Drug Coverage Policy

Effective Date.....4/1/2025
Coverage Policy Number.....IP0431
Policy Title.....Kalydeco

Cystic Fibrosis Transmembrane Conductance Regulator – Kalydeco

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

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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 ≥ 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 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 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 CF. 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.

Coverage Policy

POLICY STATEMENT
Prior Authorization is required 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.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, and/or other information.

Ivacaftor (Kalydeco) is considered medically necessary when the following criteria 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)** Documentation is provided that the 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

Employer Plans:

Product	Criteria
Kalydeco (ivacaftor tablets and oral granules)	**Total Savings Drug List Plans:** **ONE** of the following: 1. Patient is ≥ 2 years of age AND the patient meets ONE of the following (a or b): a. Patient has tried, and according to the prescriber has experienced inadequate efficacy OR a significant intolerance with Trikafta (tablets or oral granules) [may require prior authorization] b. Patient has at least one mutation in the cystic fibrosis transmembrane conductance regulator gene that is considered to be a pathogenic or likely pathogenic variant that is not covered by Trikafta (tablets or oral granules) [may require prior authorization] 2. Patient is < 2 years of age 3. Patient has already been started on therapy with 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.

Ivacaftor (Kalydeco) for any other use is considered not medically necessary, 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 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, Patients with Unknown Cystic Fibrosis Transmembrane Conductance 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 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 tablets and oral granules) contain ivacaftor, the active agent in Kalydeco and therefore are 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 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 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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**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
Selected Revision	The Policy title was changed to Cystic Fibrosis Transmembrane Conductance Regulator – Kalydeco. Previously, Cystic Fibrosis – Kalydeco. **Added "<u>Documentation</u>: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, and/or other information."**	4/1/2025

	Cystic Fibrosis: **Updated** criteria **from** "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:" **to** "Documentation is provided that the 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:" **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 covered. **Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation.** "Conductance" was added to the verbiage for this condition not covered. **Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s).** This condition not covered 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. **Preferred Product Table:** **Added** "Patient is ≥ 2 years of age AND the patient meets ONE of the following (a or b):" **Updated from** "Failure, contraindication, or intolerance with to elexacaftor/tezacaftor /ivacaftor (Trikafta™)" **to** "Patient has tried, and according to the prescriber has experienced inadequate efficacy OR a significant intolerance with Trikafta (tablets or oral granules) [may require prior authorization]" **Added** "Patient has at least one mutation in the cystic fibrosis transmembrane conductance regulator gene that is considered to be a pathogenic or likely pathogenic variant that is not covered by Trikafta (tablets or oral granules) [may require prior authorization]." **Updated from** "Individual has previously been started on, or is currently receiving Kalydeco" **to** "Patient has already been started on therapy with Kalydeco." **Removed** "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.”	

The policy effective date is in force until updated or retired.