del mutation (homozygous or heterozygous) or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212273	≥ 12 years

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, or elexacaftor/tezacaftor/ivacaftor)?	Yes: Go to Renewal Criteria	No: Go to #2

Approval Criteria		
2. Does the patient have a diagnosis of Cystic Fibrosis?	Yes: Record ICD10 code. Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the request for an FDA approved age and CFTR gene mutation as defined in Table 1?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
5. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #6	
6. Is the request for ivacaftor?	Yes: Go to #7	No: Go to #8

Approval Criteria

<p>7. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?</p>	<p>Yes: Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.</p>	<p>No: Go to #8</p> <p>If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.</p> <p>CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).</p>
<p>8. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function?</p> <ul style="list-style-type: none"> • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)? 	<p>Yes: Go to #9</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>9. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness</p>	<p>No: Go to #10</p>
<p>10. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?</p>	<p>Document labs. Go to #11</p> <p>If unknown, these labs need to be collected prior to approval.</p>	

Approval Criteria		
11. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	<p>Yes: Approve for 6 months.</p> <p>If approved, a referral will be made to case management by the Oregon Health Authority.</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	<p>Yes: Go to #2</p>	<p>No: Pass to RPh; Deny (medical appropriateness)</p>
<p>2. Does the patient have documented response to therapy as defined as below :</p> <p>For patients age ≥6 years:</p> <ul style="list-style-type: none"> • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? <p>For patients age 2-5 years (cannot complete lung function tests)</p> <ul style="list-style-type: none"> • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity 	<p>Yes: Go to #3</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Renewal Criteria		
<p>3. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)?</p> <p>Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.</p>	<p>Document. Go to #4</p> <p>Note: Therapy should be interrupted in patients with AST or ALT >5x the upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN.</p>	
<p>4. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?</p>	<p>Yes: Approve for additional 12 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Dosage and Administration:

Ivacaftor:

- Adults and pediatrics age ≥6 years: 150 mg orally every 12 hours with fat-containing foods
- Children age 6 months to <6 years:
 - 5 kg to < 7 kg: 25 mg packet every 12 hours
 - 7 kg to < 14 kg: 50 mg packet every 12 hours
 - ≥ 14 kg: 75 mg packet every 12 hours
- Hepatic Impairment
 - Moderate Impairment (Child-Pugh class B):
 - Age ≥6 years: one 150 mg tablet once daily
 - Age 6 months to < 6 years
 - with body weight < 14 kg: 50 mg packet once daily
 - with body weight ≥ 14 kg : 75 mg packet of granules once daily
 - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet or 1 packet of oral granules once daily or less frequently. For infants, children and adolescents: administer usual dose once daily or less frequently. Use with caution.
- Dose adjustment with concomitant medications:

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with IVA	Co-administered drug category	Recommended dosage adjustment for IVA
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules twice weekly (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules once daily (half of normal dose)
Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort	CYP3A4 strong inducers	Concurrent use is NOT recommended
Grapefruit Juice	CYP3A4 moderate inhibitors	

Lumacaftor/ivacaftor

- Adults and pediatrics age ≥12 years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100mg/IVA 125 mg) every 12 hours
- Children age 2 to <6 years:

- < 14 kg: 1 packet (LUM 100mg/IVA125mg) every 12 hours
- ≥ 14 kg: 1 packet (LUM 150mg/IVA 188mg) every 12 hours
- Hepatic impairment
 - Moderate impairment (Child-Pugh class B):
 - Age ≥ 6 years: 2 tablets in the morning and 1 tablet in the evening
 - Age 2 to <6 years: 1 packet in the morning and 1 packet every other day in the evening
 - Severe impairment (Child-Pugh class C): Use with caution after weighing the risks and benefits of treatment.
 - Age ≥ 6 years: 1 tablet twice daily, or less
 - Age 2 to <6 years: 1 packet once daily, or less
- Dose adjustment with concomitant medications:
 - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

Tezacaftor/ivacaftor:

- Adults and pediatrics age ≥6 years weighing ≥30 kg : 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Pediatrics age ≥ 6 years weighing < 30 kg: TEZ 50mg/IVA 75 mg in the morning and IVA 75 mg in the evening
- Hepatic impairment
 - Moderate impairment (Child-Pugh class B):
 - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning. The evening IVA dose should not be administered.
 - Severe impairment (Child-Pugh class C):
 - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning (or less frequently). The evening IVA dose should not be administered.
- Dose adjustment with concomitant medications:
 - When initiating therapy in patients taking moderate CYP3A inhibitors (see table above), reduce dose to:
 - On day 1, TEZ 100/IVA 150 once daily in the morning, and on day 2, IVA 150 mg once daily in the morning; continue this dosing schedule.
 - When initiating therapy in patients taking strong CYP3A4 inhibitors (See table above), reduce dose to:
 - TEZ 100 mg/IVA 150 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

Elexacaftor/tezacaftor/ivacaftor:

- Adults and pediatrics age ≥12 years: 2 tablets (ELX 100mg/TEZ 50 mg/IVA 75 mg) in the morning and IVA 150 mg in the evening
- Hepatic impairment
 - Moderate impairment (Child-Pugh class B): Use only if the benefits outweigh the risks.
 - 2 tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in the morning. The evening IVA dose should not be administered.
 - Severe impairment (Child-Pugh class C): Use not recommended
- Dose adjustment with concomitant medications:

- Dosage adjustment for concomitant therapy with moderate CYP3A inhibitors (see table above):
 - 2 tablets (ELX 100 mg/ TEZ 50 mg/IVA 75 mg once daily in the morning, alternating with one IVA 150 mg tablet in the morning every other day.
 - Dosage adjustment for concomitant therapy with strong CYP3A4 inhibitors (See table above), reduce dose to:
 - 2 tablets (ELX 100 mg/TEZ 50 mg/IVA 75 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.
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P&T Review: 6/21(MH); 6/20 (MH);(9/19); 9/18; 7/18; 11/16; 11/15; 7/15; 5/15; 5/14; 6/12

Implementation: 7/1/21; 7/1/20; 11/1/19; 11/1/2018; 1/1/16; 8/25/15; 8/12