# Clinical Policy: Ivacaftor (Kalydeco)

Reference Number: ERX.SPA.23
Effective Date: 07.01.16
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

**Description**
Ivacaftor (Kalydeco®) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator.

**FDA Approved Indication(s)**
Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Kalydeco is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Cystic Fibrosis** (must meet all)**:**

1. Diagnosis of CF confirmed by all of the following (a, b, c, and d):
   a. Clinical symptoms consistent with CF in at least one organ system, or positive newborn screen or genetic testing for siblings of patients with CF;
   b. Evidence of CFTR dysfunction confirmed by one of the following (i or ii) (*see Appendix D*):
      i. Elevated sweat chloride ≥ 60 mmol/L;
      ii. Genetic testing confirming the presence of two disease-causing mutations in CFTR gene, one from each parental allele;
   c. Presence of one mutation in the CFTR gene responsive to ivacaftor based on clinical and/or in vitro assay data *(see Appendix E)*;
   d. Confirmation that a homozygous F508del mutation in the CFTR gene is not present;
2. Age ≥ 4 months;
3. Prescribed by or in consultation with a pulmonologist;
4. Chart notes indicate that pulmonary function tests performed within the last 90 days show one of the following (a or b):
   a. For age > 2 years: Documentation of a percent predicted forced expiratory volume in 1 second (ppFEV1) that is between 40-90%;
   b. For age < 6 years: Documentation of a lung clearance index (LCI) that is ≥ 7.4;
5. Kalydeco is not prescribed concurrently with other CFTR modulators (e.g., Orkambi®, Symdeko®, Trikafta™);
6. Dose does not exceed one of the following (a, b, c, d, or e):
   a. Age ≥ 6 years: 300 mg (2 tablets) per day;
   b. Age 4 months to < 6 months and weight ≥ 5 kg: 50 mg (2 packets) per day;

c. Age 6 months to < 6 years and weight 5 kg to < 7 kg: 50 mg (2 packets) per day;
d. Age 6 months to < 6 years and weight 7 kg to < 14 kg: 100 mg (2 packets) per day;
e. Age 6 months to < 6 years and weight ≥ 14 kg: 150 mg (2 packets) per day.

**Approval duration: 6 months**

**B. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. Cystic Fibrosis** (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
   a. For age > 2 years: Stabilization in ppFEV1 if baseline was ≥ 70%, or increase in ppFEV1 if baseline was < 70%;
   b. For age < 6 years: Stabilization in LCI if baseline was ≥ 7.4;
3. Kalydeco is not prescribed concurrently with other CFTR modulators (e.g., Orkambi, Symdeko, Trikafta);
4. If request is for a dose increase, new dose does not exceed one of the following (a, b, c, d, or e):
   a. Age ≥ 6 years: 300 mg (2 tablets) per day;
   b. Age 4 months to < 6 months and weight ≥ 5 kg: 50 mg (2 packets) per day;
   c. Age 6 months to < 6 years and weight 5 kg to < 7 kg: 50 mg (2 packets) per day;
   d. Age 6 months to < 6 years and weight 7 kg to < 14 kg: 100 mg (2 packets) per day;
   e. Age 6 months < 6 years and weight ≥ 14 kg: 150 mg (2 packets) per day.

**Approval duration: 12 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

ACFLD: advanced cystic fibrosis lung disease
CF: cystic fibrosis
CFF: Cystic Fibrosis Foundation
CFTR: cystic fibrosis transmembrane conductance regulator
FDA: Food and Drug Administration
LCI: lung clearance index
MBW: multiple-breath washout
ppFEV1: percent predicted forced expiratory volume in 1 second

*Appendix B: Therapeutic Alternatives*

Not applicable

*Appendix C: Contraindications/Boxed Warnings*

None reported

*Appendix D: General Information*

- The Cystic Fibrosis Foundation (CFF) Mutation Analysis Program (MAP) available here: http://www.cfpaf.org/ResourceCenter/MutationAnalysisProgram) offers free and confidential genetic testing to patients with a confirmed diagnosis of cystic fibrosis. It can take up to 60 days to receive genotyping results and additional time if further testing is needed.
- Kalydeco is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.
- It is recommended that transaminases (ALT and AST) be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment, and annually thereafter. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal.
- Data from the study of CF patients with nine *CFTR* mutations did not support approval of the drug in patients with the G970R mutation. As of 2014, it is estimated that there are about 10 people worldwide who have this mutation, including two in the United States.
- Regarding the diagnostic criteria for CF of "genetic testing confirming the presence of two disease-causing mutations in CFTR gene," this is to ensure that whether heterozygous or homozygous, there are two disease-causing mutations in the CFTR gene, one from each parental allele.
- Most children can do spirometry by age 6, though some preschoolers are able to perform the test at a younger age. Some young children aren't able to take a deep enough breath and blow out hard and long enough for spirometry. Forced oscillometry is another way to test lung function in young children. This test measures how easily air flows in the lungs (resistance and compliance) with the use of a machine.
- The two most commonly reported parameters from multiple-breath washout (MBW) tests are the lung clearance index (LCI) and moment ratios (MRs). Measurements of LCI and MR are taken during the washout period. During the washout phase, subjects inhale gases that do not contain the test gas of interest. The principles of the washout are the same regardless of the test gas measured. The washout is stopped once the test gas reaches 1/40 of the initial gas concentration
- NHS Clinical Guidelines: Care of Children with Cystic Fibrosis: Normal ranges for LCI are device specific and still being established, but in general a value > 8.0 is above the normal range and > 10.0 is significantly abnormal.
- CFF 2020 guidelines for advanced cystic fibrosis lung disease (ACFLD):
  - Define ACFLD as ppFEV1 < 40% when stable or referred for lung transplantation evaluation or previous intensive care unit (ICU) admission for respiratory failure, hypercarbia, daytime oxygen requirement at rest (excluding nocturnal use only), pulmonary hypertension, severe functional impairment from respiratory disease (New York Heart Association Class IV), six-minute walk test distance < 400 m.
  - No recommendations on the start or continuation of CFTR modulator therapy with ACFLD guidelines.
  - Treatment recommendations included: lung transplantation, supplemental oxygen, continuous alternating inhaled antibiotics, and systemic corticosteroids.

*Appendix E: CFTR Gene Mutations that are Responsive to Kalydeco*

| **CFTR Mutations that are Responsive to Kalydeco** | | | | |
|---|---|---|---|---|
| *711+3A→G* | *F311del* | *I148T* | *R75Q* | *S589N* |
| *2789+5G→A* | *F311L* | *I175V* | *R117C* | *S737F* |
| *3272-26A→G* | *F508C* | *I807M* | *R117G* | *S945L* |
| *3849+10kbC→T* | *F508C; S1251N*[†] | *I1027T* | *R117H* | *S977F* |
| *A120T* | *F1052V* | *I1139V* | *R117L* | *S1159F* |
| *A234D* | *F1074L* | *K1060T* | *R117P* | *S1159P* |
| *A349V* | *G178E* | *L206W* | *R170H* | *S1251N* |
| *A455E* | *G178R* | *L320V* | *R347H* | *S1255P* |
| *A1067T* | *G194R* | *L967S* | *R347L* | *T338I* |
| *D110E* | *G314E* | *L997F* | *R352Q* | *T1053I* |
| *D110H* | *G551D* | *L1480P* | *R553Q* | *V232D* |

| CFTR Mutations that are Responsive to Kalydeco | | | | |
|---|---|---|---|---|
| *D192G* | *G551S* | *M152V* | *R668C* | *V562I* |
| *D579G* | *G576A* | *M952I* | *R792G* | *V754M* |
| *D924N* | *G970D* | *M952T* | *R933G* | *V1293G* |
| *D1152H* | *G1069R* | *P67L* | *R1070Q* | *W1282R* |
| *D1270N* | *G1244E* | *Q237E* | *R1070W* | *Y1014C* |
| *E56K* | *G1249R* | *Q237H* | *R1162L* | *Y1032C* |
| *E193K* | *G1349D* | *Q359R* | *R1283M* | |
| *E822K* | *H939R* | *Q1291R* | *S549N* | |
| *E831X* | *H1375P* | *R74W* | *S549R* | |

† Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| CF | Adults and pediatric patients age 6 years and older: one 150 mg tablet PO every 12 hours with fat-containing food. | Age ≥ 6 years: 300 mg/day |
| | *Pediatric patients 4 months to less than 6 months of age and weighing at least 5 kg:* one 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and PO every 12 hours with fat containing food. | Age 4 months to < 6 months and weight ≥ 5 kg: 50 mg/day |
| | *Pediatric patients 6 months to less than 6 years of age weighing 5 kg to less than 7 kg:* one 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and PO every 12 hours with fat containing food. | Age 6 months to < 6 years and weight 5 kg to < 7 kg: 50 mg/day |
| | Pediatric patients 6 months to less than 6 years of age weighing 7 kg to less than 14 kg: one 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid PO every 12 hours with fat containing food. | Age 6 months to < 6 years and weight 7 kg to < 14 kg: 100 mg/day |
| | Pediatric patients 6 months to less than 6 years of age weighing 14 kg or greater: one 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid PO every 12 hours with fat-containing food. | Age 6 months to < 6 years and weight ≥ 14 kg: 150 mg/day |

## VI. Product Availability

- Tablet: 150 mg
- Unit-dose packets (56 packets per carton) containing oral granules: 25 mg, 50 mg, 75 mg

## VII. References

1. Kalydeco Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; December 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203188s034,207925s013lbl.pdf. Accessed October 29, 2021.
2. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013; 187(7): 680-689
3. Farrell PM, White TB, Ren CL et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017;181S:S4-15.
4. 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.

5. Davies J, Sheridan P, Lee P, et al. Effect of ivacaftor on lung function in subjects with CF who have the G551D-CFTR mutation and mild lung disease: a comparison of lung clearance index (LCI) vs. spirometry. Journal of Cystic Fibrosis. 2012;11(1):S15.
6. Alexander S, Alshafi K, Al-Yaghchi C, et al. Clinical Guidelines: Care of Children with Cystic Fibrosis. Royal Brompton and Harefield NHS. 2020;(8):22-23.
7. Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros. 2020 May;19(3):344-354.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q18 annual review:<br>No significant changes. References reviewed and updated. | 10.26.17 | 02.18 |
| RT4: revised minimum age requirement from 2 years to 1 year and older; references reviewed and updated. | 09.13.18 | |
| 1Q 2019 annual review: no significant changes; references reviewed and updated. | 10.16.18 | 02.19 |
| Updated age limit to reflect newly FDA-approved indication for use in patients 6 months of age and older; added new dosage form of 25 mg oral granule packets; references reviewed and updated. | 05.29.19 | |
| 1Q 2020 annual review: added the following criteria to initial approval: comprehensive diagnostic criteria (e.g., clinical symptoms in at least one organ, positive newborn screen, siblings genetic testing, and evidence of CFTR dysfunction) to confirm diagnosis of CF, prescriber requirement of pulmonologist, chart notes indicate that pulmonary function tests (ppFEV1 between 40-90%), not prescribed concurrently with other CFTR modulators; added the following to continued therapy criteria: positive response as evidenced by stabilization in ppFEV1 in lieu of an increase is acceptable if baseline was ≥ 70%, not prescribed concurrently with other CFTR modulators; added diagnosis clarification in Appendix D; references reviewed and updated. | 12.17.19 | 02.20 |
| Revised initial approval criteria requiring chart notes for pulmonary function test: added “for age > 2 years” for ppFEV1; added alternative option for ppFEV1 for age < 6 years to allow for LCI ≥ 7.4; revised continuation criteria to include stabilization in LCI if baseline was ≥ 7.4; added information regarding LCI in Appendix D. | 05.19.20 | 08.20 |
| RT4: FDA approved pediatric age extension added from 6 months to 4 months with updated dosing. | 10.05.20 | |
| 1Q 2021 annual review: no significant changes; updated Appendix D; RT4: updated Appendix E with CFTR mutations that are responsive to Kalydeco based on the updated Prescribing Information; references reviewed and updated. | 01.19.21 | 02.21 |
| 1Q 2022 annual review: no significant changes; references reviewed and updated. | 10.22.21 | 02.22 |

**Important Reminder**
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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