

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Symdeko Prior Authorization Policy

- Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets – Vertex)

REVIEW DATE: 02/03/2021

OVERVIEW

Symdeko is indicated for the **treatment of patients ≥ 6 years of age with cystic fibrosis (CF)** who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.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. Table 1 lists responsive CFTR mutations based on: 1) a clinical forced expiratory volume in 1 second (FEV₁) response and/or 2) *in vitro* data in FRT cells, indicating that tezacaftor/ivacaftor increases chloride transport to $\geq 10\%$ of untreated normal over baseline. CFTR gene mutations that are not responsive to ivacaftor alone (Kalydeco®) are not expected to respond to Symdeko except for F508del homozygotes.

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.¹

E56K	E193K	S945L	F1074L
P67L	L206W	S977F	D1152H
R74W	R347H	F1052V	D1270N
D110E	R352Q	E831X	2789+5G→A
D110H	A455E	K1060T	3272-26A→G
R117C	D579G	A1067T	3849 + 10kC→T
F508del*	711+3A→G	R1070W	G622D
A120T	E60K	F1016S	G970D
A234D	E92K	F1099L	G1069R
A349V	E116K	G126D	G1244E
A554E	E403D	G178E	G1249R
A1006E	E558V	G178R	G1349D
D192G	E822K	G194R	H939R
D443Y	F191V	G194V	H1054D
D443Y;G57A; R668C	F311del	G314E	H1375P
D614G	F311L	G551D	I148T
D836Y	F508C	G551S	I175V
D924N	F508C;S1251N	G576A	I336K
D979V	F575Y	G576A;R668C	I601F
I618T	L346P	M952T	R74Q
I807M	L967S	P5L	R74W;D1270N
I980K	L997F	P205S	R74W;V201M
I1027T	L1324P	Q98R	R74W;V201M;D1270N
I1139V	L1335P	Q237E	R75Q
I1269N	L1480P	Q237H	R117G
I1366N	M152V	Q359R	R117H
L15P	M265R	Q1291R	R117L
L320V	M952I	R31L	R117P
R170H	R1066H	S1251N	W1282R
R258G	R1070Q	S1255P	Y109N
R334L	R1162L	T338I	Y161S
R334Q	R1283M	T1036N	Y1014C

Table 1 (continued). List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.¹

<i>R347L</i>	<i>R1283S</i>	<i>T1053I</i>	<i>Y1032C</i>
<i>R347P</i>	<i>S549N</i>	<i>V201M</i>	<i>R792G</i>
<i>R352W</i>	<i>S549R</i>	<i>V232D</i>	<i>R933G</i>
<i>R553Q</i>	<i>S589N</i>	<i>V562I</i>	<i>S1159F</i>
<i>R668C</i>	<i>S737F</i>	<i>V754M</i>	<i>S1159P</i>
<i>R751L</i>	<i>S912L</i>	<i>V1153E</i>	<i>V1240G</i>
<i>V1293G</i>	<i>546insCTA</i>		

CFTR – Cystic fibrosis transmembrane regulator; * A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 1 to be indicated.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Symdeko is not addressed.⁴

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Symdeko. Because of the specialized skills required for evaluation and diagnosis of patients treated with Symdeko as well as the monitoring required for adverse events and efficacy, approval requires Symdeko to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years unless otherwise noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Symdeko is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Cystic Fibrosis (CF). Approve Symdeko for 3 years in patients who meet the following criteria (A, B, and C):

A) Patient meets ONE of the following conditions (i or ii):

- i.** Patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A → G, S945L, S977F, F1052V, E831X, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G → A, 3272-26A → G, 3849 + 10kbC → T, 546insCTA, A120T, A234D, A349V, A554E, A1006E, D192G, D443Y, D443Y;G57A;R668C, D614G, D836Y, D924N, D979V, I618T, I807M, I980K, I1027T, I1139V, I1269N, I1366N, L15P, L320V, R170H, R258G, R334L, R334Q, R347L, R347P, R352W, R553Q, R668C, R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M952I, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T338I, T1036N, T1053I, V201M, V232D, V562I, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G; OR

- ii. The patient has two copies of the F508del mutation; AND
- B) Patient is ≥ 6 years of age; AND
- C) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Symdeko is not recommended in the following situations:

1. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Symdeko¹
2. **Combination Therapy with Orkambi, Kalydeco, or Trikafta.** Symdeko contains ivacaftor, the active agent in Kalydeco and part of Orkambi and Trikafta. Symdeko also contains tezacaftor, part of Trikafta. Symdeko is not indicated in combination with Kalydeco, Orkambi, or Trikafta.
3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2020.
2. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *New Engl J Med.* 2017;377(21):2024-2035.
3. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del. *N Engl J Med.* 2017; 377(21); 2013-2023.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Approved for FDA-approved indication	02/14/2018
Annual Revision	No criteria changes	03/06/2019
Selected Revision	Cystic Fibrosis: Criteria were modified to approve in patients ≥ 6 years of age, previously ≥ 12 years of age.	06/26/2019
Selected Revision	Combination Therapy with Orkambi or Kalydeco: Trikafta was added to this indication not recommended for approval.	10/23/2019
Annual Revision	No criteria changes	03/25/2020
Selected Revision	Cystic Fibrosis (CF): Additional mutations were added to the criteria for approval (R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M952I, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T338I, T1036N, T1053I, V201M, V232D, V562I, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G)	01/06/2021
Annual Revision	Cystic Fibrosis (CF): T338I, T1053I, and V562I mutations were amended to T338I,	02/03/2021

	T1053I, and V562I. 546insCTA was added as an approvable mutation.	
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