RXADVANCE
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Clinical Policy Title:	tezacaftor/ivacaftor
Policy Number:	RxA.487
Drug(s) Applied:	Symdeko®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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 *F508delCFTR*)] 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.

It 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
Tezacaftor/ivacaftor; ivacaftor (Symdeko®)	CF	Age 6 - 11 years weighing < 30 kg: 1 tablet (containing tezacaftor 50 mg/ivacaftor 75 mg) in the morning and 1 tablet (containing ivacaftor 75 mg) in the evening, approximately 12 hours apart with fat containing food. Age ≥ 12 years OR age 6 - 11 years weighing ≥ 30 kg: 1 tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and 1 tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart with fat-containing food.	tezacaftor 100 mg/day ivacaftor 300 mg/day

		Reduce dose in patients with moderate and severe hepatic impairment. Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.	

Dosage Forms

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

Clinical Policy

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

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. 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;

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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
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
- Contraindication(s):
  - None reported
- Boxed Warning(s):
  - None reported

APPENDIX D: General Information
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
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.**					

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.

References

1. Symdeko® Prescribing Information. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2019. Available at: https://www.symdeko.com/. Accessed October 1, 2020.
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. Accessed October 1, 2020.
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. Accessed October 1, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy was established	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to all lines of business. 2. Dosing information section updated to simplify wording for dosing regimen. 3. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 4. References were updated.	10/01/2020	12/07/2020