Clinical Policy: Ivacaftor (Kalydeco)

Reference Number: CP.PHAR.210
Effective Date: 05.01.16
Last Review Date: 02.24
Line of Business: Commercial, HIM, 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 1 month 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.

It is the policy of health plans affiliated with Centene Corporation® 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 ≥ 1 month;
3. Prescribed by or in consultation with a pulmonologist;

4. Documentation of one of the following pulmonary function tests performed within the last 90 days (a or b, *see Appendix D*):
   a. Member's baseline percent predicted forced expiratory volume in 1 second (ppFEV1);
   b. For age < 6 years: 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, e, f, or g):
   a. Age 1 month to < 2 months and weight ≥ 3 kg (both i and ii):
      i. 11.6 mg per day;
      ii. 2 packets per day;
   b. Age 2 months to < 4 months and weight ≥ 3 kg (both i and ii):
      i. 26.8 mg per day;
      ii. 2 packets per day;
   c. Age 4 months to < 6 months and weight ≥ 5 kg (both i and ii):
      i. 50 mg per day;
      ii. 2 packets per day;
   d. Age 6 months to < 6 years and weight 5 kg to < 7 kg (both i and ii):
      i. 50 mg per day;
      ii. 2 packets per day;
   e. Age 6 months to < 6 years and weight 7 kg to < 14 kg (both i and ii):
      i. 100 mg per day;
      ii. 2 packets per day;
   f. Age 6 months to < 6 years and weight ≥ 14 kg (both i and ii):
      i. 150 mg per day;
      ii. 2 packets per day;
   g. Age ≥ 6 years (both i and ii):
      i. 300 mg per day;
      ii. 2 tablets per day.

Approval duration: 6 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
   a. Stabilization or improvement in ppFEV1;
   b. For age < 6 years: Stabilization or decrease in LCI from baseline;
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, e, f, or g):
   a. Age 1 month to < 2 months and ≥ 3 kg (both i and ii):
      i. 11.6 mg per day;
      ii. 2 packets per day;
   b. Age 2 months to < 4 months and ≥ 3 kg (both i and ii):
      i. 26.8 mg per day;
      ii. 2 packets per day;
   c. Age 4 months to < 6 months and weight ≥ 5 kg (both i and ii):
      i. 50 mg per day;
      ii. 2 packets per day;
   d. Age 6 months to < 6 years and weight 5 kg to < 7 kg (both i and ii):
      i. 50 mg per day;
      ii. 2 packets per day;
   e. Age 6 months to < 6 years and weight 7 kg to < 14 kg (both i and ii):
      i. 100 mg per day;
      ii. 2 packets per day;
   f. Age 6 months to < 6 years and weight ≥ 14 kg (both i and ii):
      i. 150 mg per day;
      ii. 2 packets per day;
   g. Age ≥ 6 years (both i and ii):
      i. 300 mg per day;
      ii. 2 tablets per day.

Approval duration: 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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
MAP: Mutation Analysis Program
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: https://www.cff.org/medical-professionals/mutation-analysis-program. The MAP is a free and confidential genetic testing program for people with a strongly suspected or confirmed diagnosis of CF.
- 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.

Appendix E: CFTR Gene Mutations that are Responsive to Kalydeco

CFTR Gene 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*
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	*Pediatric patients 1 month to less than 2 months of age and weighing at least 3 kg:* one 5.8 mg packet mixed with 1 teaspoon (5 mL) of age-appropriate soft food or liquid and PO every 12 hours with fat containing food.	Age 1 month to < 2 months and weight ≥ 3 kg: 11.8 mg/day
	Pediatric patients 2 months to less than 4 months of age and weighing at least 3 kg: one 13.4 mg packet mixed with 1 teaspoon (5 mL) of age-appropriate soft food or liquid and PO every 12 hours with fat containing food.	Age 2 months to < 4 months and weight ≥ 3 kg: 26.8 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 age-appropriate 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 age-appropriate 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 age-appropriate soft food or liquid and 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 age-appropriate soft food or liquid and PO every 12 hours with fat-containing food.	Age 6 months to < 6 years and weight ≥ 14 kg: 150 mg/day
	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

VI. Product Availability

- Tablet: 150 mg
- Unit-dose packets (56 packets per carton) containing oral granules: 5.8 mg, 13.4 mg, 25 mg, 50 mg, 75 mg

VII. References

1. Kalydeco Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; May 2023. Available at: https://pi.vrtx.com/files/uspi_ivacaftor.pdf. Accessed May 4, 2023.
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.
8. Cystic Fibrosis Foundation: Clinical Care Guidelines. Available at: https://www.cff.org/medical-professionals/clinical-care-guidelines. Accessed May 4, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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; changed approval durations of commercial from length of benefit to 6 months initial and 12 months continued; 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 ≥	05.19.20	08.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
7.4; revised continuation criteria to include stabilization in LCI if baseline was ≥ 7.4; added information regarding LCI in Appendix D.		
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; references HIM.PHAR.21 revised to HIM.PA.154; 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: added legacy Wellcare initial approval duration (WCG.CP.PHAR.210 to be retired); references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	10.22.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
1Q 2023 annual review: no significant changes; consolidated Legacy Wellcare initial approval duration from 12 months to 6 months consistent with standard Medicaid initial approval duration; updated Appendix D; references reviewed and updated.	10.06.22	02.23
RT4: revised criteria to include pediatric expansion and new 5.8 mg and 13.4 mg granule strengths; references reviewed and updated.	05.04.23	06.23
3Q23 annual review: no significant changes after comprehensive review completed as part of the RT4 review in June 2023.	05.10.23	08.23
Revised initial approval criteria: removed "for age 2 > years" and "ppFEV1 that is between 40 – 90%" in criteria stating documentation of member's ppFEV1; revised "chart notes that indicate pulmonary function tests" to "documentation of one of the following pulmonary function tests"; for continued therapy criteria: revised criteria from "stabilization in ppFEV1 if baseline was ≥ 70%, or increase in ppFEV1 if baseline was <70%" to "stabilization or improvement in ppFEV1" and revised "stabilization in LCI if baseline was ≥ 7.4" to "stabilization or decrease in LCI from baseline"; revised Appendix D to remove information on advanced Cystic Fibrosis disease.	01.11.24	02.24

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.