State of California—Health and Human Services Agency
Department of Health Care Services

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TO: All County California Children's Services Program and Genetically Handicapped Persons Program Administrators, Medical Consultants, and Integrated Systems of Care Division Staff

SUBJECT: Cystic Fibrosis Transmembrane Conductance Regulator Modulator Drug Therapies

I. PURPOSE

The purpose of this Numbered Letter (N.L.) is to update California Children's Services (CCS) Program and Genetically Handicapped Persons Program (GHPP) drug coverage for the treatment of cystic fibrosis (CF). CCS and GHPP currently authorize two cystic fibrosis transmembrane conductance regulator (CFTR) drug therapies to treat CF: ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi). This N.L. establishes policy regarding authorization of all Federal Drug Administration (FDA)-approved CFTR drug therapies: ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), and a third drug, tezacaftor/ivacaftor and ivacaftor (Symdeko).

II. BACKGROUND

CF is a life-threatening autosomal recessive genetic disease that involves both exocrine and endocrine gland dysfunction. CF primarily affects the respiratory and digestive systems. CF is caused by mutations in the gene coding for the CFTR that lead to decreased secretion of chloride and increased reabsorption of sodium and water across cells. These mutations lead to viscous (sticky) secretions, which are harder to clear, resulting in increased susceptibility to life threatening pulmonary infections. In addition, the viscous secretions obstruct the process of digestion, leading to malabsorption of food.

Standard therapies for CF target amelioration of symptoms and the prevention of infection. CFTR modulators are new therapies that normalize chloride transport across the CFTR by modulating the structure and function of the CFTR. There are over 1700 known CFTR mutations. Mutation classes amenable to current CFTR

therapies include gating mutations, conduction mutations, splice mutations, protein-processing mutations, and residual function mutations.

A patient's response to CFTR modulator therapy depends on the patient's CFTR mutation class. All mutations within the same mutation class respond to the same CFTR modulator therapy. Kalydeco (ivacaftor) was the initial CFTR modulator. Later CFTR modulators, Orkambi and Symdeko, combined ivacaftor with other drugs.

III. POLICY

A. Initial authorization:

CCS independent counties and the Department of Health Care Services (Department), on behalf of CCS dependent counties and GHPP, shall authorize a six month treatment of Kalydeco, Orkambi, or Symdeko drug therapies if:

1. A CCS or GHPP client has been diagnosed with a CFTR modulator responsive gene mutation.

2. Client is under the care of a CCS-paneled pulmonologist at a CF CCS Special Care Center (SCC).

3. The SCC or pharmacy submits a service authorization request (SAR) to the Department or a CCS independent county requesting approval to treat the client's CFTR gene mutation using Kalydeco, Orkambi, or Symdeko. The SAR should be submitted in accordance with the Department's guidance regarding CF mutations responsive to CFTR modulator therapy (see Attachment 1) and FDA-approved dosages (see Attachment 2).

4. Along with the SAR, the SCC provides the following information, documented within the past 12 months:

    a. The client's CFTR drug therapy prescription.

    b. The client's genetic lab results.

    c. A completed CFTR Modulator Request Form (see Attachment 3).

    d. A report on the client's nutritional status, including the client's body mass index (BMI).

5. The request is for the least costly medically necessary treatment. For this reason:

    a. Symdeko is the preferred treatment for all clients with a genetic profile responsive to Kalydeco and Symdeko when the client is within the FDA-approved age.

    b. Orkambi is the preferred treatment for all clients with a genetic profile responsive to Orkambi and Symdeko, unless the provider submits evidence that the response to Orkambi has been suboptimal.

B. Reauthorization:

1. For CFTR drug therapy reauthorizations, SCCs should provide documentation that the client has responded to the therapy with stable or improved pulmonary function, improved BMI, fewer symptoms, or fewer inpatient admissions.

2. Reauthorizations of CFTR drug therapies shall be for a period no longer than one year.

C. If the criteria described above are not met, but the requesting provider has clinical documentation and/or scientific evidence that may be relevant to the request, the provider may submit this additional documentation to the ISCD Medical Director or designee for consideration during the eligibility determination.

IV. POLICY IMPLEMENTATION

A. SCCs or pharmacies must submit the requested materials to:

1. For clients residing in an independent county, all requests shall be submitted to the CCS County Office for processing.

2. For clients residing in a dependent county, all requests shall be submitted to the Special Populations Unit by email at CCS_Operations@dhcs.ca.gov or via secure RightFax number, (916) 440-5768.

3. For clients residing in a county covered by the WCM, all requests shall be submitted to, and processed by, the managed care plan.

B. Clients transitioning from CCS to GHPP:

1. SCCs treating clients who are transitioning from CCS to GHPP should:

a. Encourage clients to complete the GHPP enrollment form.

b. Submit an updated CFTR Modulator Request Form (see Attachment 3) to the Department for continued approval of the client's CFTR drug therapy under GHPP.

If you have any questions regarding this N.L., please contact the ISCD Medical Director or designee, via email at ISCD-MedicalPolicy@dhcs.ca.gov.

Sincerely,

ORIGINAL SIGNED BY

Roy Schutzengel
Medical Director
Integrated Systems of Care Division

Attachments:
CF Mutations Responsive to CFTR Modulator Therapy[1]
FDA-Approved Dosages
CFTR Modulator Request Form

[1] Official Listing of Mutations
https://www.cff.org/Research/developing-New-Treatments/CFTR-Modulator-Types/

Cystic Fibrosis (CF) Mutations Responsive to Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulator Therapy

Kalydeco (ivacaftor) is indicated for clients with CF ages 6 months and older who have at least one of the following mutations:

Gating Mutations

G178R	G1244E	S549R
G551D	G1349D	S1251N
G551S	S549N	S1255P

Residual Function Mutations

A455E	E56K	R74W
A1067T	E193K	R117C
D110E	F1052V	R347H
D110H	F1074L	R352Q
D579G	K1060T	R1070W
D1152H	L206W	S945L
D1270N	P67L	S977F
G1069R	R1070Q	

Splice Mutations

711+3A→G	3272-26A→G	E831X
2789+5G→A	3849+10kbC→T	

Conduction Mutation

R117H

Cystic Fibrosis (CF) Mutations Responsive to Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulator Therapy

Orkambi (lumacaftor/ivacaftor) is indicated for clients ages 2 and older who have two copies of the F508del protein processing mutation.

Symdeko (tezacaftor/ivacaftor and ivacaftor) is indicated for clients ages 6 and older who have two copies of the F508del protein processing mutation, or at least one of the following mutations:

Residual Function Mutations

A455E	E56K	R74W
A1067T	E193K	R117C
D110E	F1052V	R347H
D110H	F1074L	R352Q
D579G	K1060T	R1070W
D1152H	L206W	S945L
D1270N	P67L	S977F

Splice Mutations

711+3A→G	3272-26A→G	E831X
2789+5G→A	3849+10kbC→T	

FDA

	Symdeko (tezacaftor/ivacaftor and ivacaftor)	**Orkambi (lumacaftor/ivacaftor)**	**Kalydeco (ivacaftor)**
Age	6 years and older	2 years and older	6 months and older
Dosage instructions	Age 6 to less than 12 years and less than 30kg: One tablet (containing tezacaftor 50mg/ivacaftor 75mg) in the morning and one tablet (containing ivacaftor 75mg) in the evening (approximately 12 hours apart) with fat-containing food. Age 6 to less than 12 years and more than 30kg or age 12 years and over: 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) with fat-containing food.	Age 2 to 5 years and less than 14kg: One packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. Age 2 to 5 years and greater than 14kg: One packet of granules (each containing lumacaftor 150 mg/ivacaftor 188 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. Age 6 to11 years: Two tablets (lumacaftor 100mg/ivacaftor 125mg) orally every 12 hours with fat containing food. Age 12 years and older: Two tablets (lumacaftor 200mg/ivacaftor 125mg) orally every 12 hours with fat- containing food.	Age 6 months to less than 6 years and 5 kg to less than7kg: One 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. Age 6 months to less than 6 years and 7 kg to less than 14 kg: One 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. Age 6 months to less than 6 years and 14 kg or greater: One 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. Age 6 years and older: One 150mg tablet orally every 12 hours with fat containing food.
	Symdeko (tezacaftor/ ivacaftor and ivacaftor)	**Orkambi (lumacaftor/ivacaftor)**	**Kalydeco (ivacaftor)**
Dose Reductions	Dose reduction for moderate and severe hepatic impairment or potential drug-drug interaction with co-administered drugs.	Dose reduction for potential drug-drug interaction with co-administered drugs.	Dose reduction for moderate and severe hepatic impairment or potential drug-drug interaction with co-administered drugs.

CFTR Modulator Request Form

Client Name:		CCS/ GHPP #:		Date:	
CF Mutation:		Age:		County:	
Completed By (Name/ Title):		SCC Tel #:		SCC NPI:	

Clinical Baseline ☐ **Request For Reauthorization After CFTR Modulator Trial** ☐

a. BMI/Weight (date)		
b. FEV_1% **(two [2] previous in last 6 month and date of each FEV_1%)-**(if age appropriate);		
c. Sweat Chloride, if available (date)		
d. Dates & # of days of hospitalization during previous 12 months		
e. # of episodes of pulmonary exacerbation during previous 12 months		
1. Resulting in ER or hospital visit	ER ☐ Hospital Admit ☐	
2. Resulting in IV antibiotic use (# of days)		
f. AST/ALT (Dates/Results)		
g. Compliance (Check one)	Good ☐ Poor ☐	
h. Medication contraindicated with lumacaftor (if applicable)		
i. Any adverse reactions with CFTR Modulator (Check one)	Yes ☐ No ☐	If yes, provide reaction details:

Additional Comments:

For CCS Operations Official Use Only

Approved ☐ Denied ☐ Reason for Denial: