Clinical Policy: Tezacaftor/Ivacaftor; Ivacaftor (Symdeko)

Reference Number: ERX.SPA.235
Effective Date: 04.03.18
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 confirmed by all of the following (a, b, and c):
   a. Clinical symptoms consistent with CF in at least one organ system, or positive newborn screen or genetic testing for siblings of patients with CF;
   b. Evidence of CFTR dysfunction confirmed by one of the following (i or ii) (*see Appendix E*):
      i. Elevated sweat chloride ≥ 60 mmol/L;
      ii. Genetic testing confirming the presence of two disease-causing mutations in CFTR gene, one from each parental allele;
   c. One of the following (i or ii):
      i. Confirmation that member is homozygous for the F508del mutation in the CFTR gene;
      ii. 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*);
2. Age ≥ 6 years;
3. Prescribed by or in consultation with a pulmonologist;

4. Chart notes indicate that pulmonary function tests, performed within the last 90 days, show a percent predicted forced expiratory volume in 1 second (ppFEV1) that is between 40-90%;
5. Symdeko is not prescribed concurrently with other CFTR modulators (e.g., Kalydeco®, Orkambi®, Trikafta™);
6. Dose does not exceed tezacaftor 100 mg/ivacaftor 300 mg (1 tablet tezacaftor/ivacaftor and 1 tablet ivacaftor) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by a stabilization in ppFEV1 if baseline was ≥ 70% or increase in ppFEV1 if baseline was < 70%;
3. Symdeko is not prescribed concurrently with other CFTR modulators (e.g., Kalydeco®, Orkambi®, Trikafta™);
4. If request is for a dose increase, new dose does not exceed tezacaftor 100 mg/ivacaftor 300 mg (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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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*	*L346P*	*R117G*	*S589N*
711+3A→G	*E116K*	*G576A;R668C†*	*L967S*	*R117H*	*S737F*

CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko					
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*
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

- 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 < 400 m.
  - 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 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.	tezacaftor 100 mg/ivacaftor 300 mg per day

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; December 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210491s007lbl.pdf. Accessed October 29, 2021.
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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04.03.18	05.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.16.18	02.19
RT4: revised criteria to reflect newly FDA-approved lower age limit of 6 years; added new lower strength dosage form; references reviewed and updated.	07.07.19	
1Q 2020 annual review: added the following criteria to initial approval: comprehensive diagnostic criteria (e.g., clinical symptoms in at least one organ, positive newborn screen, siblings genetic testing, and evidence of	12.17.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
CFTR dysfunction) to confirm diagnosis of CF, prescriber requirement of pulmonologist, chart notes indicate that pulmonary function tests (ppFEV1 between 40-90%), not prescribed concurrently with other CFTR modulators; added the following to continued therapy criteria: positive response as evidenced by stabilization in ppFEV1 in lieu of an increase is acceptable if baseline was ≥ 70%, not prescribed concurrently with other CFTR modulators; added Appendix E; references reviewed and updated.		
1Q 2021 annual review: no significant changes; RT4: updated Appendix D with CFTR mutations that are responsive to Symdeko based on the updated Prescribing Information; updated Appendix E; references reviewed and updated.	01.19.21	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	10.22.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.