

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Kalydeco Prior Authorization Policy

- Kalydeco® (ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 02/03/2021

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 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% or greater 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 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 $\geq 10\%$ 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
D110H	G551S	M152V	R347L	V562I
D192G	G194R	M952I	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 ppFEV1 $< 90\%$. For individuals with R117H mutation, the Guidelines

recommend against treatment with Kalydeco for children 12 to 17 years of age with a percent predicted forced expiratory volume in 1 second (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 3 years. 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 (CF).** Approve Kalydeco for 3 years 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 (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, 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, M952I, 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 CF.

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 (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 FEV₁ 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 FEV₁ relative to placebo.³
 2. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Kalydeco.¹
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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 Pharmaceuticals, Inc; 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
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
Selected Revision	Combination Therapy with Orkambi or Symdeko: Trikafta was added to this indication not recommended for approval.	10/23/2019
Annual Revision	No criteria changes	03/25/2020
Selected Revision	Cystic Fibrosis (CF) approval criteria updated to reflect the new FDA indication to ≥ 4 months of age.	09/30/2020
Selected Revision	Cystic Fibrosis (CF): Added additional mutations to criteria for coverage (A120T, A234D, A349V, D192G, D924N, E882K, F311delF508C, F508C;S1251N, G194R, G314E, G576A, G970D, G1244E, G1249R, H939R, H1375P, I148T, I175V, I807M, I1027T, I1139V, L320V, L967S, L997F, L1480P, M152V, M952I, M952T, Q237E, Q237H, Q359R, Q1291R, R75Q, R117G, R117L, R117P, R170H, R347L, R553Q, R668C, R792G, R933G, R1162L, R1283M, S589N, S737F, S1159F, S1159P, T3381, T1053I, V232D, V562I, V754M, V1293G, W1282R, Y1014C, or Y1032C).	01/06/2021
Annual Revision	Cystic Fibrosis (CF): F311L and G178E were added to the list of approvable mutations. T3381, T1053I, and V562I were amended to: T338I, T1035I, and V562I.	02/03/2021