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

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DIRECTOR

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GOVERNOR

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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 previously authorized three cystic fibrosis transmembrane conductance regulator (CFTR) drug therapies to treat CF:

1. Ivacaftor (Kalydeco),

2. Lumacaftor/ivacaftor (Orkambi), and

3. Tezacaftor/ivacaftor and ivacaftor (Symdeko).

This N.L. establishes criteria for authorizing a fourth CF drug, elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta) and updates the newly approved expanded age for Ivacaftor.

The CCS Program publishes this N.L. under the program's authority to authorize services that are medically necessary to treat CCS-eligible conditions.[1,2,3]

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 protein that result in decreased secretion of chloride and increased reabsorption of sodium and water across cells. Lack of CFTR function leads to viscous secretions, which are harder to clear, resulting in increased susceptibility to life threatening pulmonary infections. In addition,

the viscous secretions obstruct the pancreatic ducts and disrupt the process of digestion, leading to malabsorption of food.

Standard therapies for CF target amelioration of symptoms and prevention of infection. CFTR modulators are new therapies that improve chloride transport across the cell membrane by modulating the structure and function of the defective CFTR. There are over 1,700 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. Certain mutations within the same mutation class respond to the same CFTR modulator therapy. Kalydeco (ivacaftor) was the initial CFTR modulator and acts as a potentiator by binding to the CFTR protein and increasing the time the channel is in the open position. Later CFTR modulators all include correctors, which help the CFTR protein fold correctly and reach the cell surface. Orkambi combined ivacaftor with lumacaftor. Symdeko combines ivacaftor with tezacaftor. The main difference between Orkambi and Symdeko is drug to drug interactions. Trikafta is a triple combination CFTR modulator drug, adding a new component elexacaftor to ivacaftor and tezacaftor. Elexacaftor works in synergy with tezacaftor, resulting in greater correction of the defective CFTR and substantial clinical benefit.

III. POLICY

A. Initial authorization

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

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

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

3. The SCC or pharmacy submits a service authorization request (SAR) to DHCS or a CCS independent county requesting approval to treat the client's CFTR gene mutation using Kalydeco, Orkambi, Symdeko, or Trikafta.

4. Along with the SAR, the provider submits the following information,

   a. Notes from visit at CF special care center within the past 12 months, which include: pulmonary function status, measured by forced expiratory volume (FEV1), change in FEV1 prior to starting the prescribed CFTR modulator

treatment, any treatment or admissions for exacerbations within the past year, current weight/Body mass index and change in nutritional status in past year,

b. The client's CFTR drug therapy prescription.

c. The client's genetic lab results.

5. The choice of specific CFTR modulator is based on the client's age and genetic profile. In cases where CFTR modulators are considered equivalent, CCS will authorize the less costly medically-necessary treatment.

   a. Kalydeco is approved for clients over four months of age with responsive mutations.

   b. Symdeko is the preferred treatment for all clients 6-12 years of age with a genetic profile responsive to Kalydeco and Symdeko, unless the provider submits evidence that the response to Symdeko has been suboptimal.

   c. Orkambi is the preferred treatment for all clients 6-12 years of age with a genetic profile responsive to Orkambi and Symdeko, unless the provider submits evidence that the response to Orkambi has been suboptimal.

   d. Trikafta is the preferred treatment for all clients at least 12 years of age with a responsive mutation.

B. Reauthorization:

1. For CFTR drug therapy reauthorizations, SCCs should demonstrate medical necessity by providing documentation that the client has responded to the CFTR therapy with stable or improved pulmonary function, stable or 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. Additional considerations for medical necessity determination:

For clients who do not meet the criteria described in sections III.A. or III.B., SCCs may demonstrate medical necessity by submitting any other clinical documentation and/or evidence that would support the initial or reauthorization of the client's CFTR drug therapy. SCCs or pharmacies should submit this documentation to the Integrated Systems of Care Division (ISCD) Medical Director or designee.

D. Whole Child Model (WCM) Counties:

For CCS clients who are enrolled in a Medi-Cal managed care plan (MCP) and reside in a WCM county, the client's MCP shall be responsible for authorizing, coordinating, and covering CFTR drug therapies. MCPs operating in WCM counties should use the authorization guidelines described in this N.L., or utilize the MCP's existing CFTR drug therapy policies, whichever is less restrictive, until April 1, 2021.

IV. POLICY IMPLEMENTATION

A. CFTR drug therapies are not included in Service Code Grouping authorizations.[4] SCCs or pharmacies should submit a separate SAR and all supporting documentation in the following manner:

1. For clients residing in an independent county, SARs should be submitted to the CCS county office.

2. For clients residing in a dependent county, SARs should be submitted to ISCD via email at CCSExpeditedReview@dhcs.ca.gov, or via secure RightFax at (916) 440-5306.

3. For clients residing in a county covered by the WCM, SARs shall be submitted to, and processed by, the MCP until April 1, 2021.

B. Clients transitioning from CCS to GHPP

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

1. Direct clients to complete GHPP enrollment form (DHCS 4000A).[5]

2. Submit documentation that the client has responded to the CFTR therapy with stable or improved pulmonary function, stable or improved BMI, fewer symptoms, or fewer inpatient admissions to DHCS 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.

Beginning April 1, 2021, all requests for prior authorization of medications billed by NDC and dispensed by a Medi-Cal enrolled pharmacy provider, shall be sent to the Medi-Cal Rx vendor, Magellan Medicaid Administration, Inc. (Magellan). The Medi-Cal RX website provides guidance: https://medi-calrx.dhcs.ca.gov/home/.

Sincerely,

ORIGINAL SIGNED BY

Roy Schutzengel

Medical Director
Integrated Systems of Care Division

Attachment(s):

Attachment: CF Mutations Responsive to CFTR Modulator Therapy[6]

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[1] 22 Cal. Code Regs. § 41515.1 et. seq. Determination of Medical Eligibility
https://govt.westlaw.com/calregs/Document/I28E30090D4B811DE8879F88E8B0DAAAE?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=%28sc.Default%29
[2] 22 Cal. Code Regs. § 41700 Availability
https://govt.westlaw.com/calregs/Document/I2F1A7E70D4B811DE8879F88E8B0DAAAE?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=(sc.Default)&bhcp=1&ignorebhwarn=IgnoreWarns
[3] 22 Cal. Code Regs. § 41740 Eligibility for Treatment Services
https://govt.westlaw.com/calregs/Document/I2FDD8050D4B811DE8879F88E8B0DAAAE?viewType=FullText&originationContext=documenttoc&transitionType=StatuteNavigator&contextData=%28sc.Default%29
[4] Service Authorization Request Tools
https://www.dhcs.ca.gov/services/ccs/cmsnet/Pages/SARTools.aspx#service
[5] Genetically Handicapped Persons Program (GHPP) Application/Referral Form
https://www.dhcs.ca.gov/services/ghpp/Pages/Apply.aspx
[6] 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 six months and older who have one copy of the F508del protein processing mutation and at least 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 years and older who have two copies of the F508del protein processing mutation.

Symdeko (tezacaftor/ivacaftor and ivacaftor) is indicated for clients ages 6 years and older who have two copies of the F508del protein processing mutation or one F508del mutation and 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	

Trikafta (elexacaftor, tezacaftor and ivacaftor; ivacaftor) is indicated for clients ages 12 years and older who have at least one copy of the F508del mutation.

On December 21, 2020 the FDA approved new mutations that can be treated by each of the CFTR Modulator Therapy Drugs. The following is a listing of all the mutations approved for each drug.

List of CFTR Gene Mutations that are Responsive to Trikafta
(elexacaftor/tezacaftor/ivacaftor and ivacaftor)
Bolded mutations are approved effective 12/21/2020

Table 1: List of CFTR Gene Mutations That Are Responsive to Trikafta					
3141del9	***E822K***	***G1069R***	***L967S***	***R117L***	***S912L***
546insCTA	***F191V***	***G1244E***	***L997F***	***R117P***	***S945L***
A46D	***F311del***	***G1249R***	***L1077P***	***R170H***	***S977F***
A120T	***F311L***	***G1349D***	***L1324P***	***R258G***	***S1159F***
A234D	***F508C***	***H139R***	***L1335P***	***R334L***	***S1159P***
A349V	***F508C;S1251N***†	***H199Y***	***L1480P***	***R334Q***	***S1251N***
A455E	*F508del**	***H939R***	***M152V***	***R347H***	***S1255P***
A554E	***F575Y***	***H1054D***	***M265R***	***R347L***	***T338I***
A1006E	***F1016S***	***H1085P***	***M952I***	***R347P***	***T1036N***
A1067T	***F1052V***	***H1085R***	***M952T***	***R352Q***	***T1053I***
D110E	***F1074L***	***H1375P***	***M1101K***	***R352W***	***V201M***
D110H	***F1099L***	***I148T***	***P5L***	***R553Q***	***V232D***

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

D192G	***G27R***	***I175V***	***P67L***	***R668C***	***V456A***
D443Y	***G85E***	***I336K***	***P205S***	***R751L***	***V456F***
D443Y;G576A;R668C†	***G126D***	***I502T***	***P574H***	***R792G***	***V562I***
D579G	***G178E***	***I601F***	***Q98R***	***R933G***	***V754M***
D614G	***G178R***	***I618T***	***Q237E***	***R1066H***	***V1153E***
D836Y	***G194R***	***I807M***	***Q237H***	***R1070Q***	***V1240G***
D924N	***G194V***	***I980K***	***Q359R***	***R1070W***	***V1293G***
D979V	***G314E***	***I1027T***	***Q1291R***	***R1162L***	***W361R***
D1152H	***G463V***	***I1139V***	***R31L***	***R1283M***	***W1098C***
D1270N	***G480C***	***I1269N***	***R74Q***	***R1283S***	***W1282R***
E56K	***G551D***	***I1366N***	***R74W***	***S13F***	***Y109N***
E60K	***G551S***	***K1060T***	***R74W;D1270N†***	***S341P***	***Y161D***
E92K	***G576A***	***L15P***	***R74W;V201M†***	***S364P***	***Y161S***
E116K	***G576A;R668C†***	***L165S***	***R74W;V201M;D1270N†***	***S492F***	***Y563N***
E193K	***G622D***	***L206W***	***R75Q***	***S549N***	***Y1014C***
E403D	***G628R***	***L320V***	***R117C***	***S549R***	***Y1032C***
E474K	***G970D***	***L346P***	***R117G***	***S589N***	
E588V	***G1061R***	***L453S***	***R117H***	***S737F***	

**F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data [see Clinical Studies (14) in the TRIKAFTA full Prescribing Information (PI)].
†Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

List of CFTR Gene Mutations that are Responsive to Symdeko
(tezacaftor/ivacaftor and ivacaftor)
Bolded mutations are approved effective 12/21/2020

Table 2: List of CFTR Gene Mutations That Produce CFTR Protein and Are Responsive to Symdeko					
546insCTA	***E92K***	***G576A***	***L346P***	***R117G***	***S589N***
*711+3A→G**	***E116K***	***G576A;R668C†***	***L967S***	***R117H***	***S737F***
*2789+5G→A**	*E193K*	***G622D***	***L997F***	***R117L***	***S912L***
*3272-26A→G**	***E403D***	***G970D***	***L1324P***	***R117P***	*S945L**
*3849+10kbC→T**	***E588V***	***G1069R***	***L1335P***	***R170H***	*S977F**
A120T	***E822K***	***G1244E***	***L1480P***	***R258G***	***S1159F***
A234D	*E831X*	***G1249R***	***M152V***	***R334L***	***S1159P***
A349V	***F191V***	***G1349D***	***M265R***	***R334Q***	***S1251N***
*A455E**	***F311del***	***H939R***	***M952I***	*R347H**	***S1255P***
A554E	***F311L***	***H1054D***	***M952T***	***R347L***	***T338I***
A1006E	***F508C***	***H1375P***	***P5L***	***R347P***	***T1036N***
A1067T	***F508C;S1251N†***	***I148T***	*P67L**	*R352Q**	***T1053I***
D110E	*F508del^*	***I175V***	***P205S***	***R352W***	***V201M***
*D110H**	***F575Y***	***I336K***	***Q98R***	***R553Q***	***V232D***
D192G	***F1016S***	***I601F***	***Q237E***	***R668C***	***V562I***
D443Y	*F1052V*	***I618T***	***Q237H***	***R751L***	***V754M***
D443Y;G576A;R668C†	*F1074L*	***I807M***	***Q359R***	***R792G***	***V1153E***
*D579G**	***F1099L***	***I980K***	***Q1291R***	***R933G***	***V1240G***
D614G	***G126D***	***I1027T***	***R31L***	***R1066H***	***V1293G***

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

D836Y	***G178E***	***I1139V***	***R74Q***	***R1070Q***	***W1282R***
D924N	***G178R***	***I1269N***	*R74W*	*R1070W**	***Y109N***
D979V	***G194R***	***I1366N***	***R74W;D1270N***†	***R1162L***	***Y161S***
*D1152H**	***G194V***	*K1060T*	***R74W;V201M***†	***R1283M***	***Y1014C***
D1270N	***G314E***	***L15P***	***R74W;V201M;D1270N***†	***R1283S***	***Y1032C***
E56K	***G551D***	*L206W**	***R75Q***	***S549N***	
E60K	***G551S***	***L320V***	*R117C**	***S549R***	

*Clinical data for these mutations in Clinical Studies [see Clinical Studies (14.1 and 14.2) in the SYMDEKO full PI].
^A patient must have 2 copies of the *F508del* mutation or at least 1 copy of a responsive mutation presented in Table 2 to be indicated.
†Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

List of CFTR Gene Mutations that are Responsive to Kalydeco
(ivacaftor)
Bolded mutations are approved effective 12/21/2020

Table 3: List of CFTR Gene Mutations That Produce CFTR Protein and Are Responsive to Kalydeco

*711+3A→G**	***F311del***	***I148T***	***R75Q***	***S589N***
*2789+5G→A**	***F311L***	***I175V***	*R117C**	***S737F***
*3272-26A→G**	***F508C***	***I807M***	***R117G***	*S945L**
*3849+10kbC→T**	***F508C;S1251N***†	***I1027T***	*R117H**	*S977F**
A120T	*F1052V*	***I1139V***	***R117L***	***S1159F***
A234D	*F1074L*	*K1060T*	***R117P***	***S1159P***
A349V	***G178E***	*L206W**	***R170H***	*S1251N**
*A455E**	*G178R**	***L320V***	*R347H**	*S1255P**
A1067T	***G194R***	***L967S***	***R347L***	***T338I***
D110E	***G314E***	***L997F***	*R352Q**	***T1053I***
D110H	*G551D**	***L1480P***	***R553Q***	***V232D***
D192G	*G551S**	***M152V***	***R668C***	***V562I***
*D579G**	***G576A***	***M952I***	***R792G***	***V754M***
D924N	***G970D***	***M952T***	***R933G***	***V1293G***
*D1152H**	*G1069R*	*P67L**	*R1070Q*	***W1282R***
D1270N	*G1244E**	***Q237E***	*R1070W**	***Y1014C***
E56K	***G1249R***	***Q237H***	***R1162L***	***Y1032C***
E193K	*G1349D**	***Q359R***	***R1283M***	
E822K	***H939R***	***Q1291R***	*S549N**	
*E831X**	***H1375P***	*R74W*	*S549R**	

*Clinical data exist for these mutations [see Clinical Studies (14) in the KALYDECO full PI].
†Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.