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Index: Benefits

TO: ALL COUNTY CALIFORNIA CHILDREN SERVICES (CCS) PROGRAM ADMINISTRATORS, MEDICAL CONSULTANTS, STATE INTEGRATED SYSTEMS OF CARE DIVISION STAFF AND GENETICALLY HANDICAPPED PERSONS PROGRAM (GHPP)

SUBJECT: IVACAFTOR (KALYDECO™) - EXPANDED INDICATION FOR USE – UPDATED

## I. PURPOSE

The purpose of this updated Numbered Letter (N.L.) is to modify the CCS Program and GHPP policy regarding the authorization of Ivacaftor as a treatment for cystic fibrosis (CF) due to gating mutations in the CF transmembrane conductance regulator (CFTR) genes. Ivacaftor is the first of a new class of drugs known as CFTR potentiators, and has been associated with significant clinical improvement in individuals that have a CFTR gating mutation in at least one allele. Previous indications for ivacaftor were gating mutations G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R with treatment age of six years or older. Later, the indication for Ivacaftor expanded to include mutation R117H and reduced the minimum age to two years. In May 2017, twenty-three additional gene mutations were approved for treatment with Ivacaftor. On July 31, 2017, the indication for ivacaftor was expanded to include 5 additional mutations.

## II. BACKGROUND

CF is a life-threatening autosomal recessive genetic disease affecting respiratory and digestive systems. In California, CF is found in all race/ethnic groups at a prevalence of around 1/3,500 in non-Hispanic whites, 1/7,900 in Hispanic whites, 1/8,000 in non-Hispanic blacks, and 1/23,500 in Asians and others. CF is caused by a defective gene for the CFTR. A defective CFTR results in decreased secretion of chloride and increased reabsorption of sodium and water across epithelial cells. This leads to viscous (sticky) secretions, which are harder to clear and increase

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 prevention of infection. Ivacaftor, on the other hand, targets the pathology of the disease. In individuals with one of the CFTR gating mutations listed above (2-5 percent of those with CF), ivacaftor binds to the defective receptor, and facilitates passage of chloride ions across the defective CFTR, normalizing the secretions. Ivacaftor efficacy for the G551D mutation over a 48-week period was demonstrated in a Phase III trial of individuals 12 years and older, in which there were 55 percent fewer exacerbations, pulmonary lung function scores (FEV1) improvement by an average of 10 percent, and better quality of life. Additional trials extending this study to 60 weeks, and with children ages 6-11, found sustained improvement in lung function. On January 31, 2012, the Food and Drug Administration (FDA) approved ivacaftor for use in persons age six and over with CF who have the G551D mutation. The recommended dose is 150 mg every 12 hours for adult and pediatric (six years and older) patients.

In February 2014, ivacaftor was approved by the FDA for expanded use for G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutations (occurring in less than 1 percent of CF patients), based on an 8-week Phase III clinical trial showing improvement in lung function as determined by the mean absolute change from baseline FEV1.

In December 2014, the FDA approved use for patients with the R117H mutation and lowered the age limit to two years.

On May 17, 2017, the approved use of ivacaftor was expanded to include twenty-three additional mutations. The decision was based partly on the results of laboratory testing of 54 rare mutations, in conjunction with, clinical evidence from earlier trials.

On July 31, 2017, ivacaftor was approved for use in patients two years and over with one of these five mutations (2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G, and E831X) that result in a splicing defect in the CF transmembrane conductance regulator (CFTR) gene.

### III. POLICY

Effective the date of this letter, ivacaftor is a CCS Program/GHPP benefit when:

- A. Prescribed by a physician at a CCS Program/GHPP approved pulmonology special care center, and;

B. For a CCS Program/GHPP client with CF and a CFTR gating mutation in at least one allele as follows:

CFTR Mutations Treated with Kalydeco™								
FDA Approved January 31, 2012	G551D							
FDA Approved February 21, 2014	G1244E	G1349D	G178R	G551S	S1251N	S1255P	S549N	S549R
FDA Approved December 29, 2014	R117H							
FDA Approved May 17, 2017	A1067T	A455E	D110E	D110H	D1152H	D1270N	D579G	E193K
FDA Approved May 17, 2017	E56K	F1052V	F1074L	G1069R	K1060T	L206W	P67L	R1070Q
FDA Approved May 17, 2017	R1070W	R117C	R347H	R352Q	R74W	S945L	S977F	
FDA Approved July 31, 2017	<b>2789+5G→A</b>	<b>3272-26A→G</b>	<b>3849+10kbC→T</b>	<b>711+3A→G</b>	E831X			

C. And whose care is under the supervision and monitoring of a CCS Program/GHPP approved CF and Pulmonology Center.

#### IV. POLICY IMPLEMENTATION

- A. Ivacaftor (Kalydeco™) requires separate authorization.
- B. All requests shall be reviewed by a local county CCS program Medical Director or designee before authorization of ivacaftor.

C. Initial Authorization:

1. Shall be for a 6-month trial.
2. Prior to authorization, documentation must be submitted showing positive genetic test for CFTR mutations identified in the above table, using a testing method that can detect the mutation.
3. Dosage to follow FDA approved guidance as outlined in the Kalydeco™ package insert.
4. Baseline levels of at least two of the following are required:
  - a. FEV1;
  - b. Sweat chloride if available;
  - c. Symptom record;
  - d. Weight/nutritional status/BMI.

D. Extension of the initial authorization shall be granted when:

1. Documentation is submitted by the CCS Program/GHPP approved pulmonary special care center consistent with clinical response in at least one domain :
  - a. FEV1;
  - b. Sweat chloride (reduction from baseline);
  - c. Symptom Record;
  - d. Weight/BMI.
2. Extensions shall be for a twelve month period or until program eligibility end date, whichever is shorter.

E. The following shall be considered when reviewing requests for ivacaftor:

1. Ivacaftor is not effective in individuals with two copies of the F508del CFTR mutation (i.e., F508del/F508del).
2. Ivacaftor is not a replacement for conventional adjunctive therapy.

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F. Integrated Systems of Care Division (ISCD) Medical Director or designee will review exceptions on a case-by-case basis.

If you have any questions regarding this N.L., please contact Edan Lum, Pharm D., by telephone at (916) 327-2399 or (415) 557-0222 or via e-mail at [edan.lum@dhcs.ca.gov](mailto:edan.lum@dhcs.ca.gov).

Sincerely,

**ORIGINAL SIGNED BY**

Jacey Cooper, Acting Division Chief  
Integrated Systems of Care Division