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PA Update: Oral Cystic Fibrosis Modulators

Date of Review: September 2018

Conclusions:

- Lumacaftor/ivacaftor was recently approved for patients 2 to 5 years of age who are homozygous for the F508del mutation based on one 24-week, non-randomized, open-label safety and pharmacokinetic study.[1] There is insufficient evidence that lumacaftor/ivacaftor is effective in improving outcomes including lung function, quality of life, or pulmonary exacerbations in this patient population.
- Ivacaftor was FDA approved for children ages 12 to 24 months of age based one open-label, 24-week study demonstrating similar pharmacokinetic response and overall tolerability as seen in older children.[2,3] There is insufficient evidence that ivacaftor is effective in improving clinical outcomes including lung function, quality of life, or pulmonary exacerbations in this patient population. Although the approval includes any mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor, ivacaftor was only studied in 8 of the gating mutations.
- A significant safety concern for both lumacaftor/ivacaftor and ivacaftor in pediatric populations is elevated liver transaminases and the potential long-term impact of treatment on liver function. The incidence of increased liver transaminases in clinical trials in adults with ivacaftor was 6%, while this rate increased to 14.7% in patients ages 2 to 6 and 27.8% in those less than 24 months of age.[2] Treatment with lumacaftor/ivacaftor resulted in elevated liver transaminases in 19% of patients ages 2 to 5 years of age.[1]
- Tezacaftor/ivacaftor was FDA approved for patients who have at least one mutation in the CFTR gene that is responsive to therapy. This is based on one trial that included patients who were heterozygous for the F508del mutation with a second allele predicted to be responsive.[4] However, the FDA approval did not reflect this study population. The FDA division of drug information was not able to provide additional insight into the reasoning behind the specific FDA approval and language used in the drug label. The PA criteria has been updated to reflect the FDA approved indication.

Recommendations:

- Approve amended PA criteria to reflect updated FDA labeling based on approved indications.

New FDA Approved Indications:

1. In August 2018, lumacaftor/ivacaftor was FDA approved for patients 2 to 5 years of age who are homozygous for the F508del mutation. The previous FDA label was for patients 6 years of age and older.[1] There are approximately 1300 patients age 2 through 5 years of age homozygous for the F508del mutation in the United States. The approval was based on a 24-week, unpublished, phase 3, non-randomized, open-label trial in 60 patients aged 2 to 5 years with a mean baseline percent predicted forced expiratory volume at 1 second (ppFEV1) of 89.8%. The study was designed as a safety and pharmacokinetic study and was funded by Vertex Pharmaceuticals. Any clinically significant laboratory abnormality was an exclusion criterion of the study. Study results in their entirety are not available at this time on clinicaltrials.gov or in the FDA review documents. 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, the incidence of elevated liver transaminases greater than 8, greater than 5 and greater than 3 times the upper limit of normal (ULN) was 8.3% (5/60), 11.7% (7/60) and 15% (9/60).[1]

Additionally, there was a significant reduction in sweat chloride (-31.7 mmol/L; 95% CI -35.7 to -27.6). There was no correlation between decrease in sweat chloride and improvement in ppFEV1.

There is insufficient information available to fully assess this trial for quality or to assess the efficacy of lumacaftor/ivacaftor in this population on clinically important outcomes. Minimal study results are available from the package insert. Current prior authorization criteria requires medical director review for lumacaftor/ivacaftor if the patient is younger than 12 years of age based on an open-label study resulting in no difference in FEV1 in children ages 6 to 11 years and the safety concern of elevations in liver transaminases compared to what was seen in studies with adult patients (19.3% vs. 5%).

2. Also in August 2018, ivacaftor was FDA approved for children ages 12 to <24 months who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in in vitro assay data.[2] Approval is based on data from an ongoing phase 3 open-label safety and pharmacokinetic study (n=25) including children with one of 10 gating mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H).[3] Part A of the study assessed safety and pharmacokinetics after 4 days of treatment, while part B was a 24-week assessment of safety and exploratory efficacy outcomes. 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. Seven children 12 to 24 months were enrolled in part A of the study. Six of these children had the G551D mutation on one allele. Only one of these children was eligible to continue to part B of the study. A total of 17 (94%) of children included in the 24-week assessment were younger than 24 months. A total of 18 (95%) of children experienced at least one treatment-emergent adverse event during the 24 weeks. The most common were cough, pyrexia, increased liver transaminases, otitis media and upper respiratory tract infection. Twenty eight percent (n=5) of children experienced increased concentrations of liver transaminases to more than three times the ULN. There were no discontinuations due to adverse events. The mean sweat chloride concentration decreased from baseline with a mean change of 73.5 mmol/l (95% CI -86 to -61). However, this outcome was only measured in ten subjects and study authors did not provide details on the remaining nine.

References

1. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. August 2018. https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf.
2. Kalydeco Prescribing Information. Vertex Pharmaceuticals. August 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203188s028,207925s007lbl.pdf.
3. 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. *The Lancet Respiratory medicine.* 2018;6(7):545-553.
4. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *The New England journal of medicine.* 2017;377(21):2024-2035.

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/

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. What diagnosis is being treated?	Record ICD10 code. Go to #3	
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. 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 #5	
5. Is the request for ivacaftor?	**Yes:** Go to #6	**No:** Go to #10

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Approval Criteria		
6. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #7	
7. Does the patient have a diagnosis of cystic fibrosis and is 12 months of age or older?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented mutation in the CFTR gene that ivacaftor is FDA approved for (see below)? FDA approved CFTR mutations include: 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	**Yes:** Go to #17	**No:** Go to #9 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. 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:** 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. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).

Approval Criteria		
10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Go to #13
11. Does the patient have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an CF mutation test?	**Yes:** If the patient is younger than 12 years of age, refer case to OHP Medical Director; otherwise, Go to #17	**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. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)
13. Is the request for tezacaftor/ivacaftor?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Does the patient have a diagnosis of cystic fibrosis and is 12 years of age or older?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Go to #17	**No:** Go to #16 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.

Approval Criteria		
16. Does the patient have at least one mutation that is responsive to tezacaftor/ivacaftor based on in vitro data and FDA labeling? Note: A list of CFTR gene mutations that produce CFTR protein and are responsive to tezacaftor/ivacaftor include: 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	**Yes:** Go to #17	**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.
17. 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 #18	**No:** Pass to RPh. Deny; medical appropriateness
18. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #19
19. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #20 If unknown, these labs need to be collected prior to approval.	

Approval Criteria		
20. 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**)	**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
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)

Renewal Criteria		
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 1 to <6 years:
  - < 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	CYP3A4 strong inducers	Concurrent use is **NOT** recommended

Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort Grapefruit Juice		

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 ≥12 years: 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 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: *7/18 (MH); 11/16; 11/15; 7/15; 5/15; 5/14; 6/12*
Implementation: *TBD; 1/1/16; 8/25/15; 8/12*