MEDICAL MUTUAL®

Drug Policy

Policy:	Symdeko (tezacaftor/ivacaftor and ivacaftor)	Annual Review Date: 02/20/2025 Last Revised Date: 02/20/2025

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 Kalydeco® (ivacaftor granule or tablet) alone 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	*M9521*	*R31L*	*R117P*
R170H	*R1066H*	*S1251N*	*W1282R*
R258G	*R1070Q*	*S1255P*	*Y109N*
R334L	*R1162L*	*T338I*	*Y161S*
R334Q	*R1283M*	*T1036N*	*Y1014C*
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 conductance 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.

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POLICY STATEMENT

This policy involves the use of Symdeko. Prior authorization is recommended for pharmacy benefit coverage of Symdeko. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

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 long-term efficacy, initial approval requires Symdeko be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

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

1. <u>Cystic Fibrosis (CF), new starts</u>

Criteria. *Patient must meet the following criteria (A, B, C, D, <u>and</u> E):*

A. The patient is 6 years of age or older; AND

B. Symdeko is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of Cystic Fibrosis (CF); AND

C. The patient meets ONE of the following (i <u>or</u> ii):

i. The patient has 2 copies of the F508del mutation; OR

ii. The patient has at least one mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene that laboratory testing shows is susceptible to treatment with Symdeko (Note: See Table 1 above for list of mutations).

D. Patient meets at least ONE of the following (i, ii, or iii):
- i. Positive cystic fibrosis newborn screening test; OR
- ii. Family history of cystic fibrosis; OR
- iii. Clinical presentation consistent with signs and symptoms of cystic fibrosis; AND
  Note: Examples of clinical presentation of cystic fibrosis include but are not limited to meconium ileus, sino-pulmonary symptoms (e.g., persistent cough, wheezing, pulmonary function tests consistent with obstructive airway disease, excess sputum production), bronchiectasis, sinusitis, failure to thrive, pancreatic insufficiency.

E. Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):
- i. Elevated sweat chloride test; OR
- ii. Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations; OR
- iii. Abnormal nasal potential difference;

2. Cystic Fibrosis (CF), continuation of therapy

Criteria. *Patient must meet the following criteria (a, b, and c):*

a. The patient has been using Symdeko for at least 6 months; AND
b. The patient meets all criteria in (1) for new starts; AND
c. Compared to baseline, the patient has experienced clinical benefit in response to therapy, such as;
   - i. Increase in weight, OR
   - ii. Improvement in sweat chloride, OR
   - iii. Improvement in predicted FEV1 or other lung function tests, OR
   - iv. Decrease in amount/frequency of pulmonary exacerbations, OR
   - v. Decrease in amount/frequency of pulmonary infections, OR
   - vi. Decrease in hospitalizations.

Initial Approval/ Extended Approval.
A) *Initial Approval:* 6 months
B) *Extended Approval:* 1 year

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Symdeko has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

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 Symdeko.[1]

2. **Combination Therapy with Other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s).** Symdeko contains ivacaftor, the active agent in Kalydeco (tablets and oral granules) and part of Orkambi (lumacaftor/ivacaftor tablets and oral granules) and Trikafta (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and granules). Symdeko also contains tezacaftor, part of Trikafta.
   Note: Examples of other cystic fibrosis transmembrane conductance regulator modulators are: Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets), Kalydeco (ivacaftor tablets and oral granules), Orkambi (lumacaftor/ivacaftor tablets and oral granules), Trikafta (elexacaftor/tezacaftor/ivacaftor; ivacaftor co-packaged tablets and granules).

3. **Infertility**. Symdeko is indicated for the treatment of cystic fibrosis in a patient ≥ 6 years of age who is homozygous for the F508del mutation or who has at least one mutation in the cystic fibrosis transmembrane conductance regulator gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.1
   Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex; August 2023.
2. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. J Cyst Fibros. 2024;21-28..
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-S15.
4. Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. J Pediatr. 2017;181S:S33-S44.

5. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. J Cyst Fibros. 2024;21-28.