

Cystic Fibrosis Oral modulators and Inhalation solutions
Ivacaftor (Kalydeco), Lumacaftor/Ivacaftor (Orkambi) and Tezacaftor / Ivacaftor (Symdeko)
Dornase alfa (Pulmozyme), Tobramycin, Aztreonam (Cayston)

Oral Modulators

1. Does the member have a diagnosis of cystic fibrosis and are they under the care of a pulmonologist with experience in treating cystic fibrosis?
 - a. Yes- Go to question 2
 - b. No – Deny- Not medically appropriate- *Member with Cystic Fibrosis should be linked to a provider able to provide comprehensive management to reduce risk of adverse outcomes.*

2. Has the member been hospitalized or had exacerbations for CF in the past 12 months
 - a. Yes- Document the number of each as baseline for comparison, go to question 3.
 - b. No- - Forward to Medical Director for review of disease severity and clinical appropriateness of treatment. *Provider must provide documentation that member needs escalation of therapy.*

3. Is the request for ivacaftor (Kalydeco)
 - a. Yes- go to question 4
 - b. No- go to question 7

4. Is there a baseline sweat chloride level?
 - a. Yes – Record level for comparison and go to question 5
 - b. No- Deny- Not medically appropriate- *Medication improves salt and water absorption and secretion and sweat chloride levels are an important measurement of medication efficacy, baseline levels are required for assessment.*

5. Does the patient have a documented G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene detected by an FDA-cleared CF mutation test?
 - a. Yes- Go to question 11
 - b. No - Go to question 6 -*There needs to be a FDA-approved 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).*

6. Does the patient have a documented R117H mutation in the CFTR gene detected by an FDA-cleared CF mutation test?
 - a. Yes – Go to question 11
 - b. No – Deny Cat 5- not medically appropriate- *There needs to be a FDA-approved CF mutation test to detect the presence of the CFTR mutation prior to use. OR*
** CF due to other CFTR gene mutations are not approved indications (including the F508del mutation) and should be denied Cat 3- Use is outside FDA approved indication*

7. Is the request for lumacaftor/ivacaftor in a member with CF who is at least 2 years old?
 - a. Yes – Go to question 8
 - b. No- Go to question 9

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8. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an FDA-approved CF mutation test?
 - a. Yes- Go to question 11
 - b. No- If unknown,- Deny Cat 5- *there needs to be a FDA-approved CF mutation test to detect the presence of the CFTR mutation prior to use.*
 If member does not have mutation – Deny Cat 3- *CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)*

9. Is the request for tezacaftor/ivacaftor (Symdeko) in a member who is at least 12 years of age?
 - a. Yes – Go to question 10
 - b. No- Deny Cat 3 – *Medication is being prescribed outside of FDA approved use*

10. Does the member have documented homozygous Phe508del mutation OR heterozygous for the F508del mutation AND have a second mutation in the CFTR gene as listed below detected by an FDA approved CF mutation test to detect the presence of the CFTR mutation?

List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO					
<i>E56K</i>	<i>R117C</i>	<i>A455E</i>	<i>S945L</i>	<i>R1070W</i>	<i>3272-26A→G</i>
<i>P67L</i>	<i>E193K</i>	<i>F508del*</i>	<i>S977F</i>	<i>F1074L</i>	<i>3849+10kbC→T</i>
<i>R74W</i>	<i>L206W</i>	<i>D579G</i>	<i>F1052V</i>	<i>D1152H</i>	
<i>D110E</i>	<i>R347H</i>	<i>711+3A→G</i>	<i>K1060T</i>	<i>D1270N</i>	
<i>D110H</i>	<i>R352Q</i>	<i>E831X</i>	<i>A1067T</i>	<i>2789+5G→A</i>	

*A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in table

- a. Yes – Go to question 11
 - b. No -- If unknown,- Deny Cat 5- *there needs to be a FDA-approved CF mutation test to detect the presence of the CFTR mutation prior to use.*
 If member does not have mutation – Deny Cat 3- *CF due to other CFTR gene mutations are not FDA approved indications for the use of this medication.*

11. Is baseline FEV1 between 40% and 90% of predicted normal value for member age, sex and height for those 12 and older OR at least 40% of predicted for children ages 6 through 11 years?
 - a. Yes- Go to question 12
 - b. No – Deny- Cat 5- Not medically appropriate- *Member does not meet FEV1 requirements of clinical trials for FDA approval.*

12. Is the member on ALL of the following treatments (unless contraindicated), taken on a regular basis (80% of the time or more) for an adequate trial and still having exacerbations?
 - Dornase alfa (Pulmozyme); AND
 - Hypertonic saline* AND
 - Inhaled or oral antibiotics (if appropriate)?

*Hypertonic saline is not indicated for use in children under age 6

 - a. Yes – Go to question 13
 - b. No- Deny Cat 5 or forward to Medical Director- *escalation of therapy not appropriate unless preferred treatments taken regularly have resulted in inadequate response.*

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13. Is the member currently using a medication that is considered a strong CYP3A4 inducer?

Drug	CYP3A4 effect
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	Strong inhibitors of CYP3A4 Dose reduction required
Fluconazole Erythromycin Clofazimine	Moderate inhibitors of CYP3A4 Dose reduction required
Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St John's Wort Grapefruit juice	Strong inducers of CYP3A4 Concurrent use is not recommended

- a. Yes- Deny Cat 5- *Concurrent use of CYP3A4 inducer is not recommended as this will compromise the efficacy of the medication.*
- b. No- Go to question 14

14. Are there baseline liver function tests (AST/ALT) and bilirubin levels taken within 3 months of request? (note that moderate hepatic impairment requires dose adjustment, use is not recommended in severe hepatic impairment)

- a. Yes- Go to question 15
- b. No - Deny Cat 5- *Medication may increase hepatic transaminases with or without concomitant elevations in total serum bilirubin. Manufacturer indicates that providers must monitor ALT, AST, and bilirubin at baseline, every 3 months for the first year of therapy, and annually thereafter.*

15. Is medication dosed appropriately?

- a. Yes –Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval- May be approved for a maximum of 90 days.
- b. No – Deny Cat 3- *Medication is being prescribed outside of FDA approved use and has not been demonstrated to be effective and safe*

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Ivacaftor: (Kalydeco)

Adults and pediatrics age ≥ 6 years: 150 mg orally every 12 hours with fat-containing foods

Children age 2 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 2 to < 6 years with body weight < 14 kg: 50 mg packet once daily;

with body weight ≥ 14 kg: 75 mg packet once daily

Severe impairment (Child-Pugh class C): Use with caution

Lumacaftor/ivacaftor: (Orkambi)

Adults and pediatrics age ≥ 12 years: 2 tablets (lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours

Pediatrics ages 6 through 11 years: 2 tablets (lumacaftor 100mg/ivacaftor 125 mg) every 12 hours

Hepatic impairment:

Moderate impairment (Child-Pugh class B): 2 tablets in the morning and 1 tablet in the evening

Severe impairment (Child-Pugh class C): Use with caution

Tezacaftor/ivacaftor (Symdeko)

Adults and children ≥ 12 years of age: Tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening, about 12 hours apart.

Hepatic impairment:

Moderate impairment (Child-Pugh class B): Tezacaftor 100 mg/ivacaftor 150 mg once daily in the morning. The evening dose of ivacaftor 150 mg should not be administered

Severe impairment (Child-Pugh class C): Tezacaftor 100 mg/ivacaftor 150 mg once daily in the morning (or less frequently). The evening dose of ivacaftor 150 mg should not be administered.

Renal impairment:

Medication has not been studied in $\text{CrCl} \leq 30$ mL/minute or ESRD and should not be used

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Renewal Criteria

1. Is this the first renewal request since initial referral approved?
 - a. Yes- Go to question 2
 - b. No- Go to question 4

2. Is the request for ivacaftor?
 - a. Yes- Go to question 3
 - b. No – Go to question 4- Renewal for lumacaftor/ivacaftor or tezacaftor/ivacaftor

3. Does the member have a documented response to therapy as defined by a sweat chloride test that has decreased by at least 20mmo/L from baseline AND adherence to therapy?
 - a. Yes – Go to question 5
 - b. No - Assess member’s adherence to therapy and allow amended therapy up to 45 days for a repeated test. If sodium chloride still has not decreased by 20mmo/L- Deny Cat 5- Therapy is not proving effective in this member.

4. Is there documentation of adherence to therapy with lumacaftor/ivacaftor or tezacaftor/ivacaftor (or ivacaftor on second or later renewal) and tolerance to side effects?
 - a. Yes- Go to question 5
 - b. No – Assess medical appropriateness of continued therapy. Possible Cat 5 denial

5. Does the patient have documented response to therapy as defined as below :

For members 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 members age 2-5 years (cannot complete lung function tests) - Ivacaftor only

 - 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?
 - a. Yes – Go to question 6
 - b. No- Assess appropriateness of continued therapy – Possible Cat 5 denial

6. Have liver function test been monitored appropriately – Monitoring LFTs is recommended every 3 months for the first year, then yearly afterward.** Therapy should be stopped if AST or ALT 5 times the upper limit of normal without elevated bilirubin OR 3 times the upper limit of normal with bilirubin 2 times the upper limit of normal**
 - a. Yes – Go to question 7
 - b. No – Assess appropriateness of continued therapy, LFT monitoring is a required assessment

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7. Is the CFTR modulator dosed appropriately based on age, weight, co-morbid conditions and/or concomitant drugs?
 - a. May approve for additional 3 months if clinically appropriate
 - b. No- Assess for appropriateness of therapy- possible Cat 3 or Cat 5 denial

Inhaled therapies – Dornase alfa (Pulmozyme), Tobramycin, Aztreonam (Cayston)

1. Is the request for a member with cystic fibrosis under the care of a pulmonologist with experience in the care of patients with cystic fibrosis?
 - a. Yes – Go to question 2
 - b. No – Deny Cat 5 -*Member with Cystic Fibrosis should be linked to a provider able to provide comprehensive management to reduce risk of adverse outcomes*
2. Is the request for dornase alfa (Pulmozyme)?
 - a. Yes – Go to question 3
 - b. No – Go to question 4
3. Is the request for a member at least 6 years of age, with cystic fibrosis and with a forced vital capacity (FVC) $\geq 40\%$ of predicted?
 - a. Yes – Go to question 9
 - b. No – Deny Cat 3- *Medication is being prescribed outside of FDA approved indications where safety and efficacy has not been established*
4. Is the request for tobramycin 300mg/5ml inhalation solution?
 - a. Yes – Go to question 5
 - b. No- Go to question 6
5. Is the request for a member at least 6 years of age, with cystic fibrosis, positive for Pseudomonas aeruginosa?
 - a. Yes – Go to question 9
 - b. No- Deny Cat 3 – *Medication is being prescribed outside of FDA approved indications where safety and efficacy has not been established*
6. Is the request for aztreonam inhalation solution (Cayston)?
 - a. Yes – Go to question 7
 - b. No- Evaluate request for FDA indication and clinical appropriateness.
7. Is the request for the member age 7 or older, with cystic fibrosis, with documented Pseudomonas aeruginosa infection and with FEV1 $< 25\%$ or $> 75\%$ predicted?
 - a. Yes – Go to question 8
 - b. No – Deny Cat 3- *Medication is being prescribed outside of FDA approved indications where safety and efficacy has not been established*

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8. Does the member meet one of the following conditions?
 - Had an inadequate response or intolerance to tobramycin therapy (pulmonary status is declining despite regular use of tobramycin)
 - Requires continuous antibiotic treatment and will be alternating aztreonam with tobramycin.
 - Is pregnant
 - a. Yes – Go to question 9
 - b. No – Deny Cat 5 – *Member has not had adequate trial of preferred treatment tobramycin*
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9. Is the inhalation treatment dosed appropriately?
 - Dornase alfa (Pulmozyme)- 2.5 mg daily
 - Tobramycin inhalation solution (Kitabis, Bethkis)-300 mg every 12 hours in cycles of 28 days on followed by 28 days off.
 - Aztreonam inhalation solution (Cayston) – 75 mg three times daily for 28 days, do not repeat for 28 days after completion of cycle.
 - a. Yes – May approve for up to 6 months on initial request, 12 months on renewal
 - b. No – Deny Cat 3 *Medication is being prescribed outside of FDA approved indications where safety and efficacy has not been established*