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Prior Authorization

Cystic Fibrosis – Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets)

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Product Identifier(s)

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INSTRUCTIONS FOR USE

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National Formulary Medical Necessity

Cigna covers tezacaftor/ivacaftor and ivacaftor products (Symdeko®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior Authorization is recommended for prescription benefit coverage of Symdeko. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of individuals 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.

FDA Indications:

1. Cystic Fibrosis (CF). Approve for 3 years if the individual meets the following criteria (A, B, and C):

A) Individual is ≥ 6 years of age; AND

B) Individual meets ONE of the following conditions (i or ii):

- i. Individual has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator 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. Individual has two copies of the F508del mutation; AND
- c) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Conditions Not Covered

Tezacaftor/ivacaftor and ivacaftor (Symdeko®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. **Cystic Fibrosis (CF), Individuals 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.

Background

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 Fischer rat thyroid cells, indicating that tezacaftor/ivacaftor increases chloride transport to ≥ 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 + 10kbC → 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

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

CFTR – Cystic fibrosis transmembrane regulator; ¹ 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

References

1. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex; 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.

Revision History

Type of Revision	Summary of Changes	Approval Date
Annual Revision	No criteria changes.	02/08/2023

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