VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Kalydeco® (ivacaftor tablets and oral granules – Vertex)

TAC APPROVAL DATE: 03/27/2019; selected revision 05/08/2019

OVERVIEW

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of cystic fibrosis (CF) in patients ≥ 6 months of age who have who have one mutation in the CFTR gene that is responsive to Kalydeco potentiation based on clinical and/or *in vitro* assay data. Mutations with an increase in chloride transport of 10% or greater are considered responsive.[1] In patients with unknown genotype, a FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use. Kalydeco is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR.[1] A patient must have at least one CFTR mutation responsive to ivacaftor to be indicated. Table 1 lists mutations that are responsive to Kalydeco based on 1) a positive clinical response and/or 2) *in vitro* data in FRT cells indicating that Kalydeco increases chloride transport to ≥ 10% over baseline (% of normal).

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco.[1]

E56K	*G178R*	*S549R*	*K1060T*	*G1244E*
P67L	*E193K*	*G551D*	*A1067T*	*S1251N*
R74W	*L206W*	*G551S*	*G1069R*	*S1255P*
D110E	*R347H*	*D579G*	*R1070Q*	*D1270N*
D11OH	*R352Q*	*S945L*	*R1070W*	*G1349D*
R117C	*A455E*	*S977F*	*F1074L*	*2789+5G—>A*
R117H	*S549N*	*F1052V*	*D1152H*	*3272-26A—>G*
3849+10kbC—>T	*711+3A—>G*	*E831X*		

CFTR – Cystic fibrosis transmembrane regulator.

Disease Overview

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Kalydeco facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.[1] More than 1,800 disease-associated changes or mutations have been identified in the CFTR gene.[2] According to the CF patient registry (2017) about 45.3% of patients have two copies of the F508del (Delta F508) mutation; about 40.9% of patients with CF have one F508del mutation; 13.7% of patients do not have an F508del mutation or it is unknown if they have such a mutation.[2,5]

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF.[3] For patients ≥ 6 years of age with CF due to a gating mutation other than G551D or R117H (e.g., G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1249D), the Guidelines make a conditional recommendation for treatment with Kalydeco. For those with the R117H mutation, the Guideline panel make a conditional recommendation for treatment with Kalydeco for adults (≥ 18 years) of age and for children (6 to 17 years of age) with a ppFEV1 < 90%. For patients with R117H mutation, the Guidelines recommend against treatment with Kalydeco for children 12 to 17 years of age with ppFEV1 > 90% and in children < 6 years of age. Among patients who are homozygous for F508del, the guidelines make a strong recommendation for treatment with Orkambi (lumacaftor/ivacaftor tablets and

oral granules) in adults and children ≥ 12 years of age with ppFEV1 < 90%; and make a conditional recommendation for treatment with Orkambi in adults and children ≥ 12 years of age with ppFEV1 > 90% and for children 6 to 11 years of age.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kalydeco. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kalydeco as well as the monitoring required for adverse events and efficacy, approval requires Kalydeco to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years unless otherwise noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kalydeco is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cystic Fibrosis (CF).** Approve Kalydeco for 3 years in patients who meet the following criteria A, B, and C:
   - **A)** The patient has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, 2789+5G—>A, 3272-26A—>G, 3849+10kbC—>T, 711+3A—>G, E831X, OR R117H; AND
   - **B)** The patient is ≥ 6 months of age; AND
   - **C)** Kalydeco is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis (CF).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kalydeco has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Cystic Fibrosis (CF), Patients who are Homozygous for the phe508del (F508del) Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene.** Efficacy results from a double-blind, placebo controlled trial in patients with CF who were homozygous for the phe508del mutation in the CFTR gene showed no statistically significant difference in FEV_1 over 16 weeks of Kalydeco treatment compared with placebo.[1] In a Phase II trial in patients homozygous for the F508del (n = 112) Kalydeco did not result in an improvement in FEV_1 relative to placebo.[4]

2. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** A Food and Drug Administration (FDA)-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Kalydeco.[1]

3. **Combination Therapy with Orkambi or Symdeko.** Orkambi and Symdeko contain ivacaftor, the active agent in Kalydeco and therefore are not indicated in combination with Kalydeco.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kalydeco® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; April 2019.
2. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153:S4-S14.
3. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis trasmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280
4. Flume PA, Liou TG, Borowitz DS, et al; VX08-770-104 Study Group. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. 2012;142(3):718-724.
5. Cystic Fibrosis Foundation. Patient registry. Annual data report of the center directors, 2017. Available at: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf.. Accessed on March 19, 2019.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Integrated policy		02/06/2013
Annual revision	New FDA-approved indication added gating mutations other than G5551D. Exclusion for these other gating mutations was removed.	02/26/2014
Selected revision	Approvals changed from 12 months to 3 years	09/03/2014
Selected revision	New FDA-approved indication added for R117H mutation. Removed verbiage about gating mutations.	01/07/2015
Annual revision	No criteria changes.	03/11/2015
Selected revision	To add Kalydeco granules	04/01/2015
Selected revision	Age requirement for patients to be ≥ 2 years of age added to approval criteria. Specialty prescribing physician added to approval indication. Combination use with Orkambi added to conditions not recommended for approval.	07/01/2015
Annual revision	No criteria changes	03/16/2016
Annual revision	No criteria changes	03/08/2017
Selected revision	Update to criteria based on new FDA approved mutation types.	05/24/2017
Selected revision	Update to criteria based on new FDA approved mutation types.	08/09/2017
Annual revision	Added concomitant use with Symdeko to conditions not recommended for approval.	03/07/2018
Selected revision	Update to criteria based on new FDA approved age indication to ≥ 12 months.	08/22/2018
Annual revision	No criteria changes	03/27/2019
Selected revision	Cystic Fibrosis (CF) approval criteria updated to reflect the new FDA indication to ≥ 6 months of age.	05/08/2019

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; FDA – Food and Drug Administration.