

## Clinical Policy: Tezacaftor/Ivacaftor; Ivacaftor (Symdeko)

Reference Number: CP.PHAR.377

Effective Date: 04.03.18

Last Review Date: 02.20

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  $\geq 60$  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  $\geq$  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: 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): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

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

1. Currently receiving medication via Centene benefit 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  $\geq$  70% or increase in ppFEV1 if baseline was  $<$  70%;
3. Symdeko is not prescribed concurrently with other CFTR modulators (e.g., Kalydeco<sup>®</sup>, Orkambi<sup>®</sup>, Trikafta<sup>™</sup>);
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 Centene benefit and documentation supports positive response to therapy.  
**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): CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid 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

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					
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 <i>F508del</i> 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.

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
CF	<p>Pediatric patients age 6 to &lt; 12 years weighing &lt; 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 &lt; 12 years weighing 30 kg or</p>	tezacaftor 100 mg/ivacaftor 300 mg per day

Indication	Dosing Regimen	Maximum Dose
	<p>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>	

**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; June 2019. Available at: <https://www.symdeko.com/>. Accessed October 28, 2019.
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.

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	12.31.19	02.20

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

**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.

©2018 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.