

Clinical Policy: Tezacaftor/Ivacaftor; Ivacaftor (Symdeko)

Reference Number: CP.PHAR.377

Effective Date: 04.03.18

Last Review Date: 02.22

Line of Business: Commercial, HIM, 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.

It is the policy of health plans affiliated with Centene Corporation[®] 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 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 \geq 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:

Medicaid/HIM/Commercial – 6 months

Legacy Wellcare – 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Cystic Fibrosis (must meet all):

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is responding positively to therapy as evidenced by a stabilization in ppFEV1 if baseline was \geq 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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
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	M952I	R347H	S1255P
A554E	F311L	H1054D	M952T	R347L	T338I
A1006E	F508C	H1375P	P5L	R347P	T1036N
A1067T	F508C; S1251N [†]	I148T	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	
<p>*A patient must have two copies of the <i>F508del</i> 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.</p>					

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 < 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	<p>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.</p> <p>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.</p> <p>Reduce dose in patients with moderate and severe hepatic impairment.</p> <p>Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.</p>	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 January 14, 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 HIM line of business; 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 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 $\geq 70\%$, not prescribed concurrently with other CFTR modulators; added Appendix E; changed approval durations of commercial from length of benefit to 6 months initial and 12 months continued; references reviewed and updated.	12.31.19	02.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; RT4: updated Appendix D with CFTR mutations that are responsive to Symdeko based on the updated Prescribing Information; references reviewed and updated.	01.18.21	02.21
1Q 2022 annual review: added legacy Wellcare initial approval duration (WCG.CP.PHAR.377 to be retired); references reviewed and updated.	10.22.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.22.22	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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