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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Respiratory Agents	**Original Policy Date:**	February 10, 2012
Subject:	Kalydeco	**Page:**	1 of 7

Last Review Date: March 12, 2021

Kalydeco

Description

Kalydeco (ivacaftor)

Background
Kalydeco (ivacaftor) is a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR) protein and facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein. Kalydeco is effective only in patients with cystic fibrosis (CF) who have certain mutations in their *CFTR* gene. About 4 percent of those with cystic fibrosis, or roughly 1,200 people in the US, are believed to have the G551D mutation. Kalydeco has not been shown to be effective in patients with two copies (homozygous) of the *F508del* mutation in the *CFTR* gene, which is the most common mutation that results in cystic fibrosis. If a patient's mutation status is not known, an FDA-cleared mutation test should be used to determine whether a CFTR approved mutation is present (1-2).

Regulatory Status
FDA-approved indication: Kalydeco is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator 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 (1).

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 (1).

List of *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 *	

* Clinical data exist for these mutations.
† 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.

Trial 3 results indicate that Kalydeco is not effective in patients with two copies (homozygous) of the *F508del* mutation in the *CFTR* gene (1).

Transaminases (ALT and AST) should be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (1).

Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's Wort) substantially decreases exposure of Kalydeco which may diminish effectiveness. Therefore, co-administration is not recommended (1).

The safety and efficacy of Kalydeco in patients less than 4 months of age have not been established. The use of Kalydeco in children under the age of 4 months is not recommended (1).

Related policies
Orkambi, Pulmozyme, Symdeko, Trikafta

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Kalydeco may be considered **medically necessary** in patients 4 months of age or older for the treatment of cystic fibrosis (CF) and if the conditions indicated below are met.

Kalydeco may be considered **investigational** in patients less than 4 months of age and for all other indications.

Prior-Approval Requirements

Age 4 months of age or older

Diagnosis

The patient must have the following:

Cystic fibrosis (CF)

AND ALL the following:

1. Patient has one mutation in the *CFTR* gene that is responsive to Kalydeco (see Appendix 2)
2. **NO** homozygous for *F508del* mutation in the *CFTR* gene
3. Patients 6 years of age or older **only**: Pretreatment percent predicted forced expiratory volume (ppFEV1) must be provided
4. Transaminases (ALT and AST) will be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment and annually thereafter
5. Must be prescribed by a pulmonologist or gastroenterologist
6. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 4 months of age and older

Diagnosis

Patient must have the following:
Cystic fibrosis (CF)

AND ALL of the following:

1. Patients less than 6 years of age **only**: Patient's symptoms have improved or stabilized from baseline
2. Patients 6 years of age or older **only**: Stable or improvement of ppFEV$_1$ from baseline
3. Transaminases (ALT and AST) will be assessed annually
4. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 168 units per 84 days
Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Cystic fibrosis is caused by mutations in a gene that encodes for a protein called cystic fibrosis transmembrane regulator (CFTR) which regulates chloride and water transport in the body. The defect results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body. Kalydeco is a potentiator of the CFTR protein and is effective in various mutations in their *CFTR* gene. About 4 percent of those with cystic fibrosis are believed to have the G551D mutation. Kalydeco is indicated for patients 4 months of age and older. Transaminases (ALT and AST) should be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment and annually thereafter (1).

Prior approval is required to ensure the safe, clinically appropriate and cost-effective use of Kalydeco while maintaining optimal therapeutic outcomes.

References

1. Kalydeco [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; December 2020.
2. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med. DOI: 10.1056/NEJMoa1409547. Accessed February 2021.

Policy History

Date	Action
March 2013	Annual editorial review
February 2014	Expansion of approvable genetic mutations based on revised FDA indication
January 2015	Addition of R117H mutation
February 2015	Change in quantity to 168 tablets to accommodate new blister packaging
March 2015	Annual review and reference update FDA lowered age limit to 2 years of age.
June 2015	Annual editorial review and reference update
September 2015	Annual Review
December 2015	Annual review
March 2016	Addition of requirements: pretreatment percent predicted forced expiratory volume (ppFEV1) must be provided; patient has had 2 negative respiratory cultures for any of following organisms: burkholeria cenocepacia, burkholderia dolosa, or mycobacterium abscessus in past 12 months; baseline levels of ALT, AST and bilirubin must be obtained and must be tested yearly; prescribed by a pulmonologist or gastroenterologist; and no dual therapy with another a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator Addition of renewal requirements after 6 months of therapy
June 2016	Annual review Policy number change from 5.13.03 to 5.45.03
September 2016	Annual editorial review and reference update.
March 2017	Annual editorial review and reference update
May 2017	Addition more approvable mutations
August 2017	Addition of more mutations 711+3A-G, E831X, 2789+5G-A, 3272-26A-G, 3849+10kbC-T
September 2017	Annual review
December 2017	Annual review
March 2018	Annual editorial review

June 2018	Annual editorial review Removal of requirement: patient has had 2 negative respiratory cultures for any of the following organisms: burkholeria cenocepacia, burkholderia dolosa, or mycobacterium abscessus in the past 12 months per SME
August 2018	Age requirement reduced from 2 years and older to 12 months and older
November 2018	Annual review
March 2019	Annual review
May 2019	Revised age requirement from 12 months and older to 6 months and older
June 2019	Annual review
March 2020	Annual review
October 2020	Revised age requirement from 6 months and older to 4 months and older. Removed limitations of use language. Removed requirement for bilirubin testing. Added requirement for transaminases testing every 3 months for the first year of treatment. Changed initiation duration from 6 months to 12 months
December 2020	Annual review
January 2021	Updated the list of *CFTR* gene mutations with additional mutations that have been identified as responsive to Kalydeco. Added Appendix 2.
March 2021	Annual review and reference update. Revised ppFEV$_1$ requirements so that they only apply to patients age 6 and older. Added renewal requirement for patients less than 6 years old to have symptom improvement or stabilization

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

Appendix 1 - List of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiators

Generic Name	Brand Name
ivacaftor	Kalydeco
ivacaftor/lumacaftor	Orkambi
ivacaftor/tezacaftor	Symdeko
ivacaftor/tezacaftor/elexacaftor	Trikafta

Appendix 2 - List of *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 *	

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