Effective Date **7/1/2023**
Next Review Date… **7/1/2024**
Coverage Policy Number **IP0431**

Ivacaftor (Kalydeco®)

Table of Contents

Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions
Pharmacogenetic Testing

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. 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

This policy supports medical necessity review for ivacaftor tablets and oral granules (**Kalydeco®**).

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

Medical Necessity Criteria

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

1. **Cystic Fibrosis (CF).** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
   A. Individual is 1 month of age or older
   B. 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 of two CF-causing CFTR mutations, or abnormal nasal potential differences)] [Appendix]

C. Documentation that the individual has at least **ONE** pathogenic or likely pathogenic variant in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor (Kalydeco) as defined in the FDA product information (label) [Refer to Table 1]
D. The medication is prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis
E. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Cigna Total Savings and Individual and Family Plans].

Coverage varies across plans and requires the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Employer Group Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Kalydeco (ivacaftor tablets and oral granules)	**Cigna Total Savings Drug List Plans:** There is documentation of **ONE** of the following (A, B, or C): A. The individual has had an inadequate response, contraindication, or is intolerant to elexacaftor/tezacaftor/ivacaftor (Trikafta™) B. Individual is less than 2 years of age C. Individual has previously been started on, or is currently receiving Kalydeco

Individual and Family Plans Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Kalydeco (ivacaftor tablets and oral granules)	There is documentation of **ONE** of the following (A, B, or C): A. The individual has had an inadequate response, contraindication, or is intolerant to elexacaftor/tezacaftor/ivacaftor (Trikafta™) B. Individual is less than 2 years of age C. 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.

Reauthorization Criteria

Ivacaftor (Kalydeco) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Examples of beneficial response include:

For individuals who already have measureable lung disease or end organ involvement: there is improvement in, stabilization of, or a decrease in the rate of decline of FEV1; reduced number of pulmonary exacerbations; improvement in body mass index (BMI); or improvement on the patient reported Cystic Fibrosis Questionnaire-Revised respiratory domain score

For individuals who are previously asymptomatic, or have mild clinical manifestations: there is no evidence of clinical decline

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

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) Individuals who are Homozygous for the phe508del (F508del) Variant 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 variant in the CFTR gene showed no statistically significant difference in forced expiratory volume in 1 second 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) Individuals with Unknown Cystic Fibrosis Transmembrane Regulator Gene Variant.** An FDA-cleared CF mutation test should be used to detect the presence of the cystic fibrosis transmembrane regulator variant 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. **CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis).**

5. **CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID).**

Background

OVERVIEW
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, 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.[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 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.

Appendix

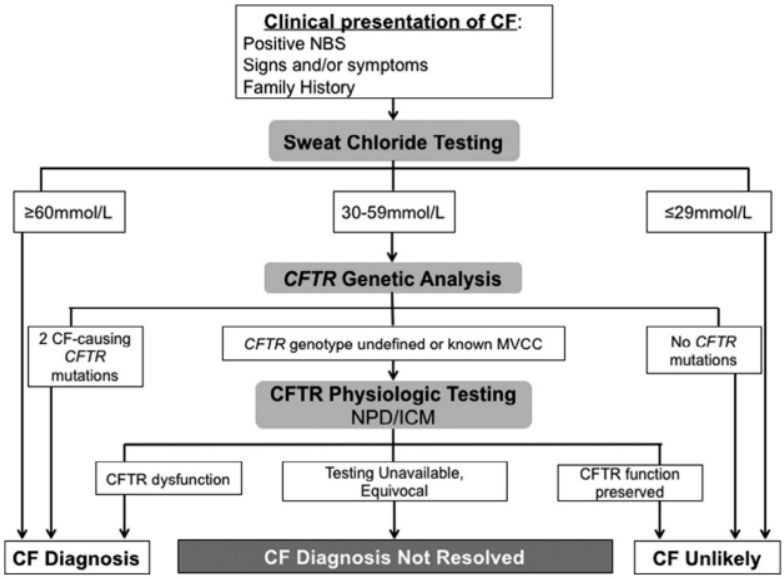

Figure. CF is diagnosed when an individual has both a clinical presentation of the disease and evidence of CFTR dysfunction. The tests of CFTR function are not always done in this order, but hierarchically to establish the diagnosis of CF, sweat chloride should be considered first, then *CFTR* genetic analysis, and then CFTR physiologic tests. All individuals diagnosed with CF should have a sweat test and a *CFTR* genetic analysis performed. Rare individuals with a sweat chloride <30 mmol/L may be considered to have CF if alternatives are excluded and the other confirmatory tests (genetic, physiologic testing) support CF. If only 1 *CFTR* variant is identified on limited analysis, further ("extended") *CFTR* testing should be performed.[22] CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence (MVCC) mutations; CF is unlikely if only non-CF-causing mutations are found. If a CF diagnosis is not resolved, CRMS/CFSPID (following NBS) or CFTR-related disorder should be considered.[9,29] Rarely, no distinct label may be appropriate but further follow-up may be warranted. In these cases, the use of "CF carrier" or the specific clinical problem should be used for characterization/labeling purposes.

NBS – newborn screen, NPD – nasal potential difference, ICM – intestinal current measurement
Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 181S:S4.[4]

References

1. Kalydeco® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; May 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.