Clinical Policy: Tezacaftor/Ivacaftor; Ivacaftor (Symdeko)

Reference Number: PA.CP.PHAR.377
Effective Date: 01.19
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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 12 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 health plans affiliated with 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 ≥ 12 years;
3. One of the following (a or b):
   a. 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*);
4. Dose does not exceed tezacaftor 100 mg/ivacaftor 300 mg per day (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 Pennsylvania Health and 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. If request is for a dose increase, new dose does not exceed tezacaftor 100 mg/ivacaftor 300 mg per day (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 Pennsylvania Health and 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
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
FDA: Food and Drug Administration

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					
2789+5G→A	*A455E*	*D579G*	*F1074L*	*R1070W*	*S945L*
3272-26A→G	*D110E*	*E193K*	*F508del**	*R117C*	*S977F*

CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko					
3849+10kbC→T	*D110H*	*E56K*	*K1060T*	*R347H*	
711+3A→G	*D1152H*	*E831X*	*L206W*	*R352Q*	
A1067T	*D1270N*	*F1052V*	*P67L*	*R74W*	
*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.					

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CF	Adults, adolescents, and children ≥ 12 years: one tablet (tezacaftor 100 mg/ivacaftor 150 mg) PO in the morning and one tablet (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.	ezacaftor 100 mg/ivacaftor 300 mg per day

VI. Product Availability

Tablets: co-packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tablets and ivacaftor 150 mg tablets

VII. References

1. Symdeko Prescribing Information. Boston, MA: Vertex Pharmaceuticals Incorporated; February 2018. Available at: https://www.symdeko.com/. Accessed November 9, 2018.
2. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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