Clinical Policy: Tezacaftor/Ivacaftor; Ivacaftor (Symdeko)

Reference Number: CP.PHAR.377
Effective Date: 04.03.18
Last Review Date: 08.24
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 ≥ 6 years;
3. Prescribed by or in consultation with a pulmonologist;
4. Documentation of member's baseline precent predicted forced expiratory volume in 1 second (ppFEV1), performed within the last 90 days;
5. Symdeko is not prescribed concurrently with other CFTR modulators (e.g., Kalydeco®, Orkambi®, Trikafta®);
6. Dose does not exceed any 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 (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 or improvement (e.g., increase) in ppFEV1 from baseline;
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 any 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. 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*	*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*
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.

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.	Age 6 to < 12 years weighing < 30 kg: Tezacaftor 50mg/ivacaftor 150 mg Age 6 to < 12 years weighing 30 kg or more and age ≥ 12 years: 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; August 2023. Available at: https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf. Accessed May 9, 2024.

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 17, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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 ≥ 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	
1Q 2023 annual review: no significant changes; consolidated Legacy Wellcare initial approval duration from 12 months to 6 months consistent with standard Medicaid initial approval duration; updated Appendix D and Appendix E; references reviewed and updated.	10.07.22	02.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2023 annual review: updated criteria to include maximum dosing stratified by age and weight; references reviewed and updated.	05.04.23	08.23
Review performed: no significant changes; references reviewed and updated.	11.12.23	02.24
3Q 2024 annual review: for initial approval criteria, removed "chart notes showing ppFEV1 that is between 40 – 90%" and revised criteria to "documentation of member's baseline precent predicted forced expiratory volume in 1 second (ppFEV1)" to align with other CFTR modulator criteria; for continued therapy, revised criteria from "stabilization in ppFEV1 if baseline was ≥ 70%, or increase in ppFEV1 if baseline was <70%" to "stabilization or improvement (e.g., increase) in ppFEV1 from baseline" to align with other CFTR modulator criteria; revised Appendix D to remove information on advanced Cystic Fibrosis disease; references reviewed and updated.	05.09.24	08.24

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members 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.