PRIOR AUTHORIZATION POLICY

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

TAC APPROVAL DATE: 03/06/2019; selected revision 06/26/2019

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 (FEV_1) response and/or 2) *in vitro* data in FRT 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*	

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)** The patient meets ONE of the following conditions (i or ii):
     - **i.** The 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, or 3849 + 10kbC → T; OR
     - **ii.** The patient has two copies of the F508del mutation; AND
   - **B)** The patient is ≥ 6 years of age; AND
   - **C)** Symdeko is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis (CF).

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. Rationale for non-coverage for these specific conditions is provided below. (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 Orkambi or Kalydeco.** Symdeko contains ivacaftor, the active agent in Kalydeco and part of Orkambi. Symdeko is not indicated in combination with Kalydeco or Orkambi.

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; June 2019.
2. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *New Negl 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 trasmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc.* 2018;15(3):271-280.

Other References Utilized

- CF patient registry 2017. Available at: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf. Accessed on February 5, 2019.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval 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

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; FDA – Food and Drug Administration.