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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Respiratory Agents	**Original Policy Date:**	March 9, 2018
Subject:	Symdeko	**Page:**	1 of 7

Last Review Date: December 8, 2023

Symdeko

Description

Symdeko (tezacaftor and ivacaftor)

Background
Cystic Fibrosis (CF) is caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encode for proteins called CFTR proteins. The CFTR proteins function as channels for chloride ions to go in and out of epithelial cells, which can be found on various parts of the body including the lungs and pancreas. Because these CFTR protein channels are mutated in CF patients, chloride (and therefore fluids) cannot be transported appropriately across cell membranes, causing a build-up of abnormally thick mucus in the lungs, pancreas, and other organs with the CFTR channels. Symdeko is a combination medication of CFTR potentiators (tezacaftor and ivacaftor) that works within cells to increase the quantity and function of the CFTR protein at the cell surface, resulting in increased chloride transport, in CF patients with certain *CFTR* gene mutations (1-2).

Regulatory Status
FDA-approved indication: Symdeko is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence (1).

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 (1).

List of *CFTR* Gene Mutations that 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*
A455E	*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*	

^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented above 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.

Elevated transaminases have been observed in patients with CF treated with Symdeko, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended for all patients prior to initiating Symdeko, every 3 months during the first year of

treatment, and annually thereafter. For patients with a history of transaminase elevations more frequent monitoring should be considered. In the event of significant elevations of transaminases, e.g., patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations consider the benefits and risks of resuming treatment (1).

Additionally, participants were excluded if they had 2 or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN) or AST or ALT ≥5 x ULN. The primary efficacy endpoint was change in lung function determined by absolute change from baseline in ppFEV$_1$ (1).

The safety and efficacy of Symdeko in patients with CF younger than 6 years of age have not been studied (1).

Related policies
Kalydeco, Orkambi, Pulmozyme, Trikafta

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Symdeko may be considered **medically necessary** if the conditions indicated below are met.

Symdeko may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 6 years of age or older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL of the following

1. Homozygous for the *F508del* mutation or at least one mutation in the *CFTR* gene that is responsive to Symdeko (see Appendix 2)
2. Pretreatment percent predicted forced expiratory volume ($ppFEV_1$) must be provided
3. Baseline ALT, AST, and bilirubin must be obtained at baseline and tested every 3 months for the first year
4. Must be prescribed by a pulmonologist or gastroenterologist
5. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 6 years of age or older

Diagnosis

Patient must have the following:

Cystic Fibrosis (CF)

AND ALL of the following:

1. Stable or improvement of $ppFEV_1$ from baseline
2. Annual testing of ALT, AST, and bilirubin levels after the first year of therapy
3. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 168 tablets for 84 days

Duration 6 months

Prior – Approval *Renewal* Limits

Quantity 168 tablets for 84 days

Duration 12 months

Rationale

Summary

Cystic Fibrosis (CF) is caused by mutations to the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encode for proteins called CFTR proteins. Mutations in these regulators lead to a build-up of sticky mucus in the lungs, pancreas, and other organs of the body. Symdeko is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. The use of this medication can improve the quantity and quality of the CFTR channels on the cell membranes and can help decrease the build-up of mucus in CF patients (1-2).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Symdeko while maintaining optimal therapeutic outcomes.

References

1. Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals, Inc.; August 2023.
2. Farinha CM, Paulo M, and Amaral MD. Control of cystic fibrosis transmembrane conductance regulator membrane trafficking: not just from the endoplasmic reticulum to the Golgi. FEBS Journal 280 (2013) 4396–4406

Policy History

Date	Action
March 2018	Addition to PA

June 2018	Annual editorial review Removal of requirement: patient has had 2 negative respiratory cultures for any of the following organisms: burkholeria cenocepacia, burkholderia dolosa, or mycobacterium abscessus in the past 12 months per SME
March 2019	Annual review
July 2019	Decreased age requirement to 6 years or older from 12 years or older
September 2019	Annual review
March 2020	Annual review and reference update
January 2021	Updated the list of *CFTR* gene mutations with additional mutations that have been identified as responsive to Symdeko. Added Appendix 2. Italicized every mention of *F508del* mutation and *CFTR* gene mutation to be consistent with PI per FEP
March 2021	Annual review
September 2022	Annual review and reference update
December 2022	Annual review
September 2023	Annual review
December 2023	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.

Appendix 1 - List of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiators

Generic Name	Brand Name
ivacaftor	Kalydeco
ivacaftor/lumacaftor	Orkambi
ivacaftor/tezacaftor	Symdeko
ivacaftor/tezacaftor/elexacaftor	Trikafta

Appendix 2 - List of *CFTR* Gene Mutations that 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*
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D443Y;G576A;R668C †	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
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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*
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