Clinical Policy: Tezacaftor/Ivacaftor; Ivacaftor (Symdeko)

Reference Number: PA.CP.PHAR.377
Effective Date: 01/2019
Last Review Date: 07/2023

Revision Log

Description
Tezacaftor/ivacaftor; ivacaftor (Symdeko®) is a combination drug for cystic fibrosis (CF).

- Tezacaftor facilitates the cellular processing and trafficking of normal and select mutant forms of cystic fibrosis transmembrane conductance regulator [*CFTR*; (including *F508del-CFTR*)] to increase the amount of mature *CFTR* protein delivered to the cell surface.
- Ivacaftor is a *CFTR* potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the *CFTR* protein at the cell surface.
- The combined effect of tezacaftor and ivacaftor is increased quantity and function of *CFTR* at the cell surface, resulting in increases in chloride transport.

FDA Approved Indication(s)
Symdeko is indicated for the treatment of patients with CF aged 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

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.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Symdeko is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cystic Fibrosis (must meet all)**:**

1. Diagnosis of CF;
2. Age ≥ 6 years;
3. Prescribed by or in consultation with a pulmonologist or cystic fibrosis specialist;
4. Documentation indicates member has baseline forced expiratory volume in 1 second (FEV1), unless member is unable to perform spirometry testing;
5. Symdeko is not prescribed concurrently with other CFTR modulator combination products (e.g., Kalydeco, Orkambi, Trikafta);
6. One of the following (a or b):
   a. Confirmation member is homozygous for the *F508del* mutation in the *CFTR* gene;
   b. Presence of at least one mutation in the *CFTR* gene that is responsive to Symdeko based on *in vitro* data and/or clinical evidence (*see Appendix D*);
7. Dose does not exceed one of the following (a or b):

a. Age 6 to < 12 years weighing <30 kg (both i and ii):
   i. Tezacaftor 50 mg/ivacaftor 150 mg;
   ii. 1 tablet tezacaftor/ivacaftor and 1 tablet ivacaftor;
b. Age 6 to < 12 years weighing ≥ 30 kg and ≥ 12 years (both i and ii):
   i. Tezacaftor 100 mg/ivacaftor 300 mg per day;
   ii. 1 tablet tezacaftor/ivacaftor and 1 tablet ivacaftor per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

II. Continued Therapy

A. Cystic Fibrosis (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy OR the member continues to benefit from therapy based on prescriber's assessment;
3. Symdeko is not prescribed concurrently with other CFTR modulator combination products (e.g., Kalydeco, Orkambi, Trikafta);
8. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Age 6 to < 12 years weighing <30 kg (both i and ii):
      i. Tezacaftor 50 mg/ivacaftor 150 mg;
      ii. 1 tablet tezacaftor/ivacaftor and 1 tablet ivacaftor;
   b. Age 6 to < 12 years weighing ≥ 30 kg and ≥ 12 years (both i and ii):
      i. Tezacaftor 100 mg/ivacaftor 300 mg per day;
      ii. 1 tablet tezacaftor/ivacaftor and 1 tablet ivacaftor per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACFLD: advanced cystic fibrosis lung disease
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
FDA: Food and Drug Administration
ppFEV1: percent predicted forced expiratory volume in 1 second

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko

CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko					
546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
711+3A→G	*E116K*	*G576A;R668C*†	*L967S*	*R117H*	*S737F*
2789+5G→A	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
3272-26A→G	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L*
3849+10kbC→T	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F*
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159P*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251N*
A445E	*F311del*	*H939R*	*M9521*	*R347H*	*S1255P*
A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036N*
A1067T	*F508C; S1251N*†	*1148T*	*P67L*	*R352Q*	*T1053I*
D110E	*F508del**	*I175V*	*P205S*	*R352W*	*V201M*
D110H	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A; R668C†	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
D579G	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240G*
D614G	*G126D*	*I1027T*	*R31L*	*R1066H*	*V1293G*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070Q*	*W1282R*
D924N	*G178R*	*I1269N*	*R74W*	*R1070W*	*Y109N*
D979V	*G194R*	*I1366N*	*R74W; D1270N*†	*R1162L*	*Y161S*
D1152H	*G194V*	*K1060T*	*R74W; V201M*†	*R1283M*	*Y1014C*
D1270N	*G314E*	*L15P*	*R74W;V201M; D1270N*†	*R1283S*	*Y1032C*

CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko					
E56K	*G551D*	*L206W*	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C*	*S549R*	
*A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in this table to be indicated. † 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.					

Appendix E: General Information

- The Cystic Fibrosis Foundation (CFF) Mutation Analysis Program (MAP) available here: https://www.cff.org/medical-professionals/mutation-analysis-program. The MAP is a free and confidential genetic testing program for people with a strongly suspected or confirmed diagnosis of CF.
- Regarding the diagnostic criteria for CF of "genetic testing confirming the presence of two disease-causing mutations in CFTR gene," this is to ensure that whether heterozygous or homozygous, there are two disease-causing mutations in the CFTR gene, one from each parental allele.
- Most children can do spirometry by age 6, though some preschoolers are able to perform the test at a younger age. Some young children aren't able to take a deep enough breath and blow out hard and long enough for spirometry. Forced oscillometry is another way to test lung function in young children. This test measures how easily air flows in the lungs (resistance and compliance) with the use of a machine.
- Cystic Fibrosis Foundation 2020 guidelines for advanced cystic fibrosis lung disease (ACFLD):
  - Define ACFLD as ppFEV1 < 40% when stable or referred for lung transplantation evaluation or previous intensive care unit (ICU) admission for respiratory failure, hypercarbia, daytime oxygen requirement at rest (excluding nocturnal use only), pulmonary hypertension, severe functional impairment from respiratory disease (New York Heart Association Class IV), six-minute walk test distance < 400m.
  - No recommendations on the start or continuation of CFTR modulator therapy with ACFLD guidelines.
  - Treatment recommendations included: lung transplantation, supplemental oxygen, continuous alternating inhaled antibiotics, and systemic corticosteroids

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CF	Pediatric patients age 6 to < 12 years weighing < 30 kg: one tablet (containing tezacaftor 50 mg/ivacaftor 75 mg) in the morning and one tablet (containing ivacaftor 75 mg) in the evening, approximately 12 hours apart with fat-containing food. Adults and pediatric patients age 12 years and older or pediatric patients age 6 to < 12 years weighing 30 kg or more: one tablet (containing tezacaftor 100 mg/ivacaftor	Age 6 to < 12 years weighing < 30 kg: Tezacaftor 50mg/ivacaftor 150 mg Age 6 to < 12 years weighing

Indication	Dosing Regimen	Maximum Dose
	150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart with fat-containing food. Reduce dose in patients with moderate and severe hepatic impairment. Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.	30 kg or more and age ≥ 12 years:

VI. Product Availability

Tablets: co-packaged as tezacaftor 50 mg/ivacaftor 75 mg fixed dose combination tablets with ivacaftor 75 mg tablets OR tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tablets with ivacaftor 150 mg tablets

VII. References

1. Symdeko Prescribing Information. Boston, MA: Vertex Pharmaceuticals Incorporated; June 2022. Available at: https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf. Accessed May 4, 2023.
2. Farrell PM, White TB, Ren CL et al. Diagnosis of cystic fibrosis: Consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017; 181S: S4-15.
3. 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.
4. Alexander S, Alshafi K, Al-Yaghchi C, et al. Clinical Guidelines: Care of Children with Cystic Fibrosis. Royal Brompton and Harefield NHS. 2020;(8):22-23.
5. Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros. 2020 May;19(3):344-354.
6. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.
7. Cystic Fibrosis Foundation: Clinical Care Guidelines. Available at: https://www.cff.org/medical-professionals/clinical-care-guidelines. Accessed May 4, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01/2019	
1Q 2020 annual review: lowered age restriction to 6 yr and older; added the following criteria to initial approval: prescriber requirement of pulmonologist or cystic fibrosis specialist, requirement for baseline FEV1 unless unable to perform spirometry,	04/2020	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
requirement that Symdeko not be prescribed concurrently with other ivacaftor-containing CFTR modulator combination products; added the following to continued therapy criteria: not prescribed concurrently with other CFTR modulators; references reviewed and updated.		
1Q 2021 annual review: references reviewed and updated.	01/2021	
1Q 2021 annual review: references reviewed and updated.	01/2022	
1Q 2023 annual review: no significant changes; updated Appendix D and Appendix E; references reviewed and updated.	01/2023	
3Q 2023 annual review: Updated criteria to include maximum dosing stratified by age and weight; references reviewed and updated.	07/2023	