Drug Coverage Policy

Effective Date 7/15/2024
Coverage Policy Number.....IP0431
Title.....Kalydeco

Cystic Fibrosis – Kalydeco

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

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Cigna Healthcare Coverage Policy

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of **cystic fibrosis (CF)** in patients ≥ 1 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]

In patients with unknown genotype, an 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.[1] 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 (tezacaftor/ivacaftor and ivacaftor tablets) and Trikafta (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged and elexacaftor/tezacaftor/ivacaftor oral granules; ivacaftor oral granules) are not addressed and neither is the lower pediatric age indication for Kalydeco.[2] 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 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.

Medical Necessity Criteria

Ivacaftor (Kalydeco) is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year in patients who meet the following (A, B, C, D, E and F):
   A) Patient is ≥ 1 month of age; AND

B) Patient has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator gene that is considered to be a pathogenic or likely pathogenic variant: 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) Patient meets at least ONE of the following (i, ii, or iii):
- **i.** Positive cystic fibrosis newborn screening test; OR
- **ii.** Family history of cystic fibrosis; OR
- **iii.** Clinical presentation consistent with signs and symptoms of cystic fibrosis; AND
  Note: Examples of clinical presentation of cystic fibrosis include but are not limited to meconium ileus, sino-pulmonary symptoms (e.g., persistent cough, wheezing, pulmonary function tests consistent with obstructive airway disease, excess sputum production), bronchiectasis, sinusitis, failure to thrive, pancreatic insufficiency.

D) Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):
- **i.** Elevated sweat chloride test; OR
- **ii.** Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations; OR
- **iii.** Abnormal nasal potential difference; AND

E) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

F) Preferred product criteria is met for the products listed in the below table(s)

Employer Plans:

Product	Criteria
Kalydeco (ivacaftor tablets and oral granules)	**Total Savings Drug List Plans:** **ONE** of the following: A. Failure, contraindication, or is intolerant to elexacaftor/tezacaftor/ivacaftor (Trikafta™) B. Patient is less than 2 years of age C. Approve if the patient has at least one of the following mutations in the cystic fibrosis transmembrane regulator (CFTR) gene: 2789+5G › A, 3272-26A › G, 3849+10kbC › T, 711+3A › G, OR E831X. D. Individual has previously been started on, or is currently receiving Kalydeco

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Cystic Fibrosis (CF), Patient Homozygous for the 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. **Infertility.** Kalydeco is indicated for the treatment of cystic fibrosis in a patient ≥ 1 month of age who has one mutation in the cystic fibrosis transmembrane regulator gene that is responsive to Kalydeco based on clinical and/or *in vitro* assay data.[1] Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

References

1. Kalydeco® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; August 2023.
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.
4. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr*. 2017;181S:S4-S15.
5. Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. *J Pediatr.* 2017;181S:S33-S44.

Type of Revision	Summary of Changes	Date
Annual Review	**Cystic Fibrosis**: Removed Documented diagnosis of cystic fibrosis (CF) [i.e., a clinical presentation consistent with signs/symptoms of CF, a positive CF newborn screening test, or family history of CF AND evidence of abnormal CFTR function (as demonstrated by elevated sweat chloride, detection	5/1/2024

	of two CF-causing CFTR mutations, or abnormal nasal potential differences)] **Conditions Not Covered**: Removed CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis) and CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID) **Preferred Product Criteria**: Added approve if the patient has at least one of the following mutations in the cystic fibrosis transmembrane regulator (CFTR) gene: 2789+5G › A, 3272-26A › G, 3849+10kbC › T, 711+3A › G, OR E831X.	
Selected Revision	**Cystic Fibrosis (CF):** The criterion that the patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene, was modified to require that the mutation be considered pathogenic or likely pathogenic. A criterion was added to require that the patient has at least one of the following: positive cystic fibrosis newborn screening test, family history of cystic fibrosis, or a clinical presentation consistent with signs and symptoms of cystic fibrosis. A criterion was added to require that the patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least one of the following: elevated sweat chloride test, two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations, or an abnormal nasal potential difference. **Cystic Fibrosis (CF), Patient Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Regulator Gene.** Reference to Phe508del was removed from this condition not recommended for approval (this is the same as F508del). **Infertility:** This indication was added to conditions not recommended for approval. **Preferred Product Table.** Remove IFP preferred product table.	7/15/2024