PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Kalydeco Prior Authorization Policy
- Kalydeco® (ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 02/08/2023

OVERVIEW

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of **cystic fibrosis (CF)** in patients ≥ 4 months of age who have one mutation in the CFTR gene that is responsive to Kalydeco potentiation based on clinical and/or in vitro assay data.[1]

Mutations with an increase in chloride transport of ≥ 10% are considered responsive. 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. A patient must have at least one CFTR mutation responsive to Kalydeco 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 Fischer rat thyroid 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]

2789+5G—>A	*F311del*	*I148T*	*R75Q*	*S549N*
3272-26A—>G	*F311L*	*I175V*	*R1070Q*	*S549R*
3849+10kbC—>T	*F508C*	*I807M*	*R1070W*	*S945L*
711+3A—>G	*F508C;S1251N*	*I1027T*	*R117C*	*S977F*
A120T	*F1052V*	*I1139V*	*R117H*	*S589N*
A234D	*F1074L*	*K1060T*	*R347H*	*S737F*
A349V	*G1069R*	*L206W*	*R352Q*	*S1159F*
A1067T	*G1244E*	*L320V*	*R117G*	*S1159P*
A455E	*G1349D*	*L967S*	*R117L*	*T338I*
D110E	*G178R*	*L997F*	*R117P*	*T1053I*
D1152H	*G551D*	*L1480P*	*R170H*	*V232D*
D11OH	*G551S*	*M152V*	*R347L*	*V562I*
D192G	*G194R*	*M9521*	*R553Q*	*V754M*
D1270N	*G314E*	*M952T*	*R668C*	*V1293G*
D924N	*G576A*	*P67L*	*R792G*	*W1282R*
D579G	*G970D*	*Q237E*	*R933G*	*Y1014C*
E193K	*Y1032C*	*Q237H*	*R1162L*	*G178E*
E882K	*G1249R*	*Q359R*	*R1283M*	
E56K	*H939R*	*Q1291R*	*S1251N*	
E831X	*H1375P*	*R74W*	*S1255P*	

CFTR – Cystic fibrosis transmembrane regulator.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF. Symdeko and Trikafta are not addressed and neither is the lower pediatric age indication for Kalydeco.[2] For adults ≥ 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 made a conditional recommendation for treatment with Kalydeco for adults ≥ 18 years of age and for children 6 to 17 years of age with a percent predicted forced expiratory volume in 1 second (ppFEV1) <

90%. For individuals with R117H mutation, the guidelines recommend against treatment with Kalydeco for children 12 to 17 years of age with a (ppFEV1) > 90% and in children < 6 years of age.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kalydeco. All approvals are provided for the duration noted below. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Cystic Fibrosis.** Approve for 1 year in patients who meet the following criteria (A, B, and C):
   - **A)** Patient is ≥ 4 months of age; AND
   - **B)** Patient has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator 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, R117H, A120T, A234D, A349V, D192G, D924N, E882K, F311L, F311delF508C, F508C;S1251N, G178E, G194R, G314E, G576A, G970D, G1249R, H939R, H1375P, I148T, I175V, I807M, I1027T, I1139V, L320V, L967S, L997F, L1480P, M152V, M9521, M952T, Q237E, Q237H, Q359R, Q1291R, R75Q, R117G, R117L, R117P, R170H, R347L, R553Q, R668C, R792G, R933G, R1162L, R1283M, S589N, S737F, S1159F, S1159P, T338I, T1053I, V232D, V562I, V754M, V1293G, W1282R, Y1014C, or Y1032C; AND
   - **C)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalydeco is not recommended in the following situations:

1. **Cystic Fibrosis (CF), Patients who are Homozygous for the phe508del (F508del) Mutation in the Cystic Fibrosis Transmembrane Regulator 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 forced expiratory volume in 1 second (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.[3]

2. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the cystic fibrosis transmembrane regulator mutation prior to use of Kalydeco.[1]

3. **Combination Therapy with Orkambi, Symdeko, or Trikafta.** Orkambi, Symdeko, and Trikafta 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; December 2020.
2. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
3. 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.