BlueCross BlueShield Federal Employee Program

KALYDECO
(ivacaftor)

RATIONALE FOR INCLUSION IN PA PROGRAM

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 1 month and older who have at least 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 1 month of age have not been established. The use of Kalydeco in children under the age of 1 month is not recommended (1).

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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 1 month 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.; August 2023.
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.