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Prior Authorization Criteria Update: Cystic Fibrosis

Purpose of Update:

1. In April 2019, the Food and Drug Administration (FDA) expanded the label of ivacaftor (Kalydeco®) for the treatment of cystic fibrosis (CF) in patients ages 6 months and older who have one mutation in the cystic fibrosis transmembrane conductance regulatory (CFTR) gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro data.[1] Previously, ivacaftor was approved in patients age 12 months and older.

   Approval is based on unpublished, low-quality data from a phase 3 open-label, 24- week safety and pharmacokinetic study including 25 children less than 24 months of age with one of ten gating mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H).[2] However, the only enrolled mutations included G551D (n=10) or G178R (n=1).[3] The study was funded by Vertex Pharmaceuticals, who had a role in study design, data collection, data analysis, data interpretation and writing of the report. Data from the first cohort of patients (age 12-24 months) has been published (n=19)[2], but data in those 6-12 months old remains unpublished (n=11).[3] The safety profile of ivacaftor 25 mg, 50 mg or 75 mg twice daily was similar to that observed in patients with CF 2 years of age and older. Only one patient experienced elevated liver transaminases, and there were no discontinuations due to adverse events.[1] Efficacy and safety from placebo-controlled trials has only been established in pediatric patients 6 years of age and older.[4] Efficacy in patients age 6 months to less than 12 months old was extrapolated from patients 6 years of age and older based on population pharmacokinetic analyses showing similar drug exposure.[1]

   The safety and efficacy of ivacaftor in patients with CF younger than 6 months of age have not been established. The use of ivacaftor in patients less than 6 months of age cannot be recommended at this time.

2. In June 2019, FDA also expanded the FDA labeling for tezacaftor/ivacaftor (Symdeko®) for the treatment of pediatric patients ages 6 years and older with CF who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[5] Previously, tezacaftor/ivacaftor was approved in patients age 12 years and older.

   Similarly, efficacy in this population was extrapolated from patients aged 12 years and older and approval was supported by a 24-week, open-label, phase 3 study designed to assess safety and pharmacokinetics (n=70).[6] The majority of patients (n=61) were homozygous for *F508del* and the remaining (n=9) were heterozygous for *F508del* with a second mutation with residual function. Patients had to weigh 15 kg or more and have a baseline percent predicated FEV_1 ($ppFEV_1$) of 40% or greater. Mean baseline $ppFEV_1$ was 91%.[6] The safety profile was observed to be similar to clinical trials in ages 12 and older, and pharmacokinetic population analysis demonstrated similar overall exposure. The most common treatment emergent adverse events were cough (35.7%), CF exacerbation (22.9%), pyrexia (18.6%) and nasal congestion (14.3%).[6] There was only one discontinuation due to an adverse event and no deaths occurred. Additionally, there was a least squares absolute change from baseline in sweat chloride of -14.5 mmol/L at week 25 (95% CI -17.4 to -11.6), but no significant effect on least squares mean absolute change in $ppFEV_1$ (0.9%; 95% CI -0.6 to 2.3).[6] This study used a weight-based dosing

regimen that differs from the FDA-approved dosing regimens for patients age 6 through 11 years. The dosing regimen in the study used a 40 kg weight-based dosing cutoff, while 30 kg is included in the FDA label.

Recommendation:

- Update prior authorization criteria to reflect recent changes in FDA approved labels for ivacaftor and tezacaftor/ivacaftor.

References:

1. KALYDECO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; April 2019
2. Rosenfeld M, Wainwright CE, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med*. 2018;6(7):545-553
3. Davies JC, Wang LT, Campbell D, et al. Ivacaftor treatment in patients 6 to <12 months old with a CFTR gating mutation: results of a Phase 3, two-part, single-arm study. Poster and abstract presented at: North American Cystic Fibrosis
4. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with *G551D* mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219–1225.
5. SYMDEKO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; June 2019.
6. Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 to 11 years with cystic fibrosis. *J Cyst Fibros.* 2019:1-6. doi: 10.1016/j.jcf.2019.06.009.

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:

- 90 days to 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)

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	≥ 6 months
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,	≥ 6 years

	S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T	

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
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 #9
7. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #8	

Approval Criteria		
8. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Go to #12 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
9. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient younger than 12 years of age?	**Yes:** Refer case to OHP Medical Director;	**No:** Go to #12
11. Is the request for tezacaftor/ivacaftor?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. 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: • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14

Approval Criteria		
14. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #15 If unknown, these labs need to be collected prior to approval.	
15. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 90 days. Note: Approve for 90 days to allow time for patient to have a sweat chloride test done after 30 days of treatment if on IVA (see **Renewal Criteria**). If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness

Renewal Criteria		
3. If the prescription is for lumacaftor/ivacaftor or tezacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • 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? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #7 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.	

Renewal Criteria		
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 3 months (total of 6 months since start of therapy)	**No:** Pass to RPh. Deny; medical appropriateness

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 less than 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 1 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.
- 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	

<u>Lumacaftor/ivacaftor</u>

- 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.

P&T Review: *9/19 (MH); 9/18; 7/18; 11/16; 11/15; 7/15; 5/15; 5/14; 6/12*
Implementation: *11/1/19; 11/1/2018; 1/1/16; 8/25/15; 8/12*