



PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis Transmembrane Conductance Regulator – Kalydeco Prior Authorization Policy

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

REVIEW DATE: 02/05/2025

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of **cystic fibrosis (CF)** in patients ≥ 1 month of age who have one mutation in the CFTR gene that is responsive to Kalydeco 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 gene. 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 $\geq 10\%$ 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 conductance regulator.

Guidelines

The most current treatment recommendations are the Standards of Care for CFTR variant-specific therapy for people with CF, from the European Cystic Fibrosis Society (2023).² However, the Standards do not reflect the currently approved age indications for Kalydeco (≥ 1 months of age), Orkambi® (lumacaftor/ivacaftor tablets and oral granules) [≥ 1 year of age], or Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and oral granules) [≥ 2 years of age]. In general, Trikafta is recommended over other agents where indications overlap. The Standards recommend Trikafta in patients ≥ 6 years of age with CF who are homozygous or heterozygous for F508del. In patients with one or more responsive non-F508del variant, Kalydeco, Symdeko® (tezacaftor/ivacaftor; ivacaftor tablets), or Trikafta are recommended. Kalydeco is recommended in patients ≥ 4 months of age with eligible CFTR gene variants. Orkambi is recommended for patients 2 to 5 years of age who are homozygous for F508del. Of note, the Standards state that after diagnosis, repeat sweat testing provides evidence of treatment effect on CFTR activity, but does not predict clinical response. The European Cystic Fibrosis Society Standards for establishing and maintaining health (2024) note that people with CF with eligible CFTR gene variants should be offered CFTR modulator therapy.⁶

According to the CF Foundation (2017), CF is diagnosed when an individual has both a clinical presentation of CF and evidence of CFTR dysfunction.^{4,5} Clinical presentation of CF includes a positive newborn screening, signs and/or symptoms of CF, and/or family history of CF. To establish a diagnosis of CF, sweat chloride tests should be considered first, then CFTR genetic analysis (CFTR genotype), and then CFTR physiologic tests (nasal potential difference [NPD] or intestinal current measurement [ICM]). However, tests of CFTR function are not always done in this order. All individuals diagnosed with CF should have a sweat chloride test and CFTR genetic analysis performed.

In a patient with a sweat chloride test ≥ 60 mmol/L, CF diagnosis is established and in patients with a sweat chloride test < 30 mmol/L, a diagnosis of CF is unlikely.^{4,5}

Rarely, patients with a sweat chloride < 30 mmol/L may be considered to have CF if alternatives are excluded and other confirmatory tests (genetic and physiologic testing) support a CF diagnosis. In patients with a sweat chloride test of ≥ 30 to < 60 mmol/L, CFTR genetic analysis is undertaken. If the genetic analysis identifies two CF-causing CFTR mutations, CF is diagnosed; if no CFTR mutations are identified, a diagnosis of CF is unlikely. In patients with a CFTR genotype that is undefined or of varying clinical consequence, full gene CFTR sequencing (if not already performed) or CFTR physiologic testing is performed (NPD or ICM). If only one CFTR variant is identified on limited analysis, full gene CFTR sequencing should be performed. CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence mutations; CF is unlikely if only no CF-causing mutations are found. If results of the NPD or ICM show CFTR dysfunction, CF is diagnosed; when testing is unavailable or equivocal, the diagnosis of CF is not resolved, and when results of the physiologic testing show CFTR function is preserved, a diagnosis of CF is considered unlikely. It is recommended that patients with challenging diagnoses be evaluated at an accredited CF Foundation Care Center.

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.

• Kalydeco® (ivacaftor tablets and oral granules – Vertex)
is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. Cystic Fibrosis. Approve for 1 year if the patient meets ALL of the following (A, B, C, D and E):

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, F311del, F508C, 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) 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.

CONDITIONS NOT COVERED

• **Kalydeco® (ivacaftor tablets and oral granules – Vertex)**
is(are) considered experimental, investigational or unproven for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. Cystic Fibrosis, Patient Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene. Efficacy results from a double-blind, placebo controlled trial in patients with cystic fibrosis who were homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator gene showed no statistically significant difference in forced expiratory volume in 1 second (FEV₁) over 16 weeks of Kalydeco treatment compared with placebo.¹ In a Phase II trial in patients homozygous for the F508del mutation (n = 112), Kalydeco did not result in an improvement in FEV₁ relative to placebo.³

2. Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation. An FDA-cleared cystic fibrosis mutation test should be used to detect the presence of the cystic fibrosis transmembrane conductance regulator mutation prior to use of Kalydeco.¹

3. Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s). Orkambi® (lumacaftor/ivacaftor tablets

and oral granules), Symdeko® (tezacaftor/ivacaftor; ivacaftor tablets), and Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and oral granules) contain ivacaftor, the active agent in Kalydeco and therefore use of these agents is not indicated in combination with Kalydeco.

Note: Examples of other cystic fibrosis transmembrane conductance regulator modulators are: Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets), Orkambi (lumacaftor/ivacaftor tablets and oral granules), Symdeko (tezacaftor/ivacaftor; ivacaftor tablets), Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and oral granules).

- 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 conductance 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. Southern KW, Castellani C, Lammertyn E, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *J Cyst Fibros.* 2023;17-30.
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.
6. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. *J Cyst Fibros.* 2024;21-28.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/08/2023
Selected Revision	Cystic Fibrosis (CF): Approval age was changed to ≥ 1 month of age, based on new indication; previously approval age was ≥ 4 months of age.	05/10/2023
Annual Revision	No criteria changes.	02/07/2024
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	04/10/2024

	<p>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.</p> <p>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).</p> <p>Infertility: This indication was added to Conditions Not Covered.</p>	
Selected Revision	<p>The Policy title was changed to Cystic Fibrosis Transmembrane Conductance Regulator – Kalydeco PA Policy. Previously, Cystic Fibrosis – Kalydeco PA Policy.</p> <p>Conditions Not Covered</p> <p>Cystic Fibrosis, Patient Homozygous for the F508del Mutation in the Cystic Fibrosis Transmembrane Conductance Regulator Gene. "Conductance" was added to the verbiage for this condition not recommended for approval.</p> <p>Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation. "Conductance" was added to the verbiage for this condition not recommended for approval.</p> <p>Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s). This condition not recommended for approval was modified to refer to the class of cystic fibrosis transmembrane conductance regulator modulator(s). Previously individual agents were listed. A Note was added to list examples of the cystic fibrosis transmembrane conductance regulators.</p>	01/02/2025
Annual Revision	No criteria changes.	02/05/2025

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