Clinical Policy: Ivacaftor (Kalydeco)

Reference Number: PA.CP.PHAR.210
Effective Date: 01/2018
Last Review Date: 07/2023

Coding Implications
Revision Log

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
It is the policy of PA Health & Wellness 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;
2. Presence of one mutation in the CFTR gene responsive to ivacaftor based on clinical and/or *in vitro* assay data *(see Appendix E)*;
3. Confirmation that a homozygous *F508del* mutation in the CFTR gene is not present;
4. Age ≥ 1 month;
5. Prescribed by or in consultation with a pulmonologist or cystic fibrosis specialist;
6. Documentation indicates member has baseline forced expiratory volume in 1 second (FEV1), unless member is unable to perform spirometry testing;
7. Kalydeco is not prescribed concurrently with other ivacaftor-containing CFTR modulator combination products (e.g., Orkambi, Symdeko, Trikafta);
8. Dose does not exceed one of the following (a-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 (2 packets) 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: Refer to PA.CP.PMN.53 for Medicaid.

II. Continued Approval

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

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy (e.g.: stable or improved pulmonary function, improved quality of life, reduced hospitalization) OR the member continues to benefit from therapy based on the prescriber's assessment;
3. Kalydeco is not prescribed concurrently with other ivacaftor-containing CFTR modulator combination products (e.g., Orkambi, Symdeko, Trikafta);
4. If request is for a dose increase, new dose does not exceed one of the following (a-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 (1 or 2):

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

III. 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.
- 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.
- 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 < 400m.
  - 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 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.

IV. 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 ≥ 6 years: 300 mg/day Age 4 months to < 6 months and

Indication	Dosing Regimen	Maximum Dose
	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. *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. *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. *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. *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. *Adults and pediatric patients age 6 years and older:* one 150 mg tablet PO every 12 hours with fat-containing food.	weight ≥ 5 kg: 50 mg/day Age 6 months to < 6 years and weight 5 kg to < 7 kg: 50 mg/day Age 6 months to < 6 years and weight 7 kg to < 14 kg: 100 mg/day Age 6 months to < 6 years and weight ≥ 14 kg: 150 mg/day

V. 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

VI. 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	Approval Date
References reviewed and updated.	02/2018	
1Q 2019 annual review: references reviewed and updated.	01/2019	
1Q 2020 annual review: added the following criteria to initial approval: prescriber requirement of pulmonologist or cystic fibrosis specialist, requirement for baseline FEV1 unless unable to perform spirometry, requirement that Kalydeco not be prescribed concurrently with other ivacaftor-containing CFTR modulator combination products; added the following to continued therapy criteria: not prescribed concurrently with other CFTR modulators; references reviewed and updated.	01/2020	
1Q 2021 annual review: FDA approved pediatric age extension added from 6 months to 4 months with updated dosing; references reviewed and updated.	01/2021	
1Q 2022 annual review: updated Appendix E with CFTR mutations that are responsive to Kalydeco based on the updated Prescribing Information; references reviewed and updated.	01/2022	
1Q 2023 annual review: no significant changes; updated Appendix D; references reviewed and updated.	01/2023	
3Q 2023 annual review: revised criteria to include pediatric expansion and new 5.8 mg and 13.4 mg granule strengths; references reviewed and updated.	07/2023	