Clinical Policy Title:	ivacaftor
Policy Number:	RxA.190
Drug(s) Applied:	Kalydeco®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of Business

Background

Kalydeco® is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. It 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ivacaftor (Kalydeco®)	CF	*Adults and pediatric patients age 6 years and older:* one 150 mg tablet PO every 12 hours with fat containing food. *Pediatric patients 4 months to less than 6 months of age and 5 kg or greater:* one 25 mg packet mixed with 1 teaspoon (5 mL) of 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 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 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 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 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

		• *Not recommended in patients less than 4 months of age.* • *Reduce dose in patients 6 months and older with moderate or severe hepatic impairment.* • *Not recommended in patients 4 months to less than 6 months of age with hepatic impairment.*	

Dosage Forms

- Tablets: 150 mg
- Unit-dose packets containing oral granules: 25 mg, 50 mg, 75 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

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

1. Diagnosis of CF;
2. Age ≥ 4 months;
3. Presence of one mutation in the CFTR gene responsive to ivacaftor based on clinical and/or in vitro assay data *(see Appendix E)*;
4. Confirmation that a homozygous F508del mutation in the CFTR gene is not present;
5. Dose does not exceed one of the following (a, b, c, d or e):
   a. Age ≥ 6 years: 300 mg per day (2 tablets per day);
   b. Age 4 months to < 6 months and weight ≥ 5 kg: 50 mg per day (2 packets per day);
   c. Age 6 months to < 6 years and weight 5 kg to < 7 kg: 50 mg per day (2 packets per day);
   d. Age 6 months to < 6 years and weight 7 kg to < 14 kg: 100 mg per day (2 packets per day);
   e. Age 6 months to < 6 years and weight ≥ 14 kg: 150 mg per day (2 packets per day).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. 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 per day (2 tablets per day);
   b. Age 4 months to < 6 months and weight ≥ 5 kg: 50 mg per day (2 packets per day);
   c. Age 6 months to < 6 years and weight 5 kg to < 7 kg: 50 mg per day (2 packets per day);
   d. Age 6 months to < 6 years and weight 7 kg to < 14 kg: 100 mg per day (2 packets per day);
   e. Age 6 months to < 6 years and weight ≥ 14 kg: 150 mg per day (2 packets per day).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CF: Cystic Fibrosis
CFTR: Cystic Fibrosis Transmembrane Conductance Regulator
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
- Not applicable

APPENDIX C: Contraindications/Boxed Warnings
- Contraindication(s):
  - None reported
- Boxed Warning(s):
  - None reported

APPENDIX D: General Information
- The Cystic Fibrosis Foundation's 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 CF. 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.

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

CFTR Gene Mutations that are Responsive to Kalydeco®				
A1067T	E56K	G551S	R347H	S977F
A455E	F1052V	K1060T	R352Q	2789+5G→A (28)
D110E	F1074L	L206W	R74W	3272-26A→G (23)
D110H	G1069R	P67L	S1251N	3849+10kBc→T (40)
D115H	G1244E	R1070Q	S1255P	711+3A→G (2)
D1270N	G1349D	R1070W	S459R	E831X (1)
D579G	G178R	R117C	S549N	

E193K	G551D	R117H	S945L	

References

1. Kalydeco® Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; December 2020. Available at https://www.kalydeco.com/. Accessed February 22, 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.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Line of Business Policy Applies to was update to all lines of business. 3. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 4. Initial Approval criteria: Commercial approval duration was updated from length of benefit to 6 months. 5. Continued Approval criteria: Commercial approval duration was updated from length of benefit to 12 months. 6. References were updated.	06/23/2020	09/14/2020
Policy was reviewed: 1. Last Review Date was updated. 2. Background was updated to change the patients minimum age from 6 months to 4 months. 3. Dosing information was updated for pediatric patients 4 months to less than 6 months. 4. Clinical policy verbiage was updated to “The provision of provider samples does not guarantee….”. 5. Initial approval criteria was updated for minimum age of 4 months. 6. Initial and continuation criteria were updated to include maximum dose for	02/22/2021	06/10/2021

patients age 4 months to less than 6 months. 7. References were updated. • Dosage regimen updated to include: *Not recommended in patients less than 4 months of age.* • *Reduce dose in patients 6 months and older with moderate or severe hepatic impairment.* • *Not recommended in patients 4 months to less than 6 months of age with hepatic impairment.*		